in peroxide content was found and the aqueous layer was observed to bleach rapidly an iodine solution.

Liberation of an Acetone Fragment from 18-Hydroperoxy-6,14-peroxy-$\Delta^{7(8)}$-dihydroabietic Acid.—A solution of 0.3164 g. of 18-hydroperoxy-6,14-peroxy-$\Delta^{7(8)}$-dihydroabietic acid in 10 ml. of 95% ethanol was charged to a small flask equipped with a nitrogen inlet tube, a gas outlet tube leading to two traps containing a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid, and a side arm closed with a serum stopper. Sodium hydroxide aqueous solution (1.58 ml. of 0.96 *N*; 1.75 NaOH/1 photoperoxide) was injected into the reactor and nitrogen sweeping carried out at room temperature for 50 minutes with no appearance of precipitate in the traps. A solution of 0.493 g. of trichloroacetic acid in 1.0 ml. of water (3.5/1 molar ratio of acid/diperoxide) was injected and the reactor heated to 90° during slow nitrogen sweeping. A very slow distillation with gentle nitrogen sweeping was carried out for 40 minutes. The yellow flaky precipitate in the first trap was collected, washed with 2 *N* hydrochloric acid, and water; yield 0.0424 g. (21%), m.p. 118.5–120.5°.; after recrystallization from 95% ethanol, m.p. 124.5–125°, mixed m.p. with authentic sample 125–125.5°.

Attempted Photosensitized Oxidation of Pimaric, Isopimaric and Dehydroabietic Acids.—In each case, 100 ml. of a 0.02 *M* solution of the pure resin acid in 95% ethanol containing 50 mg./l. of erythrosin B was simultaneously aerated and irradiated for over 12 hr. in a test-tube reactor. No titratable peroxide[36] was found at the end of this time and no change in specific rotation nor in the absorption spectrum from 220–320 mμ was observed. The solutions were stripped to dryness under reduced pressure, the unchanged resin acids recovered in quantitative yields, and identified by m.p. and by the essential identity of their infrared spectra with the infrared spectra of the starting resin acids.

Nuclear Magnetic Resonance Spectra (by Wallace S. Brey, Jr., of the University of Florida).—Hydrogen nuclear magnetic resonance spectra were obtained with a Varian 4300-2 high-resolution spectrometer operating at 56.4 megacycles. Samples were contained in precision bore tubes and a quantity of benzene sufficient to give a peak height equivalent to that of a methyl group in the solute compound was added to the solution as an internal reference. Spectral grade carbon tetrachloride was used as a solvent, except that for the ester of neoabietic acid diperoxide, spectra were also run in which a drop of acetone was added to increase the solubility. This permitted a more accurate determination of the chemical shifts, and to the accuracy that shifts could be measured for the more dilute solution in carbon tetrachloride alone, there was no effect on the spectrum except that the resonance of the hydroperoxide hydrogen was shifted downfield by the presence of the acetone. Chemical shifts were obtained by applying side bands from a calibrated audio oscillator; the averages of repeated sweeps through the spectrum and side bands were used in the computations. Chemical shifts are expressed as parts per million displacement upfield from the reference.

TABLE III

CHEMICAL SHIFTS

Hydrogen assignment	Me.V[a] (in CCl_4)	Me.III[b] (in CCl_4–acetone)
Hydroperoxide hydrogen	...	−1.7
Vinyl hydrogen	1.54[c]	1.29[d]
Hydrogen on carbon attached to transannular peroxide oxygen	2.86	2.46
Methyl ester hydrogen	3.68	3.67
Hydrogen on central carbon of isopropyl group	4.95 (center of septet)	..
Ring hydrogens, prominent peaks	5.36, 5.55 5.76, 6.02	5.74
Isopropyl methyl hydrogens	6.21, 6.25 (center of doublets)	5.91 5.98
Hydrogens on C-1 methyl	6.22	6.19
Hydrogens on C-17 (angular) methyl	6.76	6.71

[a] Methyl 6,14-peroxy-$\Delta^{7(8)}$-dihydroabietate.[2] [b] Methyl 18-hydroperoxy-6,14-peroxy-$\Delta^{7(8)}$-dihydroabietate. [c] The values[37] for the chemical shifts due to the two vinyl hydrogens in levopimaric acid in saturated CCl_4 solution are 1.46 and 1.86, and are given here for comparison purposes. [d] The value[37] for the chemical shift due to the single vinyl hydrogen in neoabietic acid in saturated CCl_4 solution is 0.82.

