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Quaternization of *cis*- and *trans*-1,2-Dimethyl-3-isopropylaziridine with Methyl Iodide[1a-c]

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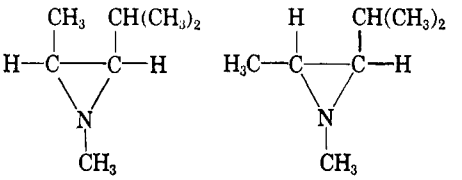
Treatment of *cis*- or *trans*-1,2-dimethyl-3-isopropylaziridine (**1** and **2**) with methyl iodide was found to give the corresponding 1,1,2-trimethyl-3-isopropylaziridinium iodide (**3** and **4**). Characterization of the aziridinium compounds was accomplished by elemental analysis, n.m.r. spectroscopy, vapor pressure osmometry, and examination of their reactions with thiosulfate ion. *trans*-1,2-Dimethyl-3-isopropylaziridine (**2**), which exists as an 80%–20% mixture of rapidly interconverting diastereomers (**2a** and **2b**) in which the isomer with *cis* methyl groups predominates, gives with methyl-d_3 iodide a nearly equal mixture of the two diastereomeric *trans*-1,1,2-trimethyl-3-isopropylaziridinium-1-d_3 iodides (**4a** and **4b**) as indicated by n.m.r. spectroscopy. *cis*-1,2-Dimethyl-3-isopropylaziridine (**1**), which we estimate is ~99% of the *trans*-, *cis*-diastereomer (**1b**), has also been quaternized with methyl-d_3 iodide; approximately half of the product is formed by quaternization of the *cis*-diastereomer (**1b**) of **1**.

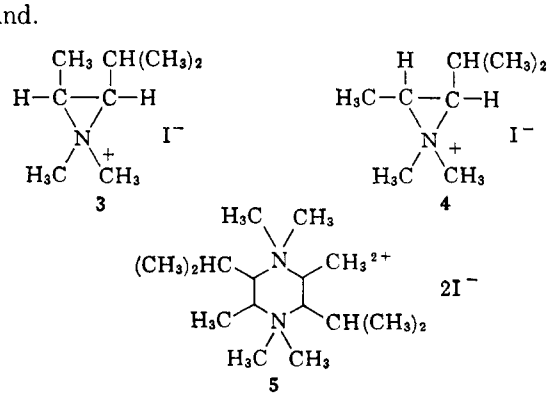
Since their implication as intermediates in the mechanism of biological action of nitrogen mustards (β-haloalkylamines),[2] a substantial number of aziridinium compounds have been prepared and characterized.[3,4] In addition, reactions with nucleophiles of other aziridinium compounds, which were generated from aziridines in the presence of acid but not isolated, have been studied.[5] Interestingly, although the large majority of known aziridinium compounds are highly reactive toward nucleophiles, there are notable exceptions, and these exceptions are aziridinium compounds that possess two secondary ring carbons.[3e]

We report here our study of the formation of aziridinium compounds by quaternization of *cis*- and *trans*-1,2-dimethyl-3-isopropylaziridine (**1** and **2**, respectively) with methyl iodide and methyl-d_3 iodide. This work was undertaken not only because of our desire to learn more of the chemistry of these potentially biologically useful compounds but also because the static geometrical requirements of the three-membered aziridinium ring make study of their formation and reactions particularly suitable for assessing the role of steric effects on reactivity.



1 **2**

Treatment of *cis*-1,2-dimethyl-3-isopropylaziridine[1b] (**1**) in benzene with an equal molar amount of methyl iodide gave *cis*-1,1,2-trimethyl-3-isopropylaziridinium iodide (**3**) as white needles in over 50% yield after recrystallization from anhydrous ethanol–ethyl acetate. The yield of crude **3** was greater than 90%. The elemental analysis of the product indicated that it was either an aziridinium compound or a polymer thereof, the most likely polymer being the dimer having the bispiperazinium structure **5**. The number average molecular weight (NAMW) of the product was determined in ethanol using the vapor pressure osmometry technique, and the value found (125 ± 3) was in accord with the aziridinium structure **3**, NAMW = 127.6, and inconsistent with the dimer structure **5**, NAMW = 170.1. The reaction of thiosulfate with **3** under conditions that did not affect N,N,N′,N′-tetramethylpiperazinium diiodide provided convincing proof that the compound was indeed an aziridinium compound.



