

Investigation on the Isomerization of 2-Amino-3-aziridino-1,4-naphthoquinones to Benzo[g]quinoxalines (1,2)

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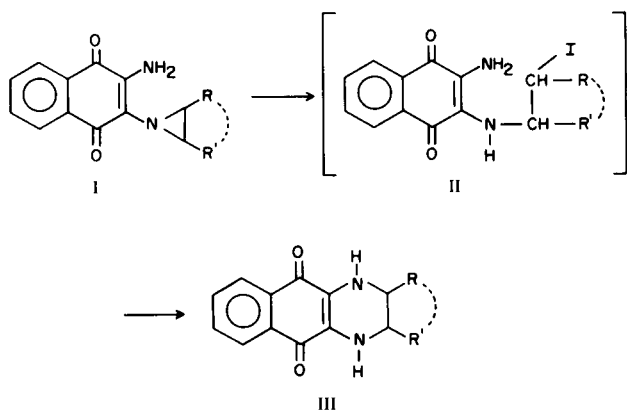
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The course of the hydriodic acid-catalysed and iodide-catalysed isomerization of various 2-amino-3-substituted-aziridino-1,4-naphthoquinones (I) to 1,2,3,4,5,10-hexahydrobenzo[g]-quinoxaline-5,10-diones (III) is investigated, and steric aspects of the reaction are also considered. Only in the case of the phenylaziridino derivative (Ie) does hydriodic acid afford direct cyclization to the corresponding benzoquinoxalinedione (IIIe); in all other cases the hydriodides (V) of the cleavage products (II) are obtained, and liberation of the free bases (II) results in cyclization to the corresponding benzoquinoxalinediones (III) when the aziridine ring is monosubstituted or *trans* disubstituted, with retention of configuration in the latter case. In contrast, the free bases (II) obtained from *cis* disubstituted (I) are relatively stable and cyclize with excess iodide yielding *trans* disubstituted (III). Correspondingly, monosubstituted and *trans* disubstituted I undergo iodide-catalysed isomerization to III whereas *cis* disubstituted I do not react.

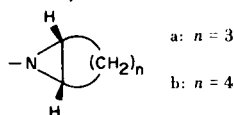
The acid-catalysed, nucleophile-catalysed, or thermal isomerization of suitable aziridine derivatives usually leads to five-membered heterocycles (3-10). We recently described an iodide induced isomerization of 2-amino-3-aziridino-1,4-naphthoquinone (I, R = R' = H), which leads, probably *via* the non-isolable intermediate (II, R = R' = H) to 1,2,3,4,5,10-hexahydrobenzo[g]quinoxaline-5,10-dione (III, R = R' = H) (11).



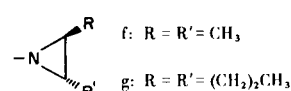
Since 1,2,3,4,5,10-hexahydrobenzo[g]quinoxaline-5,10-diones are difficult to obtain by other routes, it seemed interesting to extend the investigation of this isomerization to 2-amino-1,4-naphthoquinones substituted in posi-

tion 3 with aziridine groups different from the simple ethylenimine group in order to assess the range of application of the reaction and to study its stereochemical course. In particular, we considered the following aziridine groupings:

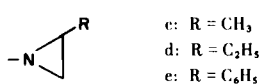
Cis alicyclic condensed:



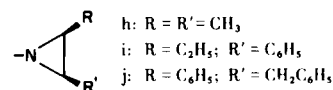
Trans disubstituted:



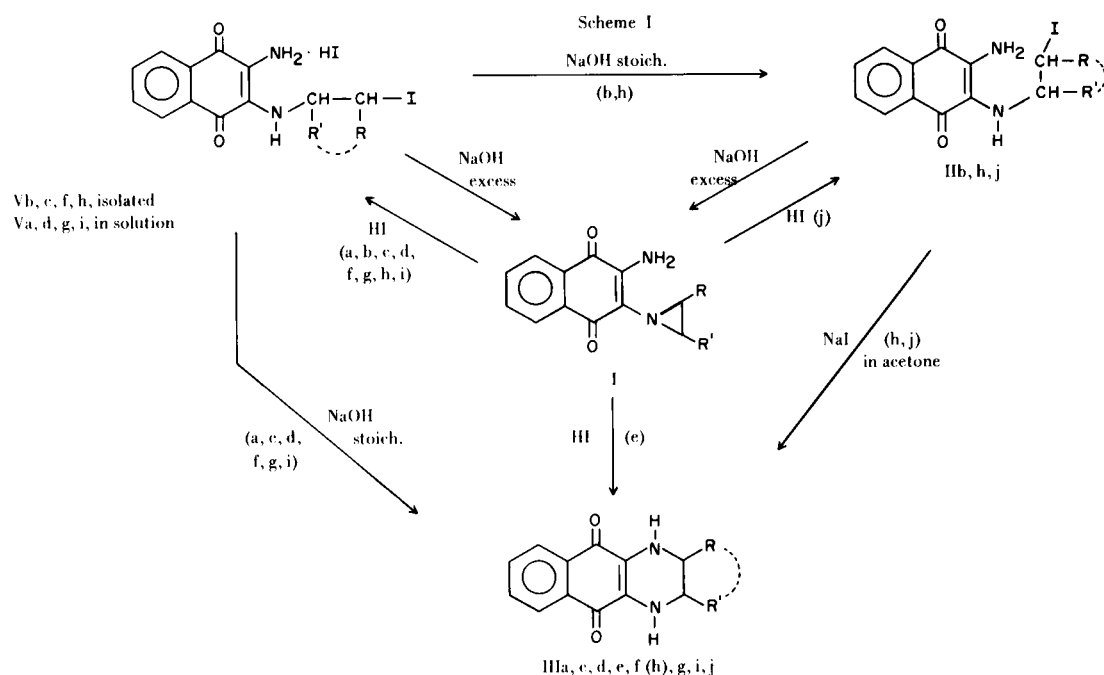
Monosubstituted:



Cis disubstituted:



The 2-amino-3-aziridino-1,4-naphthoquinones (I) listed in Table II were prepared by selective hydrolysis of the corresponding 2-chloroacetamido-3-aziridino-1,4-naphthoquinones (IV) (see Table I), which were in turn obtained from 2-chloroacetamido-3-chloro-1,4-naphthoquinone by substitution of the halogen in position 3 (11). The isomerization of the amino aziridines was carried out in two different ways: in the first method the hydriodides of the iodo derivatives obtained by cleavage of the aziridine ring with hydriodic acid in ethanol were



neutralized with a base, while the second method involved nucleophilic catalysis with sodium iodide in acetone. In both cases striking differences of behaviour were noted between the single compounds of the series.

The reaction with hydriodic acid in ethanol (Scheme I) always leads to cleavage of the aziridine ring: however, in only one case (Ie) is the cleavage followed by recyclization to the benzoquinoxaline isomer (IIIe) even in the acidic reaction medium: acids other than hydriodic acid do not afford the same result.

In all the other cases a solution is obtained containing the hydriodide V of the cleaved aziridine compound II; this salt crystallizes in some instances (Vb, c, f, h) while in one case the base (IIj) separates directly from the acidic solution. Differences in solubility could explain this variable behaviour.

It is interesting to note that the hydriodides (Vf, h) obtained from the diastereoisomeric pair of aminoaziridines (If, h) are unique and different compounds, showing that stereospecific cleavage of the aziridine ring occurs under these conditions. Also the hydriodide (Vb) and the iodobase (IIj) are unique compounds. Neutralization of the acidic solution or of the separated hydriodide with an equivalent of aqueous base leads to the formation of the corresponding benzoquinoxalinediones (III) in six of the eight cases (IIIa, c, d, f, g, i), whereas in the other two cases only the free base (IIb, h) of the salt is formed. Again, when diastereoisomerism is possible, only a single compound is obtained. Moreover, a remarkable difference in behavior is observed in the diastereoisomeric pair (If, h) the first of them (If, *trans*) cyclizing easily to the benzo-