Acknowledgment.—The authors wish to express their appreciation to Mr. L. E. Brown, Instrumentation and Analysis Group, Southern Utilization Research and Development Division, for the elemental analyses, to Mr. H. Horne for the isolation and purification of the neoabietic acid, and to Mr. G. S. Fisher of these laboratories, for many helpful discussions.

(37) W. S. Brey, Jr., W. H. Schuller and Ray V. Lawrence, unpublished results.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BUCKNELL UNIVERSITY, LEWISBURG, PENNA.]

The Isomerization and Dimerization of Aziridine Derivatives. IV

BY HAROLD W. HEINE, WILLIAM G. KENYON AND ELEANOR M. JOHNSON

RECEIVED JANUARY 28, 1961

The isomerization of 1-aroyl-2-alkylaziridines, 1-aziridinethiocarboxanilide, N,N-diphenyl-1-aziridinecarboxamide, 2,4,6-tris-(1-aziridinyl)-*s*-triazine and 1-aziridinecarboxanilide by nucleophiles such as iodide ion and thiocyanate ion in acetone into 4-alkyl-2-aroyl-2-oxazolines, 2-anilino-2-thiazoline, 2-diphenylamino-2-oxazoline, 2,3,6,7,10,11-hexahydrotrisimidazo-(1,2-a; 1′,2′-c; 1″,2″-e)-*s*-triazine and to 1-phenyl-2-imidazolidinone, respectively, are described. Nucleophiles also bring about dimerization of 1-arylsulfonylaziridines and 1-aziridinecarboxanilide to 1,4-bisarylsulfonylpiperazines and to N,N′-bisphenylcarbamylpiperazine. The isomerizations and dimerizations are of significance since they represent ring openings of aziridine derivatives without the need of the usual acid catalysts. The dimerization of 1-phenylaziridine and 1-*p*-tolylaziridine to the corresponding piperazines in aqueous ethanol containing iodide ion is noted.

Recent studies have shown that iodide ion and thiocyanate ion are effective catalysts for the isomerization of 1-aroylaziridines[2a] and 1-benzimidoylaziridines[2b] into 2-aryl-2-oxazolines and 2-aryl-2-imidazolines, respectively, in solvents such as acetone, 2-propanol or acetonitrile. The isomerizations are of interest since they represent examples of the opening of the aziridine ring by nucleophilic reagents without the need of the usual acid catalysts. Previously, acid catalysts were employed

(1) Aided by Grant No. T-143 from the American Cancer Society.

(2) (a) H. W. Heine, M. E. Fetter and E. M. Nicholson, *J. Am. Chem. Soc.*, **81**, 2202 (1959); (b) H. W. Heine and H. S. Bender, *J. Org. Chem.*, **25**, 461 (1960).

to isomerize 1-aroylaziridines,[2a,3] 1-aziridinyl-*s*-triazines[4] (a system analogous to the 1-benzimidoylaziridines), 1-aziridinethiocarboxanilides[5-7] and 1-aziridinecarboxanilide.[8a,8b] We now wish to report the isomerization and dimerization of 1-aroyl-2-alkylaziridines, 1-arylsulfonylaziridines, 1-arylaziridines, 1-aziridinethiocarboxanilide, 1-aziridinecarboxanilide, N,N-diphenyl-1-aziridinecarboxamide and 2,4,6-tris-(1-aziridinyl)-*s*-triazine by iodide ion or thiocyanate ion.

Results

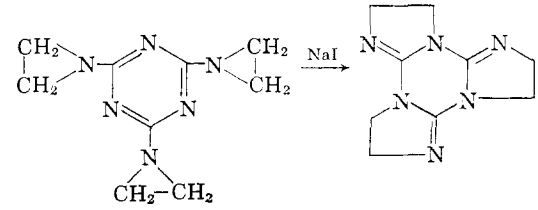
1-*p*-Nitrobenzoyl-2-methylaziridine and 1-*p*-nitrobenzoyl-2-ethylaziridine, when treated with iodide ion in acetone, form selectively and in high yields (96-98%) 2-*p*-nitrophenyl-4-methyl- and 2-*p*-nitrophenyl-4-ethyl-2-oxazoline, respectively. Structure assignments of the oxazolines are based on comparison with authentic samples prepared by cyclization of N-(1-alkyl-2-hydroxyethyl)-*p*-nitrobenzamides according to published procedures.[9a,b]

Under analogous conditions 1-aziridinethiocarboxanilide isomerized to 2-anilino-2-thiazoline in 95% yield, and N,N-diphenyl-1-aziridinecarboxamide isomerized to 2-diphenylamino-2-oxazoline in 94% yield. The reactions are the first examples of the rearrangements of these systems by a nucleophilic entity.