3 **4**

5

(1) (a) Structure–Activity Relationships of Ethylenimines. IV. Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug.–Sept. 1964. (b) Previous paper in the series: A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *J. Am. Chem. Soc.*, to be published. (c) This research was supported by Grant CA-05528 from the National Cancer Institute of the Public Health Service. (d) Public Health Service Predoctoral Fellow, 1963–1964.

(2) A leading reference is W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. (Publishers) Ltd., London, 1962. See also the papers cited in footnotes 9–18 or ref. 3b.

(3) Reports describing aziridinium compounds include (a) N. J. Leonard and K. Jann, *J. Am. Chem. Soc.*, **82**, 6418 (1960); (b) N. J. Leonard and K. Jann, *ibid.*, **84**, 4806 (1962); (c) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963); (d) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *ibid.*, **28**, 2850 (1963); (e) P. E. Fanta, L. J. Pandya, W. R. Groskopf, and H.-J. Su, *ibid.*, **28**, 413 (1963); (f) R. D. Clark and G. K. Helmkamp, *ibid.*, **29**, 1316 (1964); (g) V. B. Schatz, Ph.D. Thesis, Brown University (1954) (cited in 3f); (h) L. M. Trefonas and R. Towns, *J. Heterocyclic Chem.*, **1**, 19 (1964). See also the papers cited in footnotes 10, 20, 22, 24, 25, and 28 of ref. 3b.

(4) The number of known aziridinium compounds seems quite small when compared with the number of known nitrogen mustards and aziridines. *Cf.* R. P. Bratzel, R. B. Ross, T. H. Goodridge, W. T. Huntress, M. T. Flather, and D. E. Johnson, *Cancer Chemotherapy Rept.*, **26**, 1 (1963), and T. H. Goodridge, W. T. Huntress, and R. B. Bratzel, *ibid.*, **26**, 341 (1963).

(5) See especially (a) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958); (b) G. J. Buist and H. J. Lucas, *ibid.*, **79**, 6157 (1957).