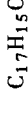


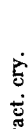

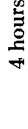

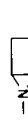


quinoxalinedione (IIIf) and the second (Ih, *cis*) giving only the free iodobase (IIh) which is apparently unable to cyclize in these reaction conditions. In a different medium however, *i.e.* in acetone with excess sodium iodide, (IIIh) is also converted to a benzoquinoxalinedione, surprisingly identical to that (IIIf) which was formed from the diastereoisomeric (If). Also the iodobase (IIj) is able to cyclize in these conditions, giving a benzoquinoxalinedione (IIIj). For this compound and for (IIIi), deriving from the third *cis* disubstituted aminoaziridine (Ii), a *trans* configuration is postulated on the basis of their nmr spectra ($J = 6$ Hz for the *trans*-diaxial protons), as compared with that of analogous benzodioxanes (12). By analogy also (IIIf) and probably (IIIa) and (IIIg) for which a similar nmr assignment is not possible, should have a *trans* configuration.

A particular behavior is shown by the iodobase (IIb), which fails to cyclize even with excess sodium iodide in acetone on prolonged refluxing.

From these seemingly inconsistent results, it can be seen that only the free iodobases (II) deriving from *cis* disubstituted aziridino derivatives are stable enough to be isolated, all the others cyclizing spontaneously to benzoquinoxalinediones; in excess sodium iodide, which favors diastereomerization of the iodobases, the stable ones are also cyclized; the failure to isolate the free iodobases deriving from the two *cis* disubstituted compounds (Ia) and (Ii) may thus be due to the presence of excess iodide in the medium, since basification is effected in a hydriodide solution containing excess hydriodic acid.

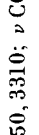


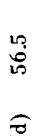
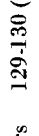


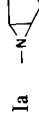


Adding the salts (V) [either isolated (b, c, f, h) or in

TABLE I
2-Chloroacetylamino-3-aziridino-1,4-naphthoquinones

Compound	R	Config-uration	Reaction Time	Purification Method	M.p., °C	Yield %	Formula (a)	Calcd.		Analyses		Found	
								C	H	N	C		H
IVa		<i>cis</i>	4 hours	Fract. cry.	198-199 (b)	43	C ₁₇ H ₁₅ ClN ₂ O ₃	61.72	4.57	8.46	61.98	4.75	8.20
IVb		<i>cis</i>	12 hours	Fract. cry.	213-214 (c)	68	C ₁₈ H ₁₇ ClN ₂ O ₃	62.70	4.96	8.12	62.91	4.74	8.32
IVc			5 hours	Fract. cry.	170-171 (b)	69.9	C ₁₅ H ₁₃ ClN ₂ O ₃	59.12	4.30	9.19	59.39	4.46	9.41
IVd			12 hours	Fract. cry.	156-157 (b)	71	C ₁₆ H ₁₅ ClN ₂ O ₃	60.28	4.74	8.78	60.41	4.65	9.02
IVe			36 hours	id. + col. chrom. (Dichloromethane)	120-122 (b)	49.6	C ₂₀ H ₁₅ ClN ₂ O ₃	65.48	4.12	7.63	65.72	4.26	7.85
IVf		<i>trans</i>	4 hours	Fract. cry.	187-188 (c)	42.4	C ₁₆ H ₁₅ ClN ₂ O ₃	60.28	4.74	8.78	60.36	4.91	8.88
IVg		<i>trans</i>	6 hours	Fract. cry.	188-189 (b)	40	C ₂₀ H ₂₃ ClN ₂ O ₃	64.08	6.18	7.47	64.13	5.97	7.69
IVh		<i>cis</i>	4 hours	Fract. cry.	204-205 (c)	44.8	C ₁₆ H ₁₅ ClN ₂ O ₃	60.28	4.74	8.78	60.46	4.56	8.50
IVi		<i>cis</i>	8 hours	Fract. cry.	171-172 (b)	32	C ₂₂ H ₁₉ ClN ₂ O ₃	66.91	4.85	7.09	67.08	4.62	7.26
IVj		<i>cis</i>	6 hours	id. + col. chrom. (benzene-ethanol 80/20)	170-172 (d)	35	C ₂₇ H ₂₁ ClN ₂ O ₃	70.97	4.63	6.13	71.09	4.91	6.33


(a) Ir spectra agree with the proposed structures. (b) From ethanol. (c) From ethanol-dioxane. (d) From ethanol-cyclohexane.