If the above conditions are applied to 1-methanesulfonylaziridine, 1-*m*-nitrophenylsulfonyl and 1-*p*-tolylsulfonylaziridine, near quantitative yields of the corresponding piperazines are obtained. Dimerization of aziridines to piperazines by nucleophiles have not been reported although isolation of piperazines as side-products from aziridine transformations under acid conditions is not uncommon.[10] The dimerization also took place with potassium thiocyanate in acetone and sodium iodide in acetonitrile or butanone. Control runs in the absence of any nucleophile resulted in recovery of the arylsulfonylaziridine; however, 1-*m*-nitrophenylsulfonylaziridine did polymerize just above its melting point to a solid which decomposes at 280°. Methanesulfonylaziridine behaves analogously.[11]

1-Aziridinecarboxanilide in the presence of sodium iodide and acetone is transformed into several products. Employment of large quantities of sodium iodide and very small quantities of acetone gave an 85% yield of 1-phenyl-2-imidazolidinone. Smaller quantities of sodium iodide and larger volumes of acetone resulted in the formation of as much as 22% of the insoluble dimer N,N'-bisphenylcarbamylpiperazine as well as some 1-phenyl-2-imidazolidinone and some impure 2-anilino-2-oxazoline. A control run without sodium iodide resulted in recovery of the 1-aziridinecarboxanilide. This system as well as other 1-aziridinecarboxanilides are currently being investigated in detail.

Chiefly to observe whether the now accomplished change of 1-benzimidoylaziridines by nucleophiles to 2-imidazolines[2b] would apply to somewhat analogous but more complicated systems, a study was made of the isomerization of 2,4,6-tris-(1-aziridinyl)-*s*-triazine by sodium iodide. Isomerization to 2,3,6,7,10,11-hexahydrotrisimidazo[1,2-a;1',2'-c;1'',2''-e]-*s*-triazine took place rapidly and in high yield at room temperature in contrast

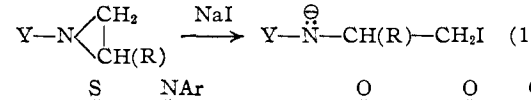


to longer reaction times and higher temperatures required for the rearrangement of 1-benzimidoylaziridines.[12]

The reaction of 1-phenylaziridine and 1-*p*-tolylaziridine with sodium iodide was carried out in refluxing aqueous ethanol. The products were N,N'-diarylpiperazines in 65 and 36% yields, respectively. Control runs in the absence of iodide ion and at room temperature resulted in rapid polymerization of the arylaziridines.[13] No dimerization occurred when the 1-arylaziridines were dissolved in acetone containing sodium iodide and the mixture refluxed for several days.

Discussion

All of the isomerizations and dimerizations with perhaps the exception of 1-phenylaziridine and 1-*p*-tolylaziridine can be explained by mechanisms involving a common first step, namely, a bimolecular displacement by a nucleophile such as iodide ion on one of the aziridine carbon atoms to yield a 2-iodoethylamine anion.



Y = ArNHC(=S)–, ArC(=NAr)–, $ArSO_2$–, ArNHC(=O)–, $(Ar)_2NC(=O)$–, ArC(=O)–

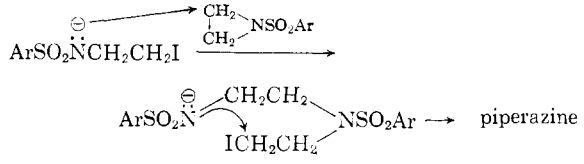
R = H, Me, Et

In the case of the 1-aroyl-2-alkylaziridines the iodide ion attacks exclusively at the less substituted carbon to yield an N-1-alkyl-2-iodoethyl-*p*-nitrobenzamido ion, $p\text{-}O_2NC_6H_4C(=O)\text{-}N^{\ominus}\text{-}CH(R)\text{-}CH_2I \leftrightarrow p\text{-}O_2NC_6H_4C(=O^{\ominus})\text{=}NCH(R)CH_2I$ which subsequently expels the halogen by internal O-alkylation to yield the 4-alkyl-2-oxazoline. Unsymmetrical epoxides also undergo ring openings by