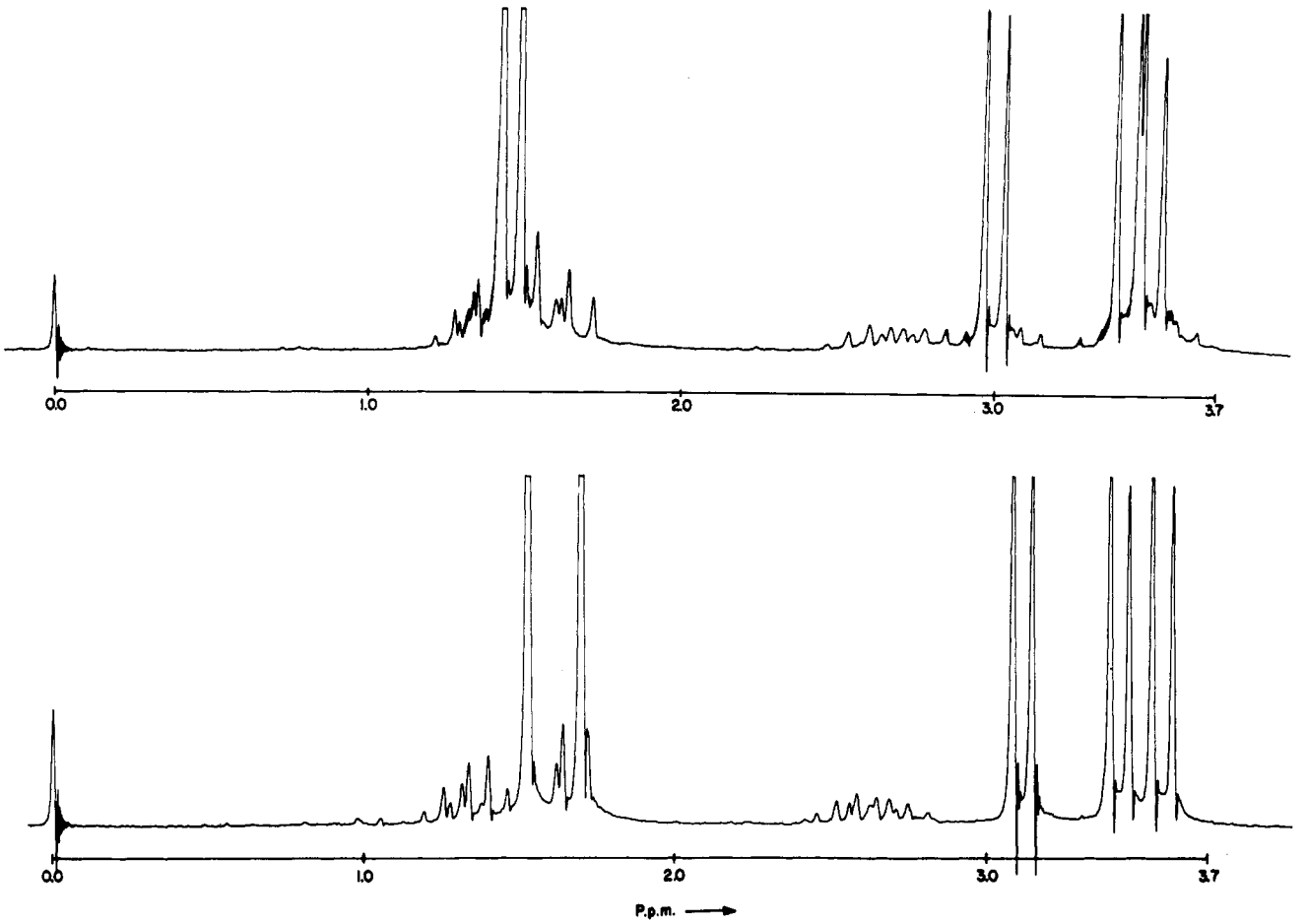


Figure 1.—N.m.r. spectra at 100 Mc. of **3** (bottom) and **4** (top) taken as 10% solutions in deuterium oxide. The band at 0 p.p.m. in both spectra is due to residual water.

trans-1,2-Dimethyl-3-isopropylaziridine[1b] (**2**) and methyl iodide in benzene gave a crystalline product whose elemental analysis, number average molecular weight, and reaction with thiosulfate were consistent with the *trans*-1,1,2-trimethyl-3-isopropylaziridinium iodide (**4**) structure.[6]

Although **3** and **4** melt with decomposition at essentially the same temperature (166.5–170°), readily apparent differences in their n.m.r. spectra taken in deuterium oxide (Figure 1) allow one to distinguish them easily and, further, to conclude that cross contamination is not significant. The n.m.r. spectrum of the *cis*-aziridinium compound **3** consisted of two N-methyl singlets at 1.52 and 1.70 p.p.m. (relative to the water signal) superimposed upon fine structure that is assigned to the ring-methyl hydrogens, a multiplet centered at approximately 2.6 p.p.m., which is assigned to the tertiary hydrogen of the isopropyl group, a doublet, $J \sim 7$ c.p.s., at 3.16 p.p.m., which is assigned to the β-methyl hydrogens, and two doublets, $J \sim 7$ c.p.s., at 3.49 and 3.61 p.p.m., which are assigned to the methyl hydrogens of the isopropyl group.[7] Although the basic features of the n.m.r. spectrum of the *trans*-aziridinium compound **4** are similar to those of **3**, significant differences include a smaller chemical shift (0.06 p.p.m.) between the N-methyl signals, appearance of the β-methyl resonance at lower field (3.00 p.p.m.), and the smaller chemical shift (0.07 p.p.m.) between the methyl resonances of the isopropyl group.[7] We would like to add that comparison of the spectra of **3** and **4** with those of other aziridinium compounds[3b,c] gave us added confidence in our assignments of the various bands, and that chemical shifts and spin–spin couplings were distinguished readily by comparison of spectra taken at 56.4 and 100 Mc.

Before coming to the intriguing subject of the stereochemistry of the quaternization reaction of **1** and **2** with methyl-d_3 iodide, we consider it necessary to discuss the successful isolation of **3** and **4**. Fanta and coworkers have isolated the corresponding 1,1-dimethylaziridinium compounds from reactions of methyl iodide with cycloheptenimine,[3h] cyclooctenimine,[3e] and cyclodecenimine.[3e] In contrast, treatment of N-methylcyclohexenimine with an equal molar amount of methyl iodide gives *trans*-2-iodo-N,N-dimethylcyclohexylamine, a distillable compound,[8] and treatment of 1-methylaziridine with methyl iodide gives 2-iodoethyltrimethylammonium iodide.[9] These results can be rationalized with the aid of the reaction sequence on p. 577, col. 1.