TABLE II
2-Amino-3-aziridino-1,4-naphthoquinones

Compound	R	Config-uration	Reaction Time	M.p., °C	Yield %	Formula	ir (cm ⁻¹) (in nujol)	Analyses					
								Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia		cis	12 hours	129-130 (d)	56.5	C ₁₅ H ₁₄ N ₂ O ₂	ν NH ₂ 3450, 3310; ν CO 1660	70.85	5.55	11.02	71.09	5.73	11.20
Ib		cis	1 hour	153-155 (a)	45.5	C ₁₆ H ₁₆ N ₂ O ₂	ν NH ₂ 3450, 3310; ν CO 1660	71.62	6.01	10.44	71.43	5.88	10.56
Ic			4 hours	75-77 (a)	60.2	C ₁₃ H ₁₂ N ₂ O ₂	ν NH ₂ 3450, 3340; ν CO 1660	68.40	5.29	12.27	68.64	5.51	12.46
Id			2 hours	87-88 (a)	46.5	C ₁₄ H ₁₄ N ₂ O ₂	ν NH ₂ 3400, 3300; ν CO 1660	69.40	5.83	11.56	69.27	5.78	11.30
Ie			4 hours	122-124 (a)	47	C ₁₈ H ₁₄ N ₂ O ₂	ν NH ₂ 3400, 3300; ν CO 1660	74.47	4.86	9.65	74.63	5.05	9.83
If		trans	5 hours	169-170 (b)	46	C ₁₄ H ₁₄ N ₂ O ₂	ν NH ₂ 3380, 3250; ν CO 1670	69.40	5.83	11.56	69.61	5.94	11.48
Ig		trans	24 hours	114-115 (a)	44.3	C ₁₈ H ₂₂ N ₂ O ₂	ν NH ₂ 3380, 3250; ν CO 1670	72.45	7.43	9.39	72.19	7.61	9.50
Ih		cis	3 hours	122-123 (b)	52.6	C ₁₄ H ₁₄ N ₂ O ₂	ν NH ₂ 3420, 3310; ν CO 1670	69.40	5.83	11.56	69.66	5.92	11.45
Ii		cis	4 hours	105-106 (c)	45.1	C ₂₀ H ₁₈ N ₂ O ₂	ν NH ₂ 3390, 3290; ν CO 1648	75.45	5.70	8.80	75.63	5.85	8.94
Ij		cis	3 hours	139-141 (a)	62.3	C ₂₅ H ₂₀ N ₂ O ₂	ν NH ₂ 3420, 3310; ν CO 1670	78.92	5.29	7.36	79.02	5.03	7.09

(a) From ethanol. (b) From methylene chloride-hexane. (c) From ethylene chloride-hexane. (d) From benzene-hexane.