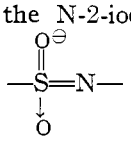
(3) H. W. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958).
(4) F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5922 (1955).
(5) S. Gabriel and R. Stelzner, *Ber.*, **28**, 2929 (1895).
(6) A. S. Deutsch and P. E. Fanta, *J. Org. Chem.*, **21**, 892 (1956).
(7) M. Tisler, *Arch. Pharm.*, **291**, 457 (1958).
(8) (a) Y. Iwakura and A. Nabeya, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **77**, 773 (1956); (b) Y. Iwakura and A. Nabeya, *J. Org. Chem.*, **25**, 1118 (1960).
(9) (a) R. N. Boyd and R. H. Hansen, *J. Am. Chem. Soc.*, **75**, 5896 (1953); (b) R. N. Boyd and R. C. Rittner, *ibid.*, **82**, 2032 (1960).
(10) L. B. Clapp, *ibid.*, **70**, 184 (1948); **73**, 2584 (1951).
(11) H. Bestian, J. Heyna, A. Bauer, G. Ehlers, B. Hirsekorn, T. Jacobs, W. Noll, W. Weibezahn and F. Romer, *Ann.*, **566**, 210 (1950).
(12) The authors wish to thank Miss Sonja Zawoiski for investigating this isomerization.
(13) H. W. Heine, B. L. Kapur and C. S. Mitch, *J. Am. Chem. Soc.*, **76**, 1173 (1954); H. W. Heine, B. L. Kapur, J. L. Bove, R. W. Greiner, K. H. Klinger and C. Mitch, *ibid.*, **76**, 2503 (1954).

nucleophiles on the least alkylated carbon.[14] In contrast, the direction of ring opening in the acid-catalyzed isomerization of 1-*p*-nitrobenzoyl-2,-2-dimethylaziridine is at the most alkylated carbon of the aziridine ring.[2a]

The dimerization of 1-alkyl- or 1-arylsulfonylaziridines seems likely to proceed through the formation of an N-2-iodoethylarylsulfonamido ion (eq. 1) which subsequently attacks a methylene carbon of a second molecule of 1-arylsulfonylaziridine to form A. The piperazine then is produced by displacement of iodide ion from A by the negatively charged nitrogen. In order to have

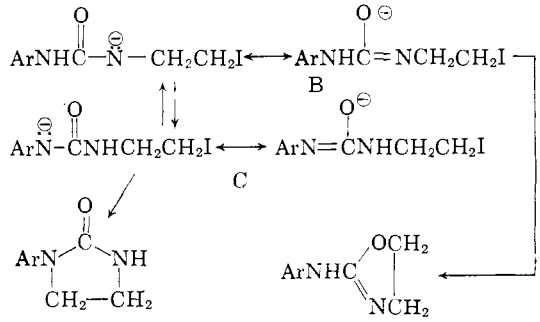


A

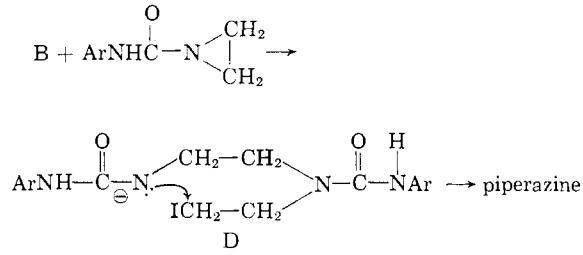
O-alkylation by the N-2-iodoethylsulfonamido ion take place and yield a five-membered heterocyclic system, in analogy with the N-2-iodoethylbenzamido ion, the structure  is required.

That such an anion does not form easily is shown by the alkaline hydrolysis of N-2-halogenoethylarylsulfonamides[15,16] where internal N-alkylation occurs to yield the strained 1-arylsulfonylaziridine in preference to internal O-alkylation leading to a five-membered ring system. In contrast, the alkaline solvolysis of N-2-bromoethylbenzamides yields quantitatively 2-aryl-2-oxazolines and not 1-aroylaziridines.

