Small Charged Rings. III. Heterocyclic Ring Expansion through Aziridinium Salts[1-3]

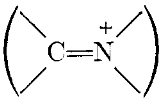
NELSON J. LEONARD, KLAUS JANN, JOSEPH V. PAUKSTELIS, AND C. K. STEINHARDT

Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois

Received December 26, 1962

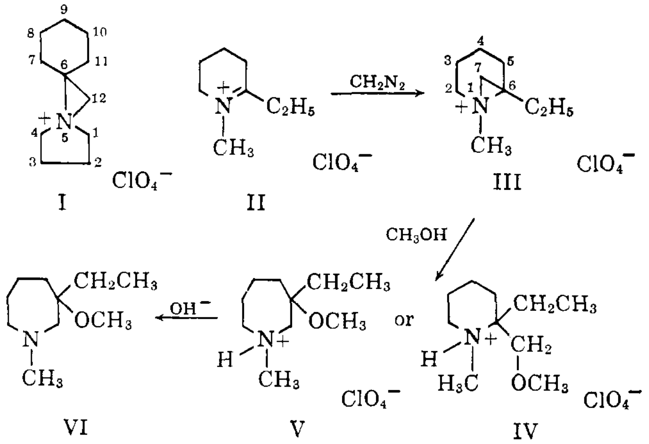
The generality of aziridinium ring synthesis by the addition of diazomethane to the $>C=\overset{+}{N}<$ grouping has been demonstrated in representative mono-, bi-, and tricyclic systems. Alcoholysis and hydrolysis of aziridinium salts in these systems lead effectively to heterocyclic ring enlargement and provide a new route to cyclic β-alkoxy- and β-hydroxyamino compounds. Examples are presented for the expansion of a six-membered ring through an aziridinium salt to a seven-membered ring (II → III → VI), a 1-azabicyclo[4.4.0]decane to a substituted 1-azabicyclo[4.4.1]undecane system (IX → X → XII), and a 2-azabicyclo[4.4.0]decane to a substituted 3-azabicyclo[5.4.0]undecane system (XV → XVI → XVIII). We found it possible to provide steric limitation to this ring enlargement reaction. Thus, the tetracyclic aziridinium compound XX resulting from the addition of diazomethane to $\Delta^{1(6)}$-tetrahydrojulolidinium perchlorate (XIX) underwent solvolysis at the less substituted aziridinium-ring carbon atom. Reconstitution of aziridinium perchlorates has been shown to be possible by treatment of substituted β-bromoalkyl-3°-amines with silver perchlorate.

The finding[1,4] that an aziridinium salt such as 5-azoniadispiro[4.0.5.1]dodecane perchlorate[5] (2,2-pentamethylene-1,1-tetramethyleneaziridinium perchlorate) (I) can be made simply and in high yield by the nucleophilic attack of diazomethane on the corresponding ternary iminium perchlorate encouraged us to extend this new method of synthesis to other representative aziridinium salts. Thus, we have added diazomethane successfully to the ternary iminium grouping



$$\left(>C=\overset{+}{N}<\right)$$

contained in monocyclic, bicyclic, and tricyclic systems. Moreover, the solvolysis of the aziridinium salt I in methanol to give a product having methoxyl attached to the more highly substituted carbon of the three-membered ring, namely N-(1-methoxycyclohexylmethyl)pyrrolidine,[1,4] suggested that this reaction might be employed for heterocyclic ring expansion if the original $>C=\overset{+}{N}<$ function were endocyclic.



The first preparation of 5-azoniadispiro[4.0.5.1]-dodecane perchlorate (I) from N-cyclohexylidenepyrrolidinium perchlorate had been run in methanol–ether at low temperature.[1,4] In order to avoid the initial employment of a hydroxylic solvent and to extend the usefulness of the diazomethane reaction other solvent–ether pairs were tried for the preparation of I. It was found that combinations of N-cyclohexylidenepyrrolidinium perchlorate in methylene chloride, dimethylformamide, or acetonitrile with diazomethane in ether at 0° were satisfactory and that methylene chloride gave the best results. The first model endocyclic iminium system employed was 2-ethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate (II),[6,7] $C_8H_{16}ClNO_4$, made *via* the mercuric acetate oxidation of 2-ethyl-1-methylpiperidine. When compound II in methylene chloride was treated with diazomethane in ether at 0° a new product was formed in 87% yield which had the correct analysis for $C_9H_{18}ClNO_4$, corresponding to the addition of a methylene group to the original compound. The structure 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]-heptane perchlorate (III), which was favored by analogy with I and by the absence of infrared absorption maxima corresponding to $>\overset{+}{N}-H$ and $>C=\overset{+}{N}<$, was secured by the n.m.r. spectrum in deuteriochloroform. The signal at lowest field, τ value 6.33,[8] appeared as an unsymmetrical triplet and integrated for two protons, consistent with an assignment to the hydrogens on C-2 (III), next to N⁺, as in models previously provided.[1,8] The integrated singlet at 6.79, which indicated three protons and was assignable to $>\overset{+}{N}-CH_3$ as in the models tetramethylammonium perchlorate (6.84) and 1,1-dimethylpyrrolidinium perchlorate (6.85),[1] was actually superimposed upon the

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[1] For the second article in the series, see N. J. Leonard and K. Jann *J. Am. Chem. Soc.*, **84**, 4806 (1962).

[2] This investigation was supported by a research grant (USPHS-RG5829) from the National Institutes of Health, U. S. Public Health Service, to whom we acknowledge our thanks.

[3] Presented at the Seventeenth National Organic Chemistry Symposium of the American Chemical Society, June, 1961, Bloomington, Ind.; see Abstracts, pp. 1-10.

[4] N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **82**, 6418 (1960).

[5] International Union of Pure and Applied Chemistry, Definitive Rules for Nomenclature of Organic Chemistry (IUPAC 1957 Rules), *ibid.*, **82**, 5545 (1960), especially p. 5572.

[6] R. Lukeš and O. Grossmann, *Collection Czech. Chem. Commun.*, **8**, 533 (1936).

[7] N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

[8] G. V. D. Tiers, "Tables of τ Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

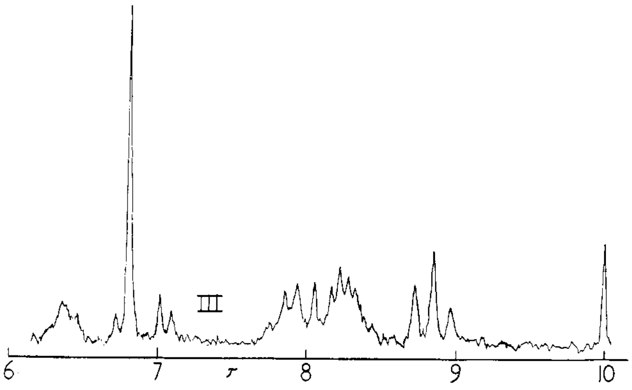


Figure 1

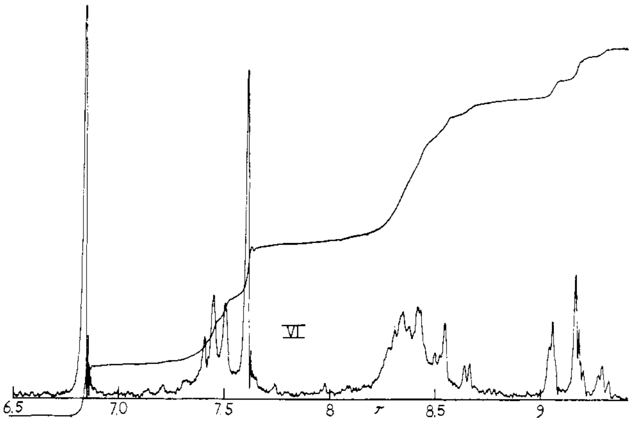
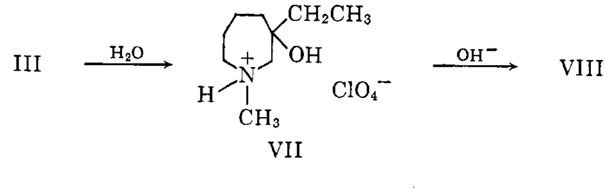