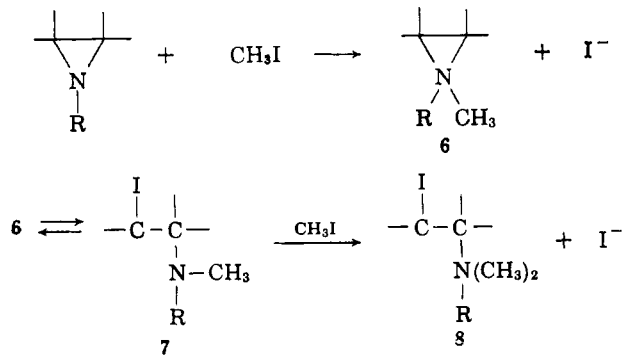
The first reaction that can be visualized is that of the aziridine with methyl iodide to give the aziridinium

(6) G. K. Helmkamp, R. D. Clark, and J. R. Koskinen, *J. Org. Chem.*, **30**, 666 (1965), have isolated and characterized (+)-*trans*-1,1,2,3-tetramethylaziridinium iodide from the reaction of (+)-*trans*-1,2,3-trimethylaziridine and methyl iodide. We are grateful to Professor Helmkamp for informing us of these results prior to publication.

(7) As the isopropyl group is separated from an asymmetric center by one bond, magnetic nonequivalence of the two sets of methyl hydrogens is not surprising. *Cf.* G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964).

(8) T. Taguchi and M. Eto, *ibid.*, **80**, 4075 (1958).

(9) W. Marckwald and O. Frobenius, *Ber.*, **34**, 3544 (1901).

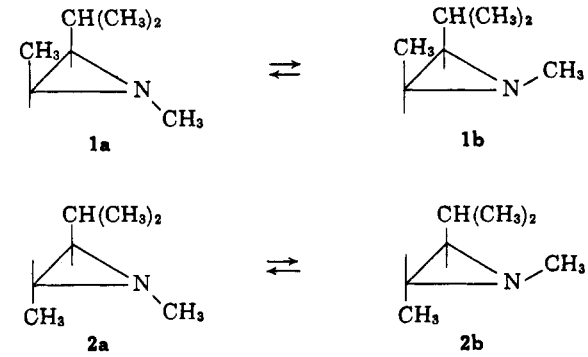


iodide **6**. Nucleophilic substitution by iodide at a ring carbon of **6** can then occur to give a 2-iodoalkylamine **7**, which can revert to **6**, react with excess methyl iodide to give a 2-iodoalkylammonium iodide **8**, or react with the aziridine or another **7** to give eventually a bispiperazinium compound.

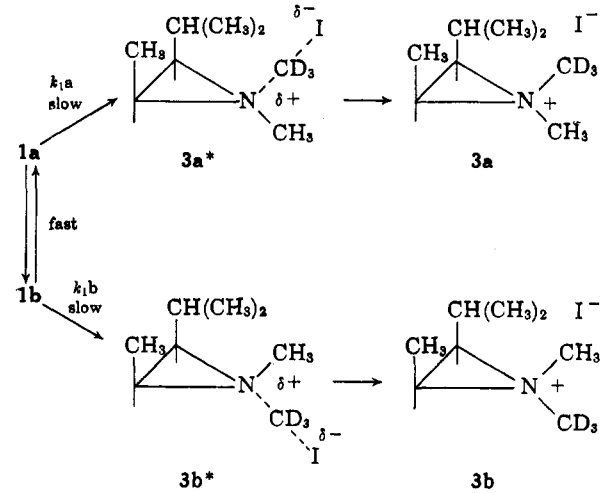
In addition to the result observed with N-methylcyclohexenimine,[8] considerable evidence exists which indicates that nucleophilic substitution at a primary or secondary carbon of an aziridinium ring occurs *via* an SN2 process.[5,10] Consequently, formation of **7** will be slowed and isolation of **6** aided by substitution of an alkyl group for a hydrogen at each of the aziridine carbons.[11] The differences observed in ease of isolation and stabilities of various 1,1,2,3-tetraalkylaziridinium compounds parallel the increasing degree of steric hindrance at the ring carbons. The 2,3-dimethylaziridinium compounds appear to be borderline as to reasonable ease of isolation and stability[6,12]; compounds such as 1-methylaziridine and cyclohexenimine that possess less hindered ring carbons defy isolation when prepared under comparable conditions, while compounds such as cyclododecenimine, **3**, and **4** that possess more hindered ring carbons can be recrystallized satisfactorily.