In the isomerization and dimerization of 1-aziridinecarboxanilide into 1-phenyl-2-imidazolidinone and into N,N′-bisphenylcarbamylpiperazine it again appears appropriate to propose eq. 1 as the first step. A ureido ion (B) would result which could tautomerize to the ureido ion C. Internal N-alkylation of C accounts for the 1-phenyl-2-imidazolidinone while the small amount of 2-anilino-2-oxazoline may arise by internal O-alkylation of B. The ureido ion C may also be the intermediate in the alkaline alcoholysis of N-phenyl-N′-2-chloroethylurea[5] and N-phenyl-N′-2-bromoethylurea.[17] In each of these instances 1-phenyl-2-imidazolidinone is the only product.

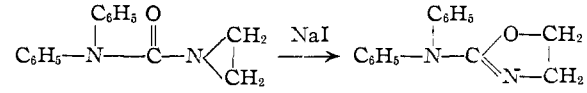


The dimerization of 1-aziridinecarboxanilide is probably closely related to the dimerization of the 1-arylsulfonylaziridines. The aziridine carbon is attacked by the electron-rich nitrogen of B to give D, the precursor to the N,N′-bisphenylcarbamylpiperazine.



D

It is of interest to examine the behavior of 1-aziridinethiocarboxanilide and N,N-diphenyl-1-aziridinecarboxamide toward iodide ion. In the former compound the nucleophilicity of sulfur seems to be the dominant factor involved since exclusive S-alkylation to the 2-thiazoline occurs. In the case of N,N-diphenyl-1-aziridinecarboxamide, tautomerization (and thus imidazolidinone formation) is precluded by substitution of a phenyl group for the anilino hydrogen.



A mechanism for the dimerization of the 1-arylaziridines by iodide ion in aqueous alcohol is difficult to assign. The dimerization process may be aided by the solvent as well as iodide ion since ring opening and polymerization of the 1-arylaziridines takes place with ease in aqueous alcohol alone or in water.[13]

Experimental

1-*p*-Nitrobenzoyl-2-ethylaziridine (I).—Into a Waring Blendor were placed 100 g. of ice, 100 g. of benzene, 3.25 g. of NaOH and 5.9 g. of 2-ethylaziridine. To this mixture was added over a period of 10 minutes 15.4 g. of *p*-nitrobenzoyl chloride. The reaction mixture was stirred for 1 hour with the continual addition of ice, the temperature never rising about 5°. The reaction mixture was worked up according to a published procedure.[2a] The crude material weighed 16.5 g. (91%) and melted at 89–90.5°. It was recrystallized in portions from petroleum ether; b. 60–110°. The recrystallized material melted at 91.0–91.8°[18] and in Nujol mull had infrared absorption bands at 8.66, 10.53, 11.45, 11.60, 12.58, 13.53 and 13.92 μ which were useful in distinguishing I from the isomerized product.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.61.

Isomerization of I to 2-*p*-Nitrophenyl-4-ethyl-2-oxazoline.—A mixture of 200 mg. of I, 1.5 g. of NaI and 35 ml. of acetone was refluxed for 21 hours. The solvent was evaporated and water added to the residue to dissolve the NaI. The solid was filtered to give 192 mg. (96%) of oxazoline melting at 73–74°. The same results are obtained if the refluxing period is omitted and the reaction mixture allowed instead to stand at room temperature overnight. A mixed melting point with an authentic sample prepared by the method of Boyd and Rittner[9b] also melted at 73–74°. A melting point of 76–77° was reported for this compound.[9b]

(14) R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

(15) (a) R. Adams and T. L. Cairns, *J. Am. Chem. Soc.*, **61**, 2464 (1939); (b) M. S. Kharasch and H. M. Priestly, *ibid.*, **61**, 3425 (1939).

(16) W. J. Gensler, *ibid.*, **70**, 1843 (1948).

(17) F. L. Scott, R. E. Glick and S. Winstein, *Experientia*, **13**, 183 (1957).

(18) All melting points uncorrected.

Infrared spectra were identical for the authentic sample and the isomerized product. Some of the absorption bands occurred at 9.25, 9.32, 9.81, 10.37, 10.48, 11.01, 11.40, 11.65 and 14.10 μ.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.72. Found: N, 12.87.

1-*p*-Nitrobenzoyl-2-methylaziridine (II) was prepared analogously to I in 67% yield and was recrystallized from petroleum ether. It melted at 81–82°.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: N, 13.58. Found: N, 13.40.

Isomerization of II.—Following the method just given, II was isomerized to 2-*p*-nitrophenyl-4-methyl-2-oxazoline in 98% yield, m.p. 84–86°. A pure sample, m.p. 86.5–87.5°, was obtained from 60% aqueous methanol. An authentic sample of this new compound prepared by another method[9a] had an identical m.p. and infrared spectra.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: N, 13.58. Found: N, 13.20.