Figure 2

second line of four in a doublet system, AB (Fig. 1), with $J_{AB} = 5.0 \pm 0.5$ c.p.s., $\delta_B - \delta_A = 16.8$ c.p.s., or chemical shifts of 6.75 and 7.03. For reference, the $\overset{+}{N}\text{-}C\underline{H}_2$ (aziridinium ring) singlet signal was reported at 7.02 for I in liquid sulfur dioxide and at 6.98 for 5-azoniadispiro[4.0.5.1.]dodecane fluoborate (I, BF_4^- in place of ClO_4^-) in deuteriochloroform.[1] (See Experimental for further values.) Compound III, unlike I, is asymmetric and the aziridinium ring protons are structurally nonidentical, magnetically nonequivalent, and hence display an AB type of n.m.r. spectrum. Even in structures less fixed, examples have been provided where a chemical shift is observed between *gem*-methylenic protons which are conformationally distinct.[9–11] The rest of the n.m.r. spectrum of III includes signals at 7.83, 7.93, 8.04, 8.15, 8.21, 8.27, and 8.31 integrating for eight protons—six ring protons plus two protons of $C\underline{H}_2\text{–}CH_3$—and a triplet at 8.84 ($J = 8.0 \pm 0.5$ c.p.s.), not completely symmetrical, integrating for three protons, corresponding to the methyl group in $CH_2C\underline{H}_3$.

The methanolysis of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate (III) was complete within two hours at reflux temperature, and the major product was isolated in pure form, $C_{10}H_{22}ClNO_5$, m.p. 111–111.5°, in 90% yield. Analysis showed the presence of a methoxyl group and the infrared spectrum showed the presence of an $>\overset{+}{N}\text{—H}$ group. The expected product of solvolytic ring cleavage of III would be 3-ethyl-3-methoxy-1-methyl-1-azacycloheptane perchlorate (V) based on analogy with the methanolysis product of I[1] and with the direction of the ring opening of 1-(3′-aminopropyl)-2,2-dimethylethylenimine with picric acid in methanol observed by Tarbell and Noble,[12] but the alternative structure, 2-ethyl-2-methoxymethyl-1-methylpiperidine perchlorate (IV), could not be ruled out. The n.m.r. spectrum of the salt in deuteriochloroform did not offer clear distinction between the two alternative structures, since the broad low-field absorption integrating for four protons could correspond to either $C\underline{H}_2\text{-}\overset{|+}{\underset{|}{N}}\text{-}C\underline{H}_2$ (V) or to $C\underline{H}_2\text{-}\overset{+}{N}<$ plus $C\underline{H}_2\text{-}O$ (IV). The common structural features of either salt structure were confirmed by τ values in the n.m.r. spectrum at 6.72 (singlet, 3 protons, $O\text{–}C\underline{H}_3$); 6.97, 6.88 (doublet, 3 protons, $\overset{+}{N}H\text{–}C\underline{H}_3$); 7.9–8.7 (broad-6 ring protons, 2 protons in $C\underline{H}_2CH_3$); 9.12 (triplet, 3 protons, $CH_2\text{–}C\underline{H}_3$). The spectrum of the liberated base (Fig. 2) was definitive since the $C\underline{H}_2\text{–}N$ signals, unlike those of $C\underline{H}_2\text{–}\overset{+}{N}$, did not interfere with the signal of $C\underline{H}_3\text{–}O$. There was no signal at lower field than that for $C\underline{H}_3\text{–}O$ (τ value 6.84),[8] indicating the absence of the $C\underline{H}_2\text{–}O$ required for formulation as the base corresponding to IV and, therefore, establishing the structure of the amine as 3-ethyl-3-methoxy-1-methyl-1-azacycloheptane (VI) and the salt as V. The ring-enlargement route offers synthetic utility for arriving at compounds like VI which would be difficulty accessible by other means. Hydrolysis of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate (III) led to 3-ethyl-3-hydroxyl-1-methyl-1-azacycloheptane perchlorate (VII), which exhibited infrared maxima corresponding to O—H and $>\overset{+}{N}\text{—H}$ stretching and an n.m.r. spectrum similar to that of V in its common features. Treatment with base yielded 3-ethyl-3-hydroxyl-1-methyl-1-azacycloheptane (VIII), the structural assignment of which was made possible by the n.m.r. spectrum. Similarities to the spectrum of VI



VII

were noted plus the absence of any low-field signal corresponding to $C\underline{H}_2OH$[13] which would be present in the product of alternative ring cleavage, at the aziridinium $\overset{+}{N}\text{—}CH_2$ bond in III. An n.m.r. spectral verification of structural assignments V and VI, VII and VIII was possible by running as a check an S_N2 type of ring opening by treatment of III with sodium methoxide

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[9] R. C. Tuites, Ph.D. thesis, University of Illinois, 1959.

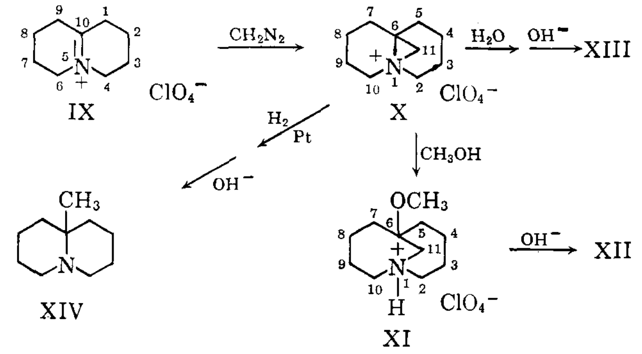
[10] G. M. Whitesides, F. Kaplan, K. Nagarajan, and J. D. Roberts, *Proc. Natl. Acad. Sci.*, **48**, 1112 (1962), and references therein.

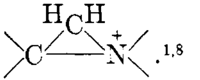
[11] H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

[12] D. S. Tarbell and P. Noble, Jr., *J. Am. Chem. Soc.*, **72**, 2657 (1950).

[13] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 55.

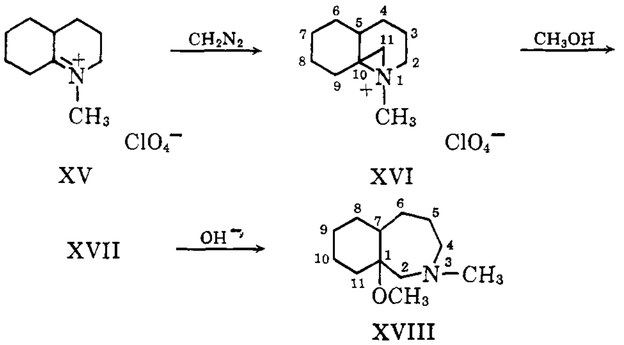
and sodium hydroxide and observing that the products showed $\mathrm{C\underline{H}_2OCH_3}$ at τ value 6.63 (base corresponding to IV) and $\mathrm{C\underline{H}_2OH}$ at 6.68, respectively.



In the bicyclic series, $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IX)[14] was converted to 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) in 90% yield by treatment with diazomethane. The structural assignment was based on the absence of $\rangle\overset{+}{\mathrm{N}}\text{—H}$ and $\rangle\mathrm{C}{=}\overset{+}{\mathrm{N}}\langle$ stretching bands in the infrared spectrum and on the presence of the singlet signal (2 protons) at a τ value of 6.83 in the n.m.r. spectrum. The appearance of this unsplit signal at higher field than that for $\mathrm{C\underline{H}_2\text{-}\overset{+}{N}}$ in five- and six-membered ring models[1] is indicative of proton attachment to a three-membered ring, .[1,8] Each of the equivalent protons on C-11 extends over a six-membered ring. The other four protons adjacent to $\overset{+}{\mathrm{N}}$, in the system $\mathrm{CH_2C\underline{H}_2\overset{+}{N}C\underline{H}_2CH_2}$ were detectable as a triplet at a τ value of 6.38. If methanol were to react with X predominantly in an S_N1 manner, it would provide a direct conversion route from a bicyclo[4.4.0]decane ring system (IX) to a bicyclo[4.4.1]undecane system (XI). Methanolysis of 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) did indeed produce 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (XI) in 81% yield, as judged by microanalysis, infrared and n.m.r. spectra of the salt, and confirmed through the n.m.r. spectrum of the base (XII) by applying the principles which have been cited above. There was no signal at lower field than 6.83, where a singlet assignable to the O–CH_3 group appeared. Instead, a singlet corresponding to two protons was found at 6.88 corresponding to the bridging $\rangle\mathrm{C—C\underline{H}_2\text{-}N}$. Hydrolysis of X at steam-bath temperature during six hours also resulted in aziridinium ring opening (93% yield) with substitution on the more substituted carbon. After treatment with base, 6-hydroxy-1-azabicyclo[4.4.1]undecane (XIII) was obtained, and the structure was determined by comparative examination of the n.m.r. spectra (see Experimental). Double ring expansion thus has been realized in the over-all conversion of IX to both XII and XIII.