TABLE III
 1,2,3,4,5,10-Hexahydrobenzo[g]quinoxaline-5,10-diones


Compound	R	R'	Config-uration	Method of Preparation	Reaction Time	Purification Method	Yield %	M.p., °C	Formula	Ultraviolet Data	
										λ max (ethanol) nm (log ϵ)	ν (cm^{-1}) in nujol
IIIa			(<i>trans</i> ?)	B	120 hours	Fract. cry. + col. chrom. Dichloromethane	29	224-225 (b)	$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$	236 (4.04), 275 (4.15) 306 (4.32), 316 (4.28) sh, 630 (3.28)	ν NH 3315; ν CO 1620
IIIc	CH_3	H		B	4 hours	Fract. cry.	87	167-169 (c)	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$	235 (4.02), 275 (4.15) 304 (4.26), 620 (3.20)	ν NH 3320; ν CO 1612
III d	C_2H_5	H		B	10 hours	Fract. cry.	91	142-144 (b)	$\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$	234.5 (4.05), 273 (4.21) 303 (4.30), 620 (3.20)	ν NH 3300; ν CO 1620
IIIe	C_6H_5	H		A C	24 hours 30 min.	Fract. cry.	93 87	203-205 (d)	$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2$	(a)	ν NH 3290; ν CO 1610
III f	CH_3	CH_3	(<i>trans</i> ?)	A (from If) E (from IIIh)	48 hours 24 hours	Fract. cry.	90 82	210-211 (c)	$\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$	235 (4.05), 272 (4.14) 304 (4.26), 620 (3.19)	ν NH 3325; ν CO 1615
III g	$(\text{CH}_2)_2\text{CH}_3$	$(\text{CH}_2)_2\text{CH}_3$	(<i>trans</i> ?)	B	2 hours	id. + col. chrom. benzene-ethyl acetate 80/20	17.5 (g)	124-125 (e)	$\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$	235 (4.04), 271 (4.18) 306 (4.36), 620 (3.20)	ν NH 3240; ν CO 1605
III i	C_6H_5	C_2H_5	<i>trans</i>	D	20 hours	id. + col. chrom. Dichloromethane	60	158-160 (f)	$\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2$	233 (3.98), 270 (3.96) 304 (4.16), 620 (3.13)	ν NH 3290; ν CO 1610
III j	C_6H_5	$\text{CH}_2\text{C}_6\text{H}_5$	<i>trans</i>	E	10 hours	Fract. cry.	70	188-190 (d)	$\text{C}_{25}\text{H}_{20}\text{N}_2\text{O}_2$	(a)	ν NH 3320; ν CO 1640

	Analyses					
	C	Calcd. H	N	Found C	Found H	N
IIIa	70.85	5.55	11.02	71.01	5.72	11.21
IIIc	68.40	5.29	12.27	68.64	5.41	12.04
III d	69.40	5.83	11.56	69.64	5.78	11.40
IIIe	74.47	4.86	9.65	74.52	4.91	9.81
III f	69.40	5.83	11.56	69.53	5.81	11.63
III g	72.45	7.43	9.39	72.56	7.51	9.53
III i	75.45	5.70	8.80	75.66	5.85	9.02
III j	78.92	5.29	7.36	79.10	5.46	7.50

(a) The solubility of these compounds in ethanol is very low. (b) From ethanol. (c) From acetone-water. (d) From acetone. (e) From ethyl-acetate. (f) From dichloromethane-hexane. (g) The yield is low due to the formation of the byproduct VI in 25.2% yield.

TABLE IV


NMR Spectra of 1,2,3,4,5,10-Hexahydrobenzo[g]quinoxaline-5,10-diones

Compound (a)	R	R'	Chemical Shifts (deuteriochloroform) (τ) and Coupling Constants (Hz)
IIIa			2.02-2.63 (4H, A_2B_2 sys., aromatics); 5.10 (2H, broad s, NH); (b) 6.19-6.56 (2H, m, N-CH-CH-N); 7.73-8.60 (6H, m, $(\text{CH}_2)_3$).
IIIc	H	CH_3	2.07-2.65 (4H, A_2B_2 sys., aromatics); 5.17 (2H, broad s, NH); (b) 6.35-7.92 (3H, m, N-CH ₂ -CH-N); 8.76 (3H, d, J = 6 Hz, CH).
III d	H	C_2H_5	2.34-2.93 (4H, A_2B_2 sys., aromatics); 5.54 (2H, broad s, NH); (b) 6.37-7.20 (3H, m, N-CH ₂ -CH-N); 8.14-8.67 (2H, m, CH ₂ -CH ₃); 8.95 (3H, t, J = 6 Hz, CH ₃).
III f	CH_3	CH_3	2.07-2.65 (4H, A_2B_2 sys., aromatics); 5.30 (2H, broad s, NH); (b) 6.85-7.19 (2H, m, N-CH-CH-N); 8.77 (6H, d, J = 6 Hz, CH ₃).
III g	$(\text{CH}_2)_2\text{CH}_3$	$(\text{CH}_2)_2\text{CH}_3$	2.34-2.90 (4H, A_2B_2 sys., aromatics); 5.10 (2H, broad s, NH); (b) 6.67-7.00 (2H, m, N-CH-CH-N); 8.25-9.34 (14H, two m partially overlapping, $(\text{CH}_2)_2\text{CH}_3$).
III i	C_6H_5	C_2H_5	2.00-2.80 (9H, m, aromatics); 5.04 (2H, broad s, NH); (b) 5.99 (1H, d, J = 6 Hz, N-CH-C ₆ H ₅); 6.70-6.92 (1H, m, N-CH-C ₂ H ₅); 8.38-8.64 (2H, m, -CH ₂); 9.03 (3H, t, CH ₃).
III j	C_6H_5	$\text{CH}_2\text{C}_6\text{H}_5$	2.03-2.94 (14H, m, aromatics); 4.90-5.01 (2H, two broad s, NH); (b) 5.88 (1H, dd, J = 1, 5.5 Hz, NCH-C ₆ H ₅); (c) 6.38-6.60 (1H, m, CH-CH ₂ -); 7.05-7.60 (2H, m, AB part of a ABX sys., -CH ₂ -).