Preparation of 2-Nitrophenyl-4-methyl-2-oxazoline.—Treatment of 2.24 g. of N-(1-methyl-2-hydroxyethyl)-*p*-nitrobenzamide with 4.5 ml. of anhydrous pyridine and 1.9 g. of *p*-toluenesulfonyl chloride according to the procedure of Boyd and Hanson[9a] gave 1.8 g. of crude oxazoline, m.p. 74–80°. Recrystallization from 50% aqueous methanol gave crystals melting at 84.5–86°.

Preparation of N-(1-Methyl-2-hydroxyethyl)-*p*-nitrobenzamide.—Employing a method previously described,[19] 10.5 g. of *p*-nitrobenzoic acid in 200 ml. of $CHCl_3$ mixed with 1.8 g. of 2-methylaziridine in 25 ml. of $CHCl_3$ gave 6.2 g. (88%) of the crude benzamide, m.p. 127–131°. Recrystallization from water four times produced material melting at 133–135°. The compound was used for the alternate synthesis of 2-*p*-nitrophenyl-4-methyl-2-oxazoline.

Anal. Calcd. for $C_{10}H_{12}N_2O_4$: N, 12.49. Found: N, 12.31.

Isomerization of 1-Aziridinethiocarboxanilide (III).—To 510 mg. of III[6] was added 132 mg. of sodium iodide and 50 ml. of acetone. The reaction mixture was refluxed for 2 hours, the solvent evaporated and the residue washed with water and filtered. The product weighed 476 mg. (93%) and melted 159–162°. The reported melting point of 2-anilino-2-thiazoline[6] is 158–160°.

Isomerization of N,N-Diphenyl-1-aziridinecarboxamide (IV).—A mixture of 551 mg. of IV,[12] 170 mg. of NaI and 50 ml. of acetone was refluxed for 20 hours. The product was worked up in a similar manner as in the isomerization of III to give 518 mg. of crude 2-diphenylamino-2-oxazoline which melted at 99–104°. Recrystallization from aqueous ethanol gave product melting at 101–104°. A mixed melting point with a sample of 2-diphenylamino-2-oxazoline prepared by the alkaline solvolysis of N,N-diphenyl-N'-2-bromoethylurea melted at 101–103.5°. The infrared spectra of the two samples were identical. A control run without sodium iodide was refluxed for 18 hours and resulted in recovery of IV.

Anal. Calcd. for $C_{15}H_{14}N_2O$: N, 11.75. Found: N, 11.49.

Preparation of 2-Diphenylamino-2-oxazoline from N,N-Diphenyl-N'-2-bromoethylurea (V).—A mixture of 498 mg. of V, 735 mg. of $NaOCH_3$ and 70 ml. of methanol was refluxed for 14 hours. The solvent was evaporated and the residue washed with water and filtered. The crude product weighed 334 mg. Two recrystallizations from aqueous ethanol gave product melting 101–103.5°. It was identical with the product obtained from the isomerization of IV.

Preparation of V.—Into a Waring Blendor was placed 20.5 g. of bromoethylamine hydrobromide dissolved in 150 ml. of water and 25.5 g. of diphenylcarbamyl chloride dissolved in 70 ml. of benzene. To this mixture was added over a period of 35 minutes a solution containing 8.4 g. of NaOH in 90 ml. of water. The mixture was stirred for an additional 20 minutes. The organic layer was separated and saved. The aqueous portion was extracted several times with benzene. The benzene extracts were pooled, dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. An oil was obtained. Addition of approximately 50 ml. of cyclohexane caused precipitation of 2.5 g. of product which was immediately filtered. Evaporation of the solvent and further addition of cyclohexane gave 2.2 g. more of product. The crude product melted 121–126°. Twice recrystallized material from petroleum ether (b.p. 60–110°) melted at 126–128°. The residual oil solidified after 4 days standing at room temperature to give an additional 13 g. of crude product which was not purified.

Anal. Calcd for $C_{15}H_{15}BrN_2O$: N, 8.77. Found: N, 8.46.