Hydrogenolysis of the aziridinium ring present in 1-azoniatricyclo[4.4.1.0]undecane perchlorate (X) proceeded, by contrast, with cleavage of the less hindered C–N bond of the three-membered ring, as would be suggested by previous experience.[1,15,16] The hydrogenation of X in the presence of platinum oxide was rapid and could be carried out in acetone solution. The perchlorate of the saturated product was converted to the base, which was identified as 6-methyl-1-azabicyclo[4.4.0]decane[5] (or 10-methylquinolizidine) (XIV)[14] by direct comparison with authentic material.

Another bicyclic system investigated was 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate (XV), which is readily available by the lithium-*n*-propylamine reduction of 1-methyltetrahydroquinoline to the enamine mixture, followed by neutralization with perchloric acid to give the ternary iminium salt.[17] Reaction of XV with diazomethane proceeded rapidly and in high yield. The infrared spectrum of the major product, $C_{11}H_{20}ClNO_4$, m.p. 129–129.5°, was devoid of maxima corresponding to $\rangle\overset{+}{\mathrm{N}}\text{—H}$ and $\rangle\mathrm{C}{=}\overset{+}{\mathrm{N}}\langle$ functions and exhibited an n.m.r. spectrum (Fig. 3) indicative of the structure 1-methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane perchlorate (XVI). In the spectrum the singlet at τ value 6.81 was assignable to $\mathrm{C\underline{H}_3\text{-}\overset{+}{N}}$,[1] as in III, and the pair of doublets at τ = 6.66 and 7.09 with a coupling constant $J = 5.0 \pm 0.5$ c.p.s., were indicative of the two aziridinium ring protons (AB) in the unsymmetrical molecule.[9–11]



Turning to the chemistry of 1-methyl-1-azoniatricyclo[8.1.0.0.^{5,10}]undecane (XVI), methanolysis yielded (86% over-all from XV) a product with properties consistent for 1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane perchlorate (XVII). Establishment of structure was possible by liberation of the free base, $C_{12}H_{23}NO$, which in the n.m.r. spectrum exhibited no signal at lower field than the O–CH_3 signal (τ value 6.83; N–CH_3 signal at 7.75) and therefore did not possess a $\mathrm{C\underline{H}_2OCH_3}$ grouping. This synthesis of 1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane (XVIII) represents an efficient single ring expansion from a bicyclo[4.4.0]decane (XV) to a bicyclo[5.4.0]undecane system. In another example, ethanolysis of XVI yielded as a major product 1-ethoxy-3-methyl-3-azabicyclo[5.4.0]undecane by analogy with XVII.

The diazomethane attack on the $\rangle\mathrm{C}{=}\overset{+}{\mathrm{N}}\langle$ group in a tricyclic system is exemplified with $\Delta^{1(6)}$-tetrahydrojulolidinium perchlorate (XIX). The structure of the aziridinium product, $C_{13}H_{22}ClNO_4$, m.p. 150–151° dec., was established by the usual analytical and spectral

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(14) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).

(15) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *ibid.*, **68**, 140 (1946).

(16) J. V. Karabinos and K. T. Serijan, *ibid.*, **67**, 1856 (1945).

(17) N. J. Leonard, C. K. Steinhardt, and C. Lee, *J. Org. Chem.*, **27**, 4027 (1962).

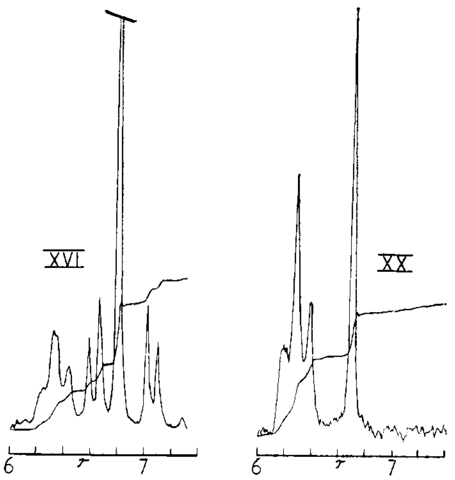
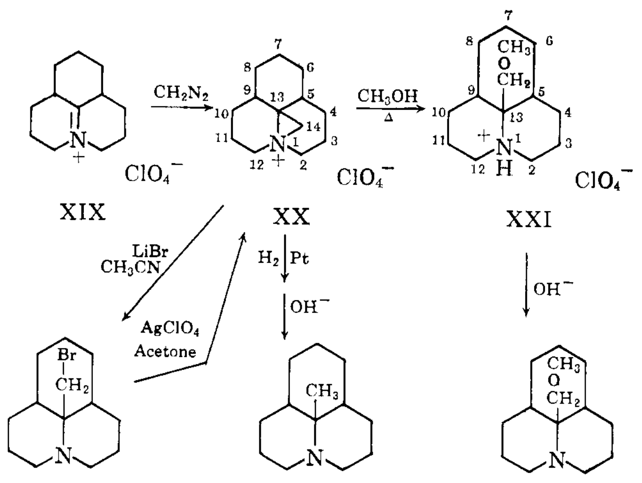


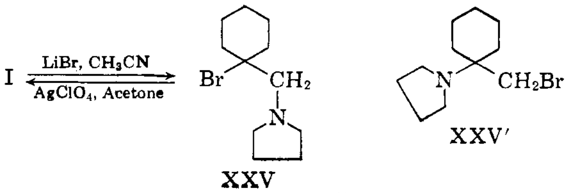
Figure 3



criteria as 1-azoniatetracyclo[7.3.2.0.^{1,13}0^{5,13}]tetradecane perchlorate (XX). In contrast to XVI and in similarity with X, the two methylenic protons in the aziridinium ring ($C\underline{H}_2$–$\overset{+}{N}$) are equivalent, and a singlet was observed at a τ value of 6.70 in the n.m.r. spectrum (Fig. 3). Methanolysis of XX proceeded slowly to yield (89%) a new product, $C_{14}H_{26}ClNO_5$, which indicated by its composition that it contained the added elements of methanol. The $\diagdown\!\!\!\!-\overset{+}{N}\text{—H}$ group was identified in this perchlorate salt by the infrared maximum at 3125 cm.$^{-1}$, and the grouping $\overset{\text{H}}{\text{N}^+}\text{—}\overset{|}{\underset{|}{\text{C}}}\text{—CH}_2\text{—O—CH}_3$ was shown—in contradistinction to the alternative $\overset{\text{H}}{\text{N}^+}\text{—CH}_2\text{—}\overset{|}{\underset{|}{\text{C}}}\text{—O—CH}_3$ grouping—by the clear *singlets* in the n.m.r. spectrum (in methylene chloride) at τ values of 6.09 and 6.55 (1.97/3.03 protons by integration). The structure 13-methoxymethyl-1-azatricyclo[7.3.1.0.^{5,13}]tridecane perchlorate XXI was, therefore, assignable to the methanolysis product of XX. For the base which was liberated from the perchlorate the lowest-field signals in the n.m.r. spectrum were two singlets at τ values (carbon tetrachloride) 6.24 and 6.75 integrating for 2 and 3 protons, respectively. The grouping CH_2—O—CH_3 was, therefore, present in the base, of structure 13-methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXII), and the sharp melting point of this compound, 79.5–80°, along with the spectral data, suggested that a single isomer had been produced from the precursor XX of m.p. 150–151° dec. It is apparent that opening of the aziridinium ring in the tetracyclic system XX has occurred in a manner different from that observed in the methanolysis of I, III, X, and XVI. The tertiary aziridinium carbon (13) in XX is sufficiently hindered, or the tetracyclic molecule is constrained so that the linkage N_1–C_{13} is not readily broken, with the result that the methoxy group becomes attached to the primary aziridinium carbon by solvolysis or displacement. A limitation to the ring-enlargement reaction, therefore, is realized in structure XX.