(a) The solubility of the compound IIIe in solvents suitable for nmr spectroscopy is very low. (b) On addition of deuterium oxide the signal disappears. (c) On addition of deuterium oxide the doublet of doublet is converted into a doublet with J = 5.5 Hz.

TABLE V


2-Amino-3-iodoalkylamino-1,4-naphthoquinones Hydriodides

Compound	R	M.p., °C (a)	Formula	Ultraviolet Data		Ultraviolet Data of the corresponding aminoaziridines		Analyses			
				λ max (ethanol) nm (log ε)	λ max (ethanol) nm (log ε)	λ max (ethanol) nm (log ε)	λ max (ethanol) nm (log ε)	Calcd. C H N	Found C H N		
Vb		157-158 dec.	C ₁₆ H ₁₇ IN ₂ O ₂ ·HI	290 (4.19), 520 (3.07)	284 (4.26), 510 (3.40)	36.66	3.46	5.34	36.57	3.51	5.28
Vc	-CH-CH ₂ -I CH ₃	187-188 dec.	C ₁₃ H ₁₃ IN ₂ O ₂ ·HI	302 (4.32), 584 (2.98)	282 (4.34), 504 (3.36)	32.25	2.91	5.78	32.41	2.90	5.63
Vf	-CH-CH-I (b) CH ₃ CH ₃	142-143 dec.	C ₁₄ H ₁₅ IN ₂ O ₂ ·HI	293 (4.26), 536 (3.20)	289 (4.37), 520 (3.42)	33.75	3.23	5.62	33.68	3.35	5.58
Vh	-CH-CH-I (b) CH ₃ CH ₃	124-126 dec.	C ₁₄ H ₁₅ IN ₂ O ₂ ·HI	297 (4.31), 550 (3.26)	283 (4.39), 496 (3.42)	33.75	3.23	5.62	33.95	3.19	5.39

(a) On a Kofler apparatus the salts Vb, c, f, h partly melt at the temperature reported in this Table; they melt completely above 300°. (b) Diastereoisomeric forms.

TABLE VI

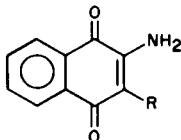
2-Amino-3-(β-iodoalkylamino)-1,4-naphthoquinones

Compound	R	R'	Method	M.p., °C	% Yield	Formula	Ultraviolet Data		Analyses					
							λ max (ethanol) nm (log ε)	ir (cm ⁻¹) in nujol	Calcd. C H N	Found C H N				
IIb			A	125-127 (a)	90	C ₁₆ H ₁₇ IN ₂ O ₂	290 (4.19), 520 (3.08)	ν NH ₂ , NH 3370 3220; ν CO 1620	48.50	4.32	7.07	48.20	4.53	7.28
IIh	CH ₃	CH ₃	A	96-98 (b)	91	C ₁₄ H ₁₅ IN ₂ O ₂	292.5 (4.28), 530 (3.28)	ν NH ₂ , NH 3410 3265; ν CO 1650	45.42	4.08	7.56	45.28	4.21	7.65
IIj	C ₆ H ₅	CH ₂ C ₆ H ₅	C	119-120 (c)	73	C ₂₅ H ₂₁ IN ₂ O ₂	257 (3.85), 295 (4.07), 536 (2.87)	ν NH ₂ , NH 3445 3315; ν CO 1650	59.06	4.16	5.51	59.17	4.35	5.39