1-*m*-Nitrobenzenesulfonylaziridine (VI).—Into a Waring Blendor containing 100 g. of ice, 100 g. of benzene, 3.3 g. of NaOH and 3.8 g. of aziridine was added in portions 15.2 g. of *m*-nitrobenzenesulfonyl chloride. After 80 minutes the organic layer was separated and the solvent evaporated. The crude product weighed 13.3 g. and melted from 97–104°. After recrystallization from a mixture of petroleum ether and hexane a melting point of 103–104° was obtained.

Anal. Calcd. for $C_8H_8N_2O_4S$: N, 12.27. Found: N, 12.11.

It resolidified above its melting point to a material which decomposed at 280°.

1,4-Bis-(*m*-nitrobenzenesulfonyl)-piperazine.—A mixture of 200 mg. of VI, 500 mg. of NaI and 50 ml. of acetone was refluxed for 3 hours. The solvent was evaporated, and the residue washed with water and filtered. The crude product weighed 193 mg. (96%) and melted 255–256°. Recrystallization from formamide yielded crystals melting at 263–264°. An infrared spectrum of the crude product was identical with a spectrum of an authentic sample of 1,4 bis-(*m*-nitrobenzenesulfonyl)-piperazine made by the method of Pollard and Gray.[20] The dimerized product gave no melting point depression on admixture with the authentic material. Dimerization also occurred if the reaction mixture was allowed to stand at room temperature for 24 hours or if KSCN was employed instead of NaI. Smaller quantities of sodium iodide (10 mg.) also caused dimerization. A control run without NaI resulted in the recovery of unchanged VI.

1,4-Bis-(*p*-toluenesulfonyl)-piperazine (VII).—A mixture of 200 mg. of *p*-toluenesulfonylaziridine,[21] 500 mg. of NaI and 50 ml. of acetone was refluxed for 8 hours. A quantitative yield of VII melting at 262–264° was obtained. Recrystallization from dioxane gave material melting at 294–295°. A true sample of VII[20] melted at 295.3–296.3°. A mixture of dimerized product and the authentic sample melted at 295–295.5° and the infrared spectra of the two samples were identical.

1,4-Bis-(methylsulfonyl)-piperazine (VIII).—A mixture of 200 mg. of 1-methylsulfonylaziridine (IX),[12] 500 mg. of NaI and 50 ml. of acetone was refluxed for 12 hours and worked up in the usual manner. A quantitative yield of VIII was obtained; it was recrystallized from dimethylformamide and decomposed at 324–326°. A sample of VIII prepared by treating piperazine with methanesulfonyl chloride melted at 328° and gave an infrared spectrum identical to the product resulting from treatment of IX with NaI.

Anal. Calcd. for $C_6H_{14}N_2O_4S$: N, 11.55. Found: N, 11.73.

Dimerization of 1-Phenylaziridine to N,N'-Diphenylpiperazine.—A mixture of 433 mg. of 1-phenylaziridine,[13] 1.003 g. of NaI, 6 ml. of ethanol and 6 ml. of water was heated gently overnight and then refluxed for 12 hours. The crude piperazine weighed 285 mg. (65%) and melted at 160–163°. A control run without the NaI gave 476 mg. (95%) of polymer melting at 269–273°. This polymer is similar to one prepared by emulsifying 1-phenylaziridine with water.[13]

Dimerization of 1-*p*-Tolylaziridine to N,N'-Di-*p*-tolylpiperazine.—A mixture of 213.8 mg. of the 1-*p*-tolylaziridine, 500 mg. of NaI, 6 ml. of ethanol and 6 ml. of H_2O if refluxed 30 hours gave a 37% yield of crude piperazine melting at 183–185°. The reported melting points are 187–188° and 185–186°.[22,23]

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Isomerization of 2,4,6-Tris-(1-aziridinyl)-*s*-triazine (X).—A mixture of 50 ml. of acetone, 500 mg. of NaI and 1.0 g. of X[4] was kept at room temperature for 2 hours. During this time 2,3,6,7,10,11-hexahydrotrisimidazo[1,2-a;1',2'-c;1'',2''-e]-*s*-triazine (XI) settled out. The filtered product weighed 881 mg. and melted at 320°. A mixed melting point with a sample of XI prepared by the method of Schaefer[4] showed no depression of melting point. Infrared spectra of the isomerized product and the authentic sample were identical.