The hydrogenation of 1-azoniatetracyclo[7.3.2.0.^{1,13}-0^{5,13}]tetradecane perchlorate (XX) in acetone using platinum oxide produced (93%) 13-methyl-1-azatricyclo[7.3.1.0.^{5,13}]tridecane perchlorate, the structure of which was assigned on the basis of infrared and n.m.r. spectra and from which the base, 13-methyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIII), m.p. 31–32°, was liberated. Indication of the C-methyl group in XXIII which had been introduced was obtained from the singlet n.m.r. signal at τ value 8.96. The treatment of XX with lithium bromide in acetonitrile solution using anhydrous reagents and extraction continuously with pentane afforded (95%) a bromine-containing base, $C_{13}H_{22}BrN$, m.p. 110–112°. The CH_2Br grouping was indicated by the singlet signal at lowest field (6.19) in the n.m.r. spectrum in benzene solution. The same compound was made by treating $\Delta^{1(6)}$-tetrahydrojulolidinium bromide (XIX, Br^- in place of ClO_4^-) with diazomethane. Assignment of the structure as 13-bromomethyl-1-azatricyclo[7.3.1.0^{5,13}]-tridecane (XXIV) was confirmed by conversion to the perchlorate salt, which likewise showed a *singlet* at 5.87 in the n.m.r. spectrum in acetonitrile solution consistent for two protons in the grouping $\overset{+}{\text{N}}\text{H—}\overset{|}{\underset{|}{\text{C}}}\text{—}$ CH_2Br, but not in the alternative structural grouping $\overset{+}{\text{N}}\text{H—CH}_2\text{—}\overset{|}{\underset{|}{\text{C}}}\text{—Br}$. The *resynthesis* of the aziridinium perchlorate XX was achieved by treating 13-bromomethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane (XXIV) with silver perchlorate in acetone solution.

In order to compare the behavior of 5-azoniadispiro-[4.0.5.1]dodecane perchlorate (I) with lithium bromide in acetonitrile to that of XX, the former was submitted to the same reaction and isolation procedure. It yielded a product which exhibited a singlet proton signal in the n.m.r. spectrum in benzene solution at 7.08. On the basis of the known methoxy compounds corresponding to XXV and XXV′ (OCH_3 in place of Br),[1] which showed $\tau_{C\underline{H}_2}$ at 7.62 and 6.65, respectively,



XXV XXV′

and on the relative deshielding of methylene protons by β- and by α-Br and OCH_3 substituents,[18] the observed $\tau_{C\underline{H}_2}$ value of 7.08 falls within the range calculated for XXV but not for XXV′. In confirmation of the assigned structure, N - (1 - bromocyclohexylmethyl)-pyrrolidine (XXV), the perchlorate salt, m.p. 165–166° dec., exhibited a doublet at 6.24 in deuteriochloroform, or 6.29 in acetonitrile, $J = 5.0 \pm 0.5$ c.p.s., consistent with splitting of the methylene protons by the proton on nitrogen in the conjugate acid ($C\underline{H}_2-\overset{+}{N}H$), plus broad absorption near 2.3 which was probably the signal corresponding to the nitrogen proton. When the salt was dissolved in heavy water, lyophilized, and redissolved in deuteriochloroform, the n.m.r. spectrum was similar to that of the original except that a singlet at 6.24 replaced the doublet and there was no absorption in the $\tau = 2.3$ region. The observed spectral changes should not be exhibited by the perchlorate of the base XXV′. Finally, the reconversion of N-(1-bromocyclohexylmethyl)pyrrolidine (XXV) to the aziridinium salt, 5-azoniadispiro[4.0.5.1]dodecane perchlorate (I), was effected by treatment of XXV with silver perchlorate in acetone while maintaining the reaction mixture cold.

Experimental[19]

Preparation of 5-Azoniadispiro[4.0.5.1]dodecane Perchlorate (2,2-Pentamethylene-1,1-tetramethyleneaziridinium Perchlorate) (I) in Methylene Chloride.—A solution of 5.0 g. (19.8 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate[1] in 200 ml. of dry methylene chloride maintained at 0° was treated with diazomethane in ether[20] until the yellow color of the diazomethane persisted. Nitrogen was evolved during the addition. On standing for 3 hr. at 0° a colorless crystalline solid separated, 4.90 g. (93%), m.p. 130.0–131.5°. An additional 0.30 g. separated on addition of ether. Recrystallization from 2-propanol–ether raised the melting point to 132–133°. The perchlorate obtained was identical with an authentic sample prepared previously.[1]

In Dimethylformamide.—A solution of 3.0 g. (11.9 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate in 100 ml. of dimethylformamide maintained at 0° was treated with diazomethane in ether until the yellow color of diazomethane persisted. Nitrogen was evolved as rapidly as the diazomethane was added. The solvent was removed on a rotary evaporator after standing at 0° for a few minutes. When ether was added to the remaining colorless oil, the oil solidified. Recrystallization from acetone–ether gave 1.96 g. (62%) of a perchlorate, m.p. 130–131°, which on further recrystallization was identical with the sample described previously.

In Acetonitrile.—A solution of 3.0 g. (11.9 mmoles) of N-cyclohexylidenepyrrolidinium perchlorate in 50 ml. of acetonitrile maintained at 0° was treated with diazomethane in ether. The product, isolated as above, was recrystallized from acetone–ether yielding 2.75 g. (87%) of colorless crystals, m.p. 134–135°, identical with the best sample of 5-azoniadispiro[4.0.5.1]dodecane perchlorate.

The typifying proton signal in the n.m.r. spectrum for this compound and the introduced aziridinium $C\underline{H}_2-\overset{+}{N}$ grouping was previously reported, on two different instruments,[1] as a singlet at τ value 7.02 in liquid sulfur dioxide and at 6.98 in deuteriochloroform for the corresponding fluoborate salt. On the Varian Associates Model A-60 spectrometer we have more recently obtained values of 6.88 for compound I in $CDCl_3$, 6.91 for I in $CDCl_3$–CH_2Cl_2, and 6.93 for I (BF_4^- in place of ClO_4^-) in $CDCl_3$.

6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A solution of 4.0 g. (17.7 mmoles) of 2-ethyl-1-methyl-Δ^1-tetrahydropyridinium perchlorate (II)[6,7] in 50 ml. of dry methylene chloride at 0° was treated with diazomethane in ether prepared from 5.0 g. of N-nitrosomethylurea. The solution was stirred for 20 min., then allowed to warm to room temperature. The solid residue obtained on removal of the solvent on a rotary evaporator was recrystallized from 2-propanol–ether yielding 3.85 g. (87%) of a colorless perchlorate, m.p. 137–138°; no infrared maxima corresponding to $>\overset{+}{N}-H$ and $>C=N^{+}<$; n.m.r. signals occur at τ values ($CDCl_3$): 6.33,[21] 6.70, 6.79 (doublet and singlet overlaid at 6.79); 7.00, 7.08 (doublet); 7.83, 7.93, 8.04, 8.15, 8.21, 8.27, 8.31; 8.84 (center of triplet, $J = 8.0 \pm 0.5$ c.p.s.) (see Fig. 1).

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.09; H, 7.56; N, 5.84. Found: C, 44.89; H, 7.51; N, 5.76.

Methanolysis of 6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A solution of 1.20 g. (4.81 mmoles) of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate in 20 ml. of absolute methanol was refluxed for 2 hr. The colorless solid obtained on removal of the methanol *in vacuo* was recrystallized from 2-propanol–ether yielding 1.22 g. (90%) of **3-ethyl-3-methoxy-1-methyl-1-azacycloheptane perchlorate (V)**, m.p. 111.0–111.5°; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($>\overset{+}{N}-H$); n.m.r. signals at τ ($CDCl_3$): 6.30, 6.40, 6.53, 6.83, 7.05 (broad, 4 protons); 6.72 (singlet, 3 protons, $O-C\underline{H}_3$); 6.97, 6.88 (doublet, 3 protons, $\overset{+}{N}H-C\underline{H}_3$); 7.9–8.7 (broad, 8 protons–6 ring protons, 2 $C\underline{H}_2-CH_3$ protons); 9.12 (triplet, $J = 7.2 \pm 0.5$ c.p.s., not completely symmetrical, 3 protons, $CH_2-C\underline{H}_3$).