The preparation of *trans*-2-iodo-N,N-dimethylcyclohexylamine and the ability of that compound to survive distillation[8] deserve further comment. These results indicate that once a 2-iodoalkylamine such as **8** is formed from the reaction of an aziridinium ion and iodide, it does not revert to the aziridinium iodide at a significant rate in a nonpolar solvent.[13] The relevance of this to the interpretation of the reactions of **1** and **2** with methyl-d_3 iodide will soon become clear.

Because of the ability of trivalent nitrogen to undergo rapid inversion,[14] a 1,2,3-trisubstituted aziridine such as **1** or **2** exists as a rapidly interconverting mixture of diastereomers. At 10°, **2** is a 78–22% mixture of diastereomers **2a** and **2b**, and the equilibrium constant for the **2a** ⇄ **2b** interconversion corresponds to ΔF = 0.71 kcal.[1b] We have estimated a ΔF of 2.9 kcal. for **1a** and **1b**, the diastereomers of **1**. The free energy of *cis*-1,2-dimethylcyclopropane is 1.1 kcal. greater than that of its *trans* isomer.[15] Assuming that the same free energy difference obtains for *cis*- and *trans*-1,2-dimethylaziridine, and taking into account the 0.7-kcal. free energy difference that can be ascribed to the difference between a *cis*-methyl–isopropyl interaction and a *cis*-methyl–methyl interaction, *i.e.*, ΔF for **2a** and **2b**, the value obtained for $F_{1b} - F_{1a}$ is (1.1 + 1.1 + 0.7) = 2.9 kcal., which corresponds to an equilibrium constant (**1b**/**1a**) <0.01 at or below 30°.



While quaternization of **1a** or **1b** with methyl iodide yields the same aziridinium iodide **3**, quaternization with methyl-d_3 iodide can lead to two products, **3a** and **3b**. As the rate of the **1a** ⇄ **1b** interconversion is certainly greater than the rate of quaternization of either isomer with methyl-d_3 iodide,[16] the product composition from the reaction of **1** and methyl-d_3 iodide will be determined by the free energy difference between the diastereomeric transition states **3a*** and **3b***.[17] If the free energies of activation of **1a** → **3a*** and **1b** → **3b*** are identical, the rate constants will be



(10) R. Ghirardelli and H. J. Lucas, *J. Am. Chem. Soc.*, **79**, 734 (1957).

(11) Comparison of rates of SN2 reactions at primary and secondary carbons indicate that such substitution at an aziridine carbon will reduce the rate constant for **6** → **7** by approximately two orders of magnitude. See J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 7.

(12) Dr. B. F. Dowden, in these laboratories, has also observed that *cis*- and *trans*-1,1,2,3-tetramethylaziridinium iodide undergo considerable decomposition on attempted recrystallization using conditions satisfactory for recrystallization of **3** and **4**.

(13) Reconstitution of two N,N-dialkylaziridinium salts has been accomplished by treatment of the corresponding 2-bromoalkylamines with silver perchlorate in acetonitrile.[3c]

(14) (a) R. F. Shriner, R. Adams, and C. S. Marvel, "Organic Chemistry, An Advanced Treatise," Vol. 1, H. Gilman, Ed., 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 402–413; (b) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958); (c) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960).

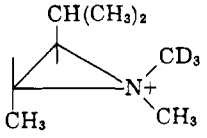
(15) This estimate, reported by D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer [*ibid.*, **83**, 4838 (1961)], was based on data of M. C. Flowers and H. M. Frey [*Proc. Roy. Soc.* (London), **A257**, 122 (1960)]. See also C. S. Elliot and H. M. Frey, *J. Chem. Soc.*, 900 (1964), and H. M. Frey and D. C. Marshall, *ibid.*, 5717 (1963).