Isomerization of 1-Aziridinecarboxanilide (XII).—A mixture of 2.015 g. of XII,[5] 1.02 g. of NaI and 7 ml. of acetone was refluxed 16 hours and then placed in an ice-bath. In a short time the 1-phenyl-2-imidazolidinone crystallized. It was filtered and weighed (1.7 g.). The crude product melted at 155–160°. Some of the imidazolidinone was recrystallized from water to give product melting at 161–163°. A mixed melting point determination and comparison of infrared spectra with an authentic sample of 1-phenyl-2-imidazolidinone prepared by the alkaline solvolysis of N-phenyl-N'-2-chloroethylurea[5] unequivocally identified the isomerized product as the imidazolidinone.

Dimerization of XII.—A mixture of 2.010 g. of XII, 100 ml. of acetone and 300 mg. of NaI was refluxed for 40–50 hours during which time N,N'-bisphenylcarbamylpiperazine (XIII) gradually precipitated. The solution was filtered while hot to give 450 mg. of XIII which decomposed at 308° with some sublimation. An authentic sample of XIII was prepared by treating phenyl isocyanate with piperazine.[24] Comparison of infrared spectra and a mixed melting point determination of the reaction product with the true sample established the structure. The literature value[24] for the decomposition point is 305–310° with accompanying sublimation. Longer reaction times (96 hours) did not increase the yield of XII.

The following experiment was so designed to give evidence that some 2-anilino-2-oxazoline also forms. A mixture of 1.01 g. of 1-aziridinecarboxanilide, 615 mg. of oven-dried NaI and 40 ml. of acetone (previously dried over K_2CO_3 and distilled) was refluxed for 52 hours. The solvent was evaporated, the residue washed with about 4 ml. of water and filtered. The residue weighed 1.01 g. and was washed with 20–25 ml. of ether. The ether extract was evaporated to give 160 mg. of material melting from 85–110°. A recrystallization from heptane gave crystals melting at 108–114° with slight sintering at 98°. The infrared spectrum was identical with that of a sample of 2-anilino-2-oxazoline prepared by the method of Gabriel and Stelzner[6] who reported a melting point of 119–120°. Two strong absorption peaks occur at 9.5 and 16.28 μ for the oxazoline. The 1-phenyl-2-imidazolidinone does not absorb in this region. The imidazolidinone strongly absorbs at 15 and 17.2 μ. The 2-anilino-2-oxazoline obtained from the reaction of 1-aziridinecarboxanilide with NaI did not show any absorption peaks at 15 and 17.2 μ. A Perkin–Elmer Infracord Spectrophotometer Model 137-KBr was used for these measurements.

A control run was made by refluxing 1.13 g. of 1-aziridinecarboxanilide and 25 ml. of acetone for 40 hours. The solvent was evaporated and the residue weighed. The recovered residue weighed (1.07 g.), melted at 78–82° and had an infrared spectrum identical with the starting compound.

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Purine Nucleosides. I. The Synthesis of Certain 6-Substituted-9-(tetrahydro-2-pyranyl)-purines as Models of Purine Deoxynucleosides[1]

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2,3-Dihydro-4H-pyran and various 2-substituted 2,3-dihydro-4H-pyrans have been shown to react with certain 6-substituted purines in the presence of a catalytic amount of acid to give the corresponding 6-substituted-9-(tetrahydro-2-pyranyl)-purines. This reaction provides a new synthetic route to the preparation of valuable models of certain purine deoxynucleosides which possess significant antitumor activity. The tetrahydropyran molecule greatly increases the solubility of purine derivatives in organic solvents and provides a useful blocking group which can be readily used to prevent undesirable side reactions due to the presence of the imidazole hydrogen. Acid hydrolysis regenerates the purine.

There is considerable evidence[2–5] that 6-purinethiol (6-mercaptopurine) exerts its antitumor activity in the form of its nucleoside or nucleotide. It would appear that resistance to this drug is due to the loss of the capacity of the cell to form the nucleotide of 6-purinethiol.[2–5] Since intact purine nucleotides are unable to penetrate mammalian cells[6] without extensive dephosphorylation, it would seem worthwhile to synthesize a number of nucleoside and nucleotide analogs which would be less polar and which might as a consequence possess the characteristics necessary for passage through the cancer cell wall. These model nucleosides should resemble the naturally occurring purine nucleosides sufficiently to be accepted by the appropriate enzymes of the cancer cell. Such compounds might well exhibit antitumor activity against the strains of tumor which have become resistant to the usual simple purine antagonists.[7]

The synthesis of a number of 9-arylpurines[8–10] has revealed that although the substitution of a phenyl ring in position 9 resulted in purines of

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