Anal. Calcd. for $C_{10}H_{22}ClNO_5$: C, 44.20; H, 8.10; N, 5.15; OCH_3, 11.42. Found: C, 43.97; H, 7.98; N, 5.21; OCH_3, 11.28.

An aqueous solution of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give **3-ethyl-3-methoxy-1-methyl-1-azacycloheptane (VI)** as a colorless liquid; n.m.r. signals (Fig. 2) at τ ($CDCl_3$): 6.83 (singlet, 3 protons, $O-C\underline{H}_3$); 7.3–7.8 (4 protons, $C\underline{H}_2NC\underline{H}_2$); 7.62 (singlet, 3 protons, $N-C\underline{H}_3$); 8.17–8.75 (6 ring protons and 2 protons in $C\underline{H}_2-CH_3$); 9.17 (unsym. triplet, $J = 7.5 \pm 0.5$ c.p.s., 3 protons, $CH_2-C\underline{H}_3$).

Hydrolysis of 6-Ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (III).—A sample of 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate liquified and then later solidified when allowed to stand in a humid atmosphere for several months. Recrystallization from 2-propanol–ether at −40° gave a colorless solid, m.p. 85.5–86.5°; ν_{max}^{Nujol} 3453 (O–H), 3090 cm.$^{-1}$ ($>\overset{+}{N}-H$); n.m.r. signals at τ ($CDCl_3 + CH_2Cl_2$): 6.30, 6.44, 6.51, 6.64, 6.72 plus a doublet at 6.88, 6.98, $J = 5.5 \pm 0.5$ c.p.s. ($\overset{+}{N}H-C\underline{H}_3$) (total 8 protons); 8.27,[21] 8.43, 8.55 (8 protons); 9.06 (triplet, unsymmetrical, $J = 7.0 \pm 0.5$ c.p.s., 3 protons, $CH_2-C\underline{H}_3$). Addition of acetic acid did not allow the assignment of the O–H proton but did show that the doublet at 6.88, 6.98 was due to $\overset{+}{N}H-C\underline{H}_3$ because the doublet became a singlet at 6.96, identifying the compound as **3-ethyl-3-hydroxy-1-methyl-1-azacycloheptane perchlorate (VII).**

Anal. Calcd. for $C_9H_{20}ClNO_5$: C, 41.95; H, 7.82; N, 5.84. Found: C, 41.78; H, 7.69; N, 5.63.

An aqueous solution of 0.300 g. (1.26 mmoles) of the perchlorate was treated with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give 0.143 g. (79%) of **3-ethyl-3-hydroxy-1-**

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(18) Ref. 13, pp. 53 and 59.

(19) All melting points are corrected, boiling points are uncorrected. We are indebted to Mr. Josef Nemeth, Miss Jane Liu, Mr. Gary D. Callahan, and Miss Mary Ann Weatherford for the microanalyses. We also wish to thank Mr. Dick H. Johnson, Mr. Oliver W. Norton, and Miss Gail Gregory for determining the n.m.r. spectra at 60 Mc. with a Varian Associates Model V-4300B spectrometer equipped with a superstabilizer, or with a Varian Associates Model A-60 spectrometer. The chemical shifts were determined using tetramethylsilane as an internal standard ($\tau = 10$), obtaining side bands by the application of an audio-frequency signal from an external source. The infrared spectra were determined using a Perkin-Elmer automatic recording infrared spectrophotometer Model 21.

(20) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

(21) Center of unresolved multiplet.

methyl-1-azacycloheptane (VIII) as a colorless liquid. The n.m.r. spectrum showed signals at τ values ($CDCl_3$): 5.29 (O-$\underline{H}$); 7.26, 7.47, 7.72 (4 protons, $C\underline{H}_2NC\underline{H}_2$ plus 2 ring protons); 7.58 (3 protons, N-$C\underline{H}_3$); 8.41 (4 ring protons); 8.55 (2 protons, J = 7.0 ± 0.5 c.p.s., $C\underline{H}_2$-CH_3, superimposed on the 4 protons centered on 8.41); 9.10 (triplet, unsym., J = 7.0 ± 0.5 c.p.s., CH_2-$C\underline{H}_3$). The ethyl group showed long range splitting both in the methylene and the methyl, $J \approx 0.7$ c.p.s. The signal at 5.29 was shifted to 4.19 by the addition of a trace of acetic acid.

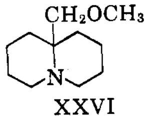
1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 10.0 g. (42.1 mmoles) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IX)[14] in 400 ml. of anhydrous methylene chloride maintained at 0° was treated with diazomethane in ether. The diazomethane was added in five portions over a 30-min. period, and the solution was stirred for an additional 0.5 hr. at 0°. The solvent was removed on a rotary evaporator leaving a colorless oil which slowly crystallized when washed with ether and cooled to −60°. The colorless perchlorate, 9.6 g. (90%), m.p. 142–144°, showed no infrared maxima corresponding to $>\!\overset{+}{\mathrm{N}}\text{—H}$ and $>\mathrm{C}{=}\overset{+}{\mathrm{N}}<$. The n.m.r. spectrum (simplified) showed signals at τ ($CDCl_3$): 6.38 (triplet, 4 protons, J = 6.0 ± 0.5 c.p.s., $\mathrm{CH_2\text{-}C\underline{H}_2\text{—}\overset{+}{N}\text{—}C\underline{H}_2CH_2}$); 6.83 (singlet, 2 protons, aziridinium $\mathrm{C\underline{H}_2\text{-}\overset{+}{N}}$); 7.85 (triplet, 4 protons, J = 6.2 ± 0.5 c.p.s.); 8.22, 8.27, 8.32 (total of 8 protons).

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.58. Found: C, 47.39; H, 7.29; N, 5.53.

Methanolysis of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 2.0 g. (8.42 mmoles) of 1-azoniatricyclo-[4.4.1.0]undecane perchlorate in 5 ml. of anhydrous methanol was refluxed for 2 hr. To the warm solution ether was added to turbidity. The solid which separated from the solution after standing at 0° overnight was recrystallized from 2-propanol–ether yielding 1.99 g. (81%), m.p. 136–137°; $\nu_{\max}^{\mathrm{Nujol}}$ 3100 cm.$^{-1}$ ($>\!\overset{+}{\mathrm{N}}\text{-H}$), of product, colorless plates, identified (later in text also) as **6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (XI)**; n.m.r. signals occur at τ ($CDCl_3$): 6.43–6.64 (total of 6 protons—including 6.43, 6.48, most probably the bridging $\mathrm{C\underline{H}_2\text{—}\overset{H}{\underset{|}{\overset{|+}{N}}}\text{—}}$ split by the proton on nitrogen: if so, J = 3.0 c.p.s.; plus 6.56, 6.64); 6.79 (singlet, 3 protons, O-$C\underline{H}_3$); 8.12 (unresolved multiplet equal to 12 protons).

Anal. Calcd. for $C_{11}H_{22}ClNO_5$: C, 46.56; H, 7.82; N, 4.94; OCH_3, 10.94. Found: C, 46.60; H, 7.78; N, 5.01; OCH_3, 10.56.

An aqueous solution of 0.154 g. (0.543 mmole) of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give 0.082 g. (82%) of **6-methoxy-1-azabicyclo[4.4.1]undecane (XII)** as a colorless oil, n.m.r. signals at τ ($CDCl_3$): 6.83 (singlet, 3 protons, O-$C\underline{H}_3$); 6.88 (singlet, 2 protons, bridging $C\underline{H}_2$-N); 7.08 (multiplet, having the outline of a triplet further split, 4 protons, $CH_2C\underline{H}_2$-N-$C\underline{H}_2CH_2$; 8.32, 8.42 (unresolved multiplets, 12 protons). For comparison, a sample of 6-methoxymethyl-1-azabicyclo[4.4.0]decane (XXVI)[22] had n.m.r. signals for O-$C\underline{H}_3$ at 6.67 and for $C\underline{H}_2$-O at 6.39.