(16) Rate constants for the reactions of **1** and **2** in 90% methanol at 19.96° are 4.45×10^{-5} and 1.59×10^{-4} M^{-1} sec.$^{-1}$, respectively (unpublished work of Dr. B. F. Dowden). The rate constants for these reactions are expected to be less in benzene. Rate constants for nitrogen inversion in the diastereomers of **1** and **2** are estimated to be ~10 sec.$^{-1}$ at room temperature (*cf.* ref. 14b and c).

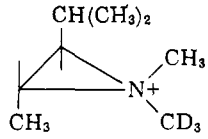
(17) References pertinent to this discussion are S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955), and D. Y. Curtin, *Record Chem. Progr.*, **15**, 111 (1954).

identical, and the ratio of products, *i.e.*, **3b/3a**, will be the same as the equilibrium constant for the related ground-state diastereomers, *i.e.*, **1b/1a**. However, as more nonbonded interactions are introduced in going from methyl-d_3 iodide and **1a** to transition state **3a*** than are introduced in going from methyl-d_3 iodide and **1b** to transition state **3b***, the rate constant for **1b** → **3b** can be expected to be significantly greater than the rate constant for **1a** → **3a**. If this is so, then the product ratio **3b/3a** will be significantly greater than the ground-state equilibrium constant **1b/1a**.

Using similar reasoning, one can argue that the product ratio **4b/4a** from the reaction of methyl-d_3 iodide and **2** at 10° will be greater than 0.28, the equilibrium constant (**2b/2a**) for the related ground-state diastereomers.



4a

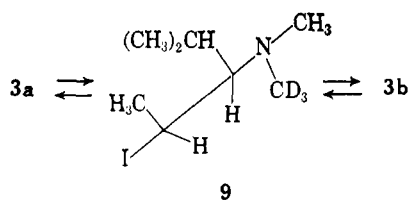


4b

The marked chemical shift between the N-methyl resonances in the n.m.r. spectrum of **3** (Figure 1) makes possible determination of the stereospecificity of the quaternization reaction of **1** with methyl-d_3 iodide. The n.m.r. spectra of unrecrystallized samples of *cis*-1,1,2-trimethyl-3-isopropylaziridinium iodide prepared from **1** and methyl-d_3 iodide in benzene and in chloroform were indistinguishable and possessed only those bands present in the spectrum of **3**. As expected, the intensity of the bands in the N–C–H region (*ca.* 1.5 p.p.m.) corresponded to five protons rather than eight as in the spectrum of unlabeled **3**. Most interestingly, the intensities of the two N-methyl bands were virtually the same, thereby indicating that the labeled diastereomers **3a** and **3b** were present in nearly equal amounts.

trans-1,2-Dimethyl-3-isopropylaziridine (**2**) was also quaternized with methyl-d_3 iodide under conditions similar to those used for quaternization of **1**. As with labeled **3**, the two diastereomeric methyl iodides **4a** and **4b** were present in nearly equal amounts as indicated by the virtually equal intensities of the two N-methyl bands in the n.m.r. spectrum of **4-1-d_3**.

One explanation that will account for the presence of equal amounts of **3a** and **3b** (and equal amount of **4a** and **4b**) is that the aziridinium iodides are in rapid equilibrium with the corresponding 2-iodoalkylamine. For example, **3a** and **3b** can be pictured in equilibrium with the 2-iodoalkylamine **9**, which, quite conceivably,



9

can undergo nitrogen inversion *and* rotation about the secondary carbon–nitrogen bond before reverting to an aziridinium iodide, thereby equilibrating the two N-methyl groups.

We consider this explanation to be most unlikely. As already discussed, the reaction of an aziridinium ion and iodide to give a 2-iodoalkylamine is an essentially irreversible reaction in a nonpolar solvent. Although scrambling of the N-methyl groups *via* the intermediacy of **9** is far more likely in water than in benzene, this likelihood can also be rejected because the aziridinium compounds react relatively slowly with thiosulfate in water and, from earlier observation, it is known that aziridinium ions react more rapidly with thiosulfate than with iodide.[5a]

Rejecting the possibility that the observed product ratios are not the kinetically controlled product ratios, one must conclude that the ratio of the rate constants for quaternization of **1a** and **1b**, *i.e.*, k_{1a}/k_{1b}, is equal to within a few per cent of the equilibrium constant **1b/1a**, and the ratio of the rate constants for quaternization of **3a** and **3b** is equal to within a few per cent of the equilibrium constant **3b/3a**. The most straightforward explanation for this, and the one we favor, is that the steric requirements of the methyl-d_3 iodide moiety in transition states for quaternization of aziridines are nearly the same energetically as those of a fully bonded N-methyl group.