XXVI

Hydrolysis of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 1.0 g. (4.21 mmoles) of 1-azoniatricyclo-[4.4.1.0]undecane perchlorate in 10 ml. of water was heated on a steam bath for 6 hr. The water was removed on a rotary evaporator and the remaining colorless oil was washed with ether until the oil solidified. Recrystallization from 2-propanol–ether gave 1.00 g. (93%) of a colorless solid, m.p. 98–99°; $\nu_{\max}^{\mathrm{Nujol}}$ 3410 cm.$^{-1}$ (O–H), 3060 cm.$^{-1}$ ($>\!\overset{+}{\mathrm{N}}\text{—H}$); n.m.r. signals observed at τ (CH_2Cl_2): 6.15 (1 proton, O-$\underline{H}$, assigned on the basis that $>\!\overset{+}{\mathrm{N}}\text{—H}$ is not usually observed); 6.41 (apparent singlet, 2 protons, bridging $\mathrm{C\underline{H}_2\text{-}\overset{+}{N}}$); 6.4–6.8 (complex multiplet, 4 protons, $\mathrm{CH_2\text{-}C\underline{H}_2\overset{+}{N}C\underline{H}_2CH_2}$); 8.13 (complex multiplet, 12 protons).

Anal. Calcd. for $C_{10}H_{20}ClNO_5$: C, 44.54; H, 7.47; N, 5.20. Found: C, 44.60; H, 7.60; N, 5.42.

An aqueous solution of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether was removed on a rotary evaporator to give a solid, **6-hydroxy-1-azabicyclo[4.4.1]undecane (XIII)**, m.p. 94–96°. Sublimation raised the melting point to 97–99°; $\nu_{\max}^{\mathrm{CCl_4}}$ 3580, 3350 cm.$^{-1}$; n.m.r. signals at τ ($CDCl_3$): 6.90 (singlet, 2 protons, bridging $C\underline{H}_2$-N); 7.07 (multiplet, 4 protons, CH_2-$C\underline{H}_2$-N-$C\underline{H}_2CH_2$); 7.60 (singlet, 1 proton, O-$\underline{H}$, since signal moved to lower field when a trace of acetic acid was added); 8.30, 8.37 (unresolved multiplet, 12 protons). For comparison, an impure (containing XIII) sample of 6-hydroxymethyl-1-azabicyclo[4.4.0]decane (XXVI, but OH in place of OCH_3) had an n.m.r. signal at 6.43 plus differences in the 8.2–8.6 region.

Catalytic Reduction of 1-Azoniatricyclo[4.4.1.0]undecane Perchlorate (X).—A solution of 1.0 g. (4.21 mmoles) of 1-azoniatricyclo[4.4.1.0]undecane perchlorate in 100 ml. of anhydrous acetone was hydrogenated at 35 p.s.i. in the presence of 0.5 g. of platinum oxide. Filtration of the reduction mixture followed by removal of the solvent on a rotary evaporator yielded a slightly colored oil. The oil was dissolved in ethanol, treated with decolorizing carbon, and cooled. An oil separated which slowly crystallized on further cooling. The crystalline solid was recrystallized from 2-propanol–ether yielding 0.758 g. (75%) of a perchlorate, m.p. 161–163°; $\nu_{\max}^{\mathrm{CHCl_3}}$ 3020 cm.$^{-1}$ ($>\!\overset{+}{\mathrm{N}}\text{—H}$); n.m.r. signals at τ ($CDCl_3$): 6.80, 6.87, 6.95 (4 protons, $\mathrm{C\underline{H}_2\text{-}\overset{+}{N}\text{-}C\underline{H}_2}$); 8.20 (12 protons); 8.57 (sharp singlet, 3 protons, C-$C\underline{H}_3$), identical, within experimental errors of the Varian A-60, with the n.m.r. spectrum of authentic **6-methyl-1-azabicyclo[4.4.0]decane perchlorate** (10-methylquinolizidine[14] perchlorate). In the 2600–2900-cm.$^{-1}$ region of the infrared spectrum,[23,24] as determined in chloroform solution (0.20 M) using a Perkin-Elmer Model 237 spectrophotometer, were observed maxima at 2945 cm.$^{-1}$ (ϵ 197), 2870 (88), 2795 (77), 2655 (23), and 2610 (22).

Anal. Calcd. for $C_{10}H_{20}ClNO_4$: C, 47.34; H, 7.95; N, 5.52. Found: C, 47.13; H, 8.04; N, 5.38.

An aqueous solution 0.140 g. (0.552 mmole) of the perchlorate was made basic with 40% potassium hydroxide and extracted with three portions of ether. The combined extracts were dried over magnesium sulfate, filtered, and the ether removed on a rotary evaporator to give 0.063 g. (87%) of **6-methyl-1-azabicyclo[4.4.0]decane (XIV)** as a colorless oil; n.m.r. signals at τ ($CDCl_3$): 7.49, 7.57, 7.75, 7.83 (4 protons, $C\underline{H}_2$-N-$C\underline{H}_2$); 8.50[21] (multiplet with peaks at 8.45, 8.50, 8.05, 8.08, 8.14, 8.17, 8.19, 12 protons); 9.07 (singlet, 3 protons, $>\!\mathrm{C\text{—}C\underline{H}_3}$). The infrared spectrum in 0.20 M carbon tetrachloride as determined using a Perkin-Elmer Model 237 spectrophotometer exhibited maxima as follows[23,24]: 2970 cm.$^{-1}$ (ϵ 102), 2925 (490), 2880 (sh) (122), 2860 (133), 2790 (130), 2745 (88), 2670 (32). An authentic sample of 6-methyl-1-azabicyclo[4.4.0]decane (10-methylquinolizidine)[14] was prepared according to the method previously used in this laboratory, and the samples proved to be identical by comparison of infrared and n.m.r. spectra and the infrared and n.m.r. spectra of their perchlorates. The melting points of mixtures of the perchlorates and of the picrates were not depressed.

1-Methyl-1-azoniatricyclo[8.1.0.0^{5,10}]undecane Perchlorate (XVI).—A solution of 1.5 g. (6 mmoles) of 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate (XV)[17] in 175 ml. of methylene chloride was treated with an ethereal solution of diazomethane at 25°. The reaction was nearly instantaneous as evidenced by im-

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[22] J. V. Paukstelis, unpublished work.

[23] F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

[24] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

mediate decolorization of the diazomethane and nitrogen evolution. Addition of ethereal diazomethane was halted after a yellow color persisted in the reaction mixture. The solution was allowed to stand overnight, solvent was removed under reduced pressure in a rotary evaporator, and oily needles were obtained, recrystallized from diethyl ketone, m.p. 129–129.5° (depends on rate of heating; values of 118° to 131° have been recorded on the same sample), yield 1.43 g. (90%); no infrared maxima corresponding to $>\overset{+}{N}-H$ or $>C=\overset{+}{N}<$; n.m.r. τ values ($CDCl_3$): 6.32,[21] 6.66 (τ for doublet, $J = 5.0 \pm 0.5$ c.p.s.), 6.81 (3 protons, $C\underline{H}_3-\overset{+}{N}$), 7.09 ($\tau$ for doublet, $J = 5.0 \pm 0.5$ c.p.s.), 8.25 (broad)[21] (Fig. 3).

Anal. Calcd. for $C_{11}H_{20}ClNO_4$: C, 49.72; H, 7.59; H, 5.27. Found: C, 49.82; H, 7.67; N, 5.28.

Methanolysis of 1-Methyl-1-azoniatricyclo$[8.1.0.0^{5,10}]$undecane Perchlorate (XVI).—The crude crystalline product obtained as described above by addition of diazomethane to 1.5 g. of 1-methyl-$\Delta^{1(9)}$-octahydroquinolinium perchlorate was heated under reflux with methanol for 45 min. The solution was concentrated and the major product was precipitated with ether to yield 1.52 g. (86% over-all) of **1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane perchlorate (XVII)**, colorless plates, m.p. 163–163.5°; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($>\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): *ca.* 2.0[21] (1 proton, $\overset{+}{N}H$); 5.6–7.6 (broad); 6.66 (singlet, 3 protons, $O-C\underline{H}_3$); 6.95 (τ for doublet, $J = 5.4 \pm 0.5$ c.p.s. $C\underline{H}_3-\overset{+}{N}H$); 8.07, 8.40 (complex multiplet).

Anal. Calcd. for $C_{12}H_{24}ClNO_5$: C, 48.40; H, 8.12; N, 4.70; OCH_3, 10.42. Found: C, 48.57; H, 8.14; N, 4.75; OCH_3, 10.52.

The salt was made basic with aqueous sodium hydroxide and extracted with ether. The ether was evaporated leaving 0.96 g. (96%) of colorless oil which was distilled under reduced pressure in a Hickman still. Gas–liquid chromatography showed a single peak. N.m.r. analysis (neat) showed no signal at lower field than the $O-C\underline{H}_3$ signal (τ value 6.83); an $N-C\underline{H}_3$ signal at 7.75, and complex absorption at higher field, consistent with the structural assignment **1-methoxy-3-methyl-3-azabicyclo[5.4.0]undecane (XVIII)** to the major product.

Anal. Calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.19; H, 11.89; N, 7.17.

Ethanolysis of 1-Methyl-1-azoniatricyclo$[8.1.0.0^{5,10}]$undecane Perchlorate (XVI).—Ethanolysis of the same aziridinium perchlorate was achieved by refluxing in ethanol overnight. Upon addition of ether colorless plates separated, m.p. 174–175°, ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($>\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): *ca.* 2.0[21] ($\overset{+}{N}H$); 6.46 (quartet, $J = 7.0 \pm 0.5$ c.p.s., $O-C\underline{H}_2CH_3$); 5.6–7.4 (broad); 6.94 (τ for doublet, $J = 5.4 \pm 0.5$ c.p.s., $C\underline{H}_3-\overset{+}{N}H$); 7.5–9.0 (broad); 8.71 (triplet, $J = 6.9 \pm 0.5$ c.p.s., $O-CH_2-C\underline{H}_3$). This major product was assigned the structure analogous to XVII, **1-ethoxy-3-methyl-3-azabicyclo[5.4.0]undecane perchlorate.**

Anal. Calcd. for $C_{13}H_{26}ClNO_5$: C, 50.07; H, 8.41; N, 4.49. Found: C, 50.15; H, 8.65; N, 4.44.

1-Azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane Perchlorate (XX).—$\Delta^{1(6)}$-Tetrahydrojulolidinium perchlorate (XIX), made by the method of Leonard, Steinhardt, and Lee,[17,25] appeared to be a single chemical individual according to the usual criteria. Only a single infrared absorption band was observed corresponding to $>C=\overset{+}{N}<$ stretch at 1680 cm.$^{-1}$ (chloroform) on the Perkin-Elmer Model 237 spectrophotometer. However, since the band was unsymmetrical and since the properties of the two isomers of XIX might be very similar, it cannot be guaranteed that the major substance was free of stereoisomeric contamination. The perchlorate was treated with diazomethane in methanol–ether at 0°, and the product, **1-azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane perchlorate (XX)**, was isolated by concentrating the methanol–ether solution to one quarter of its initial volume and cooling to −40°. It was recrystallized from acetone, colorless needles, m.p. 150–151° dec., yield 72%; no infrared maxima corresponding to $>\overset{+}{N}-H$ or $>C=\overset{+}{N}<$; n.m.r. τ values ($CDCl_3$): 6.20, 6.30, 6.40, and extending to higher field; 6.70 (singlet, 2 protons, aziridinium $C\underline{H}_2-N^+$); 8.21[21] (broad) (Fig. 3).

Anal. Calcd. for $C_{13}H_{22}ClNO_4$: C, 53.51; H, 7.61; N, 4.81. Found: C, 53.49; H, 7.44; N, 4.80.

This product appears to be a single isomer judged by the sharpness of its melting point and by spectral criteria.

Methanolysis of 1-Azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane Perchlorate (XX).—A solution of 0.78 g. (2.7 mmoles) of 1-azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane perchlorate (XX) was heated under reflux in absolute methanol for 21 hr., protected from moisture by a drying tube. Upon cooling, the methanol solution deposited 0.773 g. (89% yield) of colorless prisms, identified (see discussion) as **13-methoxymethyl-1-azatricyclo$[7.3.1.0^{5,13}]$tridecane perchlorate (XXI)**, m.p. 226–227°; ν_{max}^{KBr} 3125 cm.$^{-1}$ ($>\overset{+}{N}-H$); selected n.m.r. τ values (CH_2Cl_2): 6.09 (singlet, 1.97 protons, $C\underline{H}_2-O-CH_3$); 6.55 (singlet, 3.03 protons—as integrated—$CH_2-O-C\underline{H}_3$).

Anal. Calcd. for $C_{14}H_{26}ClNO_5$: C, 51.92; H, 8.09; N, 4.33. Found: C, 51.96; H, 8.06; N, 4.45.

13-Methoxymethyl-1-azatricyclo$[7.3.1.0^{5,13}]$tridecane (XXII).—A sample of 0.773 g. (2.39 mmoles) of 13-methoxymethyl-1-azatricyclo$[7.3.1.0^{5,13}]$tridecane perchlorate was made basic with aqueous sodium hydroxide and extracted with ether. The ether extracts were dried and concentrated. Upon cooling the ether solution deposited colorless prisms, 0.40 g. (75% yield), m.p. 79.5–80°; n.m.r. τ values (in CCl_4): on the Varian 4300 B: 6.31 (singlet), 6.70 (singlet), and complex signals near 7.57, 8.20, and 8.76. The base reacts slowly with carbon tetrachloride. N.m.r. τ values (in benzene) were observed on the Varian A-60 at: 6.24 (2 protons, $C\underline{H}_2-O$); 6.75 (3 protons, $O-C\underline{H}_3$); complex absorption 7.3–8.9 (20 protons). In the infrared spectrum, maxima were observed (10% CCl_4) at 2915, 2865, 2807, 2775, 2688 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.31; H, 11.42; N, 6.15.

Catalytic Reduction of 1-Azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane Perchlorate (XX).—A solution of 3.0 g. (10.3 mmoles) of 1-azoniatetracyclo$[7.3.2.0.^{1,13}0^{5,13}]$tetradecane perchlorate in 150 ml. of reagent grade acetone to which had been added 1.0 g. of platinum oxide was hydrogenated at 3 atm. for 7.5 hr. The filtered acetone solution was concentrated *in vacuo* and ether was added. Colorless needles separated, m.p. 256–257° dec., yield 2.82 g. (93%), identified as **13-methyl-1-azatricyclo$[7.3.1.0^{5,13}]$-tridecane perchlorate (XXIII)**; ν_{max}^{Nujol} 3120 cm.$^{-1}$ ($>\overset{+}{N}-H$); n.m.r. τ values ($CDCl_3$): 6.76[21] ($C\underline{H}_2\overset{+}{N}HC\underline{H}_2$), 7.77–8.25–8.60 (broad); 8.39 ($\overset{+}{N}-\overset{|}{\underset{|}{C}}-C\underline{H}_3$).

Anal. Calcd. for $C_{13}H_{24}ClNO_4$: C, 53.15; H, 8.23; N, 4.77. Found: C, 53.01; H, 8.33; N, 4.77.

13-Methyl-1-azatricyclo$[7.3.1.0^{5,13}]$tridecane (XXIII).—The perchlorate described above was made basic with aqueous sodium hydroxide and extracted with ether. The dried ether solution was evaporated, and the solid residue was recrystallized from pentane, m.p. 31–32°, 95% recovery from the perchlorate; $\nu_{max}^{CCl_4}$ 2900, 2850, 2795, 2770, 2675 cm.$^{-1}$, with intensities comparable to those observed for XXII; n.m.r. τ values (CCl_4 or C_6H_6): 8.96 ($C\underline{H}_3$) and complex absorption for ring protons.

Anal. Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.70; H, 12.05; N, 7.48.

13-Bromomethyl-1-azatricyclo$[7.3.1.0^{5,13}]$tridecane (XXIV).—A solution of 4.0 g. (46 mmoles) of anhydrous lithium bromide in 70 ml. of dry acetonitrile was prepared by stirring *ca.* 10 min. and the solution was filtered to remove a slight turbidity. To the filtrate was added 2.58 g. (8.7 mmoles) of 1-azoniatetracyclo$[7.3\text{-}2.0.^{1,13}0^{5,13}]$tetradecane perchlorate (XX), and the mixture was extracted continuously with olefin-free pentane for 18 hr. The pentane extracts were filtered and the filtrate was evaporated to dryness to afford 2.26 g. (95% yield) of colorless prisms, m.p. 110–112°; n.m.r. τ values (benzene): 6.19 (singlet for $C\underline{H}_2Br$), 7.5–9.2 (complex absorption of ring protons).