Experimental

N.m.r. spectra were obtained at 60 Mc. with a Varian Associates HR-60 system. Resonance frequencies were determined relative to residual water in deuterium oxide using the side-band technique with a Packard CD-200 audiooscillator. Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif.

cis-**1,1,2-Trimethyl-3-isopropylaziridinium Iodide** (**3**).—To a stirred solution of 2.26 g. (20.0 mmoles) of *cis*-1,2-dimethyl-3-isopropyl aziridine (**1**)[1b] in 30 ml. of sodium-dried benzene was added 2.84 g. (20.0 mmoles) of methyl iodide. A white precipitate began to form immediately. After several hours, the solid (4.8 g., 94%) was collected by suction filtration and recrystallized from ethyl acetate–anhydrous ethanol. White needles (3.2 g., 63%) were obtained which had m.p. 166.5–170° dec. (uncor.) when heated at *ca.* 5°/minute near the decomposition temperature. The 60-Mc. n.m.r. spectra of crude and recrystallized **3** as 10% solutions in deuterium oxide were indistinguishable and did not change perceptibly in 12 hr.

Anal. Calcd. for $C_8H_{18}IN$: C, 37.66; H, 7.11; I, 49.74. Found: C, 37.91; H, 6.83; I, 49.80.

trans-**1,1,2-Trimethyl-3-isopropylaziridinium iodide** (**4**) was obtained from the corresponding aziridine **2**[1b] and methyl iodide in the manner described for **3**. Recrystallized **4** had m.p. 166.5–170° dec. (uncor.) when heated at *ca.* 5°/minute near the decomposition temperature. (The decomposition points of **3** and **4** were indistinguishable when taken simultaneously.) As with **3**, the 60-Mc. n.m.r. spectra of crude and recrystallized **4** as 10% solutions in deuterium oxide were indistinguishable and did not change perceptibly in 12 hr.

Anal. Calcd. for $C_8H_{18}IN$: C, 37.66; H, 7.11; I, 49.74; N, 5.49. Found: C, 37.75; H, 6.96; I, 49.64; N, 5.25.

cis-**1,1,2-Trimethyl-3-isopropylaziridinium-1-d_3 iodide** (**3-1-d_3**) was prepared from 0.98 g. (6.9 mmoles) of methyl-d_3 iodide (Merck of Canada) and 0.78 g. (6.9 mmoles) of **1** in benzene. The labeled compound was also prepared using chloroform in place of benzene. The 60-Mc. n.m.r. spectra of the two samples as 10% solutions in deuterium oxide were indistinguishable and indicated that each sample contained equal amounts of **3a** and **3b**.

trans-**1,1,2-Trimethyl-3-isopropylaziridinium iodide** (**4-1-d_3**) was prepared from **2** and methyl-d_3 iodide in benzene and in chloroform. The 60-Mc. n.m.r. spectra of the products were indistinguishable and indicated that each sample contained equal amounts of **4a** and **4b**.

Molecular weights of 3 and 4 were determined using a Mechrolab Model 301A vapor pressure osmometer. Solutions of **3** and **4** and the standard compounds, which include N,N,N′,N′-tetramethylpiperazinium diiodide, N,N-dimethylpiperidinium

TABLE I

EXPERIMENTAL DATA FOR MOLECULAR WEIGHT MEASUREMENTS

Compd.	Concentration G./l.	Concentration M (solute particles) $\times 10^2$	ΔR
$C_8H_{20}I_2N_2$[a]	2.04	1.54	3.50
	4.48	3.38	6.71
$C_7H_{16}IN$[b]	4.68	3.88	7.52
	8.24	6.83	11.90
	12.19	10.11	16.10
$C_6H_{14}IN$[c]	3.53	3.11	6.09
	6.87	6.05	10.56
	10.38	9.14	14.71
	11.22	9.88	15.36
3	5.32	4.30[d]	8.18
	7.90	6.32[d]	10.90
	10.16	8.04[d]	13.30
4	6.09	4.93[d]	9.10
	10.37	8.08[d]	13.35
	11.28	9.10[d]	14.60