Anal. Calcd. for $C_{13}H_{22}BrN$: C, 57.35; H, 8.15; N, 5.14. Found: C, 57.51; H, 8.39; N, 5.24.

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(25) *Cf.* also F. Bohlmann and C. Arndt, *Chem. Ber.*, **91**, 2167 (1958).

The same compound was made starting with $\Delta^{1(6)}$-tetrahydrojulolidinium bromide (XIX, Br^- in place of ClO_4^-) made by adding anhydrous hydrogen bromide to an ethereal solution of 0.976 g. (5.5 mmoles) of tetrahydrojulolidine[17] until no more salt precipitated. The colorless hydrobromide was washed with ether, dissolved in methylene chloride and treated with excess diazomethane in ether. After standing overnight the solution was filtered and the filtrate was evaporated to dryness. The residue was recrystallized from 2-propanol, the crystals were dissolved in ether, the ethereal solution was filtered, and the ether was evaporated. The crystals gave a positive Beilstein test and an immediate precipitate upon addition of silver perchlorate in acetone. Infrared maxima were observed (10% CCl_4) at 2925, 2863, 2810, 2778, and 2690 cm.$^{-1}$. The band at 2863 cm.$^{-1}$ was more intense than the comparable band for XXI and XXIII.

The **perchlorate** of 13-bromomethyl-1-azatricyclo[7.3.1.$0^{5,13}$]-tridecane (XXIV) was formed in ether using 1:1 aqueous perchloric acid–ethanol. The precipitate (92% yield) was washed with ether, m.p. 263–265° dec.; $\nu_{\max}^{\text{Nujol}}$ *ca.* 3100 cm.$^{-1}$ $\left(\overset{\diagdown}{\underset{\diagup}{-\overset{+}{\mathrm{N}}}}-\mathrm{H}\right)$ (Infracord); n.m.r. τ value (CH_3CN): 5.87 (singlet).

Anal. Calcd. for $C_{13}H_{23}BrClNO_4$: C, 41.89; H, 6.22; N, 3.76. Found: C, 42.31; H, 6.06; N, 3.68.

Treatment of 0.232 g. (0.85 mmole) of 13-bromomethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane (XXIV) in acetone with an acetone solution of 0.219 g. (0.98 mmole) of silver perchlorate monohydrate yielded silver bromide, which was separated by filtration. The filtrate was evaporated to dryness *in vacuo* on a rotary evaporator leaving 0.216 g. (87%) of crude product which was recrystallized from ethyl methyl ketone. Colorless needles, m.p. 150–151° dec., 0.097 g. (39%), were obtained which did not depress the melting point of **1-azoniatetracyclo[7.3.2.0.^{1,13}$0^{5,13}$] tetradecane perchlorate (XX)** previously prepared.

N-(1-Bromocyclohexylmethyl)pyrrolidine (XXV).—A solution of 3.0 g. (34.6 mmoles) of dry lithium bromide in 70 ml. of anhydrous acetonitrile was filtered to remove a trace of residue. To the clear solution 2.0 g. (7.55 mmoles) of 5-azoniadispiro-[4.0.5.1]dodecane perchlorate (I) was added, and the resulting solution was extracted continuously with pentane overnight. The pentane extracts were evaporated to dryness leaving 1.42 g. (77% yield) of free base, $n^{24}\mathrm{D}$ 1.5150. This material was distilled, 73–75° (0.02 mm.), to give 0.93 g. of clear distillate, $n^{24}\mathrm{D}$ 1.5156, together with 0.157 g. of pot residue, crude m.p. 190–208°. The nature of this residue was not determined. Several attempts were made to obtain a satisfactory analysis on the free base; however, despite repeated distillation, each analysis gave a high per cent of carbon, indiating that dehydrobromination had occurred. Each distillation was accompanied by salt formation, and each time the clear distillate turned turbid after standing a short time. N.m.r. τ values were observed (neat) at: 7.05 (singlet), 7.28 (multiplet), and broad complex absorption near 8.30, in a ratio of areas of 2:4:14; (benzene): 7.08 (singlet, 2 protons), 7.35 (complex multiplet, 4 protons), ring protons at higher field.

Addition of 1:1 perchloric acid–ethanol to an ethereal solution of the free base afforded the **perchlorate,** colorless plates, m.p. 165–166° dec. The perchlorate was recrystallized from isopropyl alcohol, m.p. now 162.5–163° dec.; $\nu_{\max}^{\text{Nujol}}$ 3100 cm.$^{-1}$ $\left(\overset{\diagdown}{\underset{\diagup}{-\overset{+}{\mathrm{N}}}}-\mathrm{H}\right)$; n.m.r. τ values ($CDCl_3$): *ca.* 2.3 ($\overset{+}{\mathrm{N}}\mathrm{H}$); 6.24 (doublet, $J = 5.0 \pm 0.5$ c.p.s.) plus complex signals both sides of doublet (total of 6 protons); complex absorption at high field (14 protons).

Anal. Calcd. for $C_{11}H_{21}BrClNO_4$: C, 38.10; H, 6.11; N, 4.04. Found: C, 38.09; H, 6.02; N, 3.90.

A solution of 1.6 g. of N-(1-bromocyclohexylmethyl)pyrrolidine in benzene was filtered to remove some crystals which had formed and evaporated *in vacuo*. The residue was dissolved in 50 ml. of acetone and to this solution at −33° was added an acetone solution of 1.4 g. of silver perchlorate. An immediate precipitate of silver bromide formed and the temperature rose to −5°. The silver bromide was removed by filtration, and the filtrate was evaporated to dryness. The residue was dissolved quickly in absolute ethanol; the solution was filtered and cooled in a Dry Ice–isopropyl alcohol bath. The colorless needles were removed by filtration and washed with ether to afford 0.70 g. (40%) of I, m.p. 127–128.5°; m.m.p. with authentic 5-azoniadispiro-[4.0.5.1]dodecane perchlorate, 131.5–132°; authentic I, m.p. 132–133°. The infrared spectrum of the compound was identical with that of pure I except for very weak bands at 3400 cm.$^{-1}$ and 1700 cm.$^{-1}$.

1-N-Pyrrolidylcyclohexanemethanol.—This compound, previously described,[1] showed n.m.r. signals (CH_2Cl_2) at τ values 6.45 (2 protons), 6.95 (1 proton, O$\underline{\mathrm{H}}$), 7.35 (4), 8.29 (4), 8.50 (10). The chemical shift of the hydroxyl hydrogen was assigned by addition of a small amount of acetic acid.

Polynucleotides. I.

Synthesis of Uridylyl-(3′ → 5′)-uridine and Uridylyl-(3′ → 5′)-6-azauridine

ROSS H. HALL AND ROOSEVELT THEDFORD

Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo 3, New York

Received January 14, 1963

2′,5′-Di-*O*-trityluridine serves as a convenient starting point for the synthesis of phosphate dinucleosides containing uridine. This compound was readily phosphorylated with cyanoethylphosphate and, after removal of the cyanoethyl group, the resultant blocked nucleotide was used to phosphorylate 2′,3′-isopropylideneuridine and 2,3′-isopropylidene-6-azauridine. After removal of blocking groups, the compounds listed in the title were isolated in good yield from ion-exchange columns.

The synthesis of (3′ → 5′) linked diribonucleoside phosphates by present techniques requires extensive use of multiple blocking groups.[1,2] The major problem in these syntheses arises from the need for a suitably blocked derivative of a nucleoside with a free 3′ hydroxyl group. Blocking requirements alternatively may be minimized by synthesizing diribonucleoside phosphates consisting of mixed (2′ → 5′) and (3′ → 5′) linked isomers.[3] The mixed isomers in most cases can be separated by ion exchange chromatography. Both these synthetic approaches are applicable to general synthesis in this field; however, there may be special cases where opportune use of a particular compound can avoid many of the intermediate steps. Such a case is exemplified by 2′,5′-di-*O*-trityluridine which is readily synthesized and makes a useful starting point for synthesis of diribonucleoside phosphates containing uridine.

Tritylation of uridine with an excess of trityl chloride gives a product containing two trityl groups. This compound, first synthesized by Levene,[4] was identified

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