[a] N,N,N',N'-Tetramethylpiperazinium diiodide. [b] N,N-Dimethylpiperidinium iodide. [c] N,N-Dimethylpyrrolidinium iodide. [d] Read from plot of ΔR *vs.* M solute particle for standard compounds.

iodide, and N,N-dimethylpyrrolidinium iodide, were prepared using the same stock ethanol that was used as the instrument solvent reference. For each solution, ΔR, a measure of the temperature change caused by solvent condensation in the solutions, was obtained, and these data are included in Table I. A plot of ΔR *vs.* M solute particles gave a smooth curve with steadily decreasing slope. Using this curve, the molar concentration of solute particles for each solution of **3** and **4** was determined corresponding to the observed ΔR. These latter data, which are also included in Table I, were used to calculate the number average molecular weight (NAMW) of **3** and **4**, which were both 125. The theoretical NAMW of **3** and **4** is 127.6; for a piperazine methiodide corresponding to a dimeric product, *i.e.*, **5**, the theoretical NAMW is 170.1.

Reactions of 3 and 4 with Thiosulfate.—The method is patterned after that described in ref. 5a for the assay of aziridines.

A solution was made up to be 0.8 M acetic acid, 0.4 M sodium acetate, 0.250 M sodium thiosulfate, and 0.152 M **3**. The solution was allowed to stand at 20–25° for 12 hr., and the unchanged thiosulfate was titrated with standardized iodine–potassium iodide solution. The thiosulfate concentration was found to be 0.181 M, which indicated that 45% of the aziridinium compound had reacted with thiosulfate. Another solution, made up to be 0.8 M acetic acid, 0.4 M sodium acetate, 0.250 M sodium thiosulfate, and 0.24 M **4**, was allowed to stand for 96 hr. at 20–30°. Titration with standardized iodine–potassium iodide solution indicated that 68% of **4** had reacted with thiosulfate. The concentration of thiosulfate was not affected when similar solutions were prepared in which N,N,N',N'-tetramethylpiperazinium iodide was substituted for the aziridinium compound or in which a quaternary ammonium compound was omitted.

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The Synthesis of 17β-Amino-17-isoprogesterone

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The Neber rearrangement of 2-(3β-hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium iodide (**2**) proceeded stereospecifically to give 3'-methylspiro-[17(1')β-androst-5-en-17,2'(2'H)-azirin]-3β-ol (**4**). Acid hydrolysis of the azirine afforded 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**). When heated, the amino ketone rearranged to 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) *via* the intermediate 17-imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (**11a**). The treatment of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one (**3c**) with base afforded a mixture of 3β,17aβ-dihydroxy-17aα-methyl- and 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-ones (**11b** and **17**).

Substituents in the 17α-position of steroid hormones markedly affect the anabolic, progestational, glucocorticoid, and electrolyte-regulating activities of these compounds.[1] The pharmacological properties of progesterone, in particular, have been enhanced by the introduction of 17α-acyloxy,[2] 17α-alkoxy,[3] 17α-halo,[4] and 17α-alkyl[5] groups. The effect of introducing an amino or acetamino substituent into the 17α-position of progesterone, however, has not yet been investigated, although a synthesis of 17α-amino-11,20-diketopregnanes has been recently described by Winternitz and Engel.[6] In order to ascertain if such substitution would produce a beneficial change in activity, the synthesis of 17-aminoprogesterone and of some of its analogs was undertaken.

One feasible synthetic route to this type of compound was the Neber rearrangement[7] of a derivative of a 20-keto steroid. This reaction, the treatment of a nitrogenous derivative of a ketone (usually an oxime tosylate) with base, has been shown to introduce an amino group on one of the two carbon atoms adjacent to the ketone. Although it has been previously postulated that only α-methyl and α-methylene groups could participate in this rearrangement,[8] recent investigators have shown that an α-methinyl ketone system could also be converted into an α-amino ketone in this manner.[9]

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