(a) From benzene. (b) From hexane. (c) From ethanol.

TABLE VII

NMR Spectra of the Aminoaziridines Ib, h, j and of the Corresponding Iodo Bases IIb, h, j



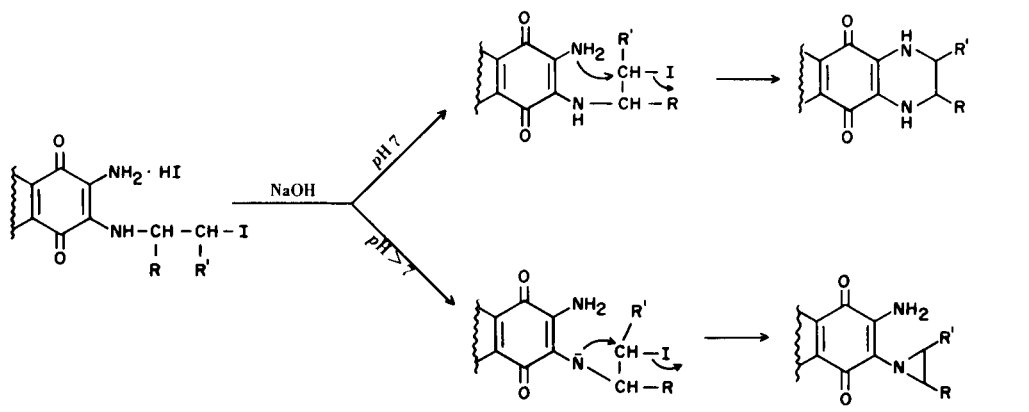
Compound	R	Chemical Shifts (deuteriochloroform) (τ) and Coupling Constants (Hz)
Ib		2.02-2.65 (4H, A ₂ B ₂ sys., aromatics); 5.22 (2H, s, NH ₂) (a); 7.51 (2H, protons of the aziridine ring); 7.93 (4H, broad s, equatorial protons); 8.55 (4H, broad s, axial protons).
IIb		2.02-2.65 (4H, A ₂ B ₂ sys., aromatics); 5.10 (3H, broad s, NH ₂ , NH) (a); 5.70-6.13 (1H, m, -CH-I); 6.23-6.75 (1H, m, -CH-NH-); 7.20-8.95 (8H, m, alicyclic protons).
Ih		1.96-2.60 (4H, A ₂ B ₂ sys., aromatics); 5.21 (2H, broad s, NH ₂) (a); 7.49-7.80 (2H, m, aziridine protons); 8.55 (6H, d, J = 6.0 Hz, CH ₃).
IIh		1.98-2.60 (4H, A ₂ B ₂ sys., aromatics); 5.00-5.90 [4H, m, NH ₂ , NH, -CH-I on addition of deuterium oxide, the signal is converted into a multiplet (1H) centered at 5.71 (-CH-I)]; 6.50 (1H, m, -CH-NH-); 8.02 (3H, d, J = 6.7 Hz, CH ₃ -C-I); 8.71 (3H, d, J = 6.0 Hz, CH ₃ -C-NH).
Ij		1.94-2.12 (2H, m, H5, H8); 2.30-3.06 (12H, m, aromatics); 5.56 (2H, s, NH ₂) (a); 6.65 (1H, d, J = 3.0 Hz); 6.83-7.59 (3H, m, -N-CH ₂ -C ₆ H ₅).
IIj		2.67-3.67 (14H, m, aromatics); 5.34 (1H, d, J = 3.5 Hz N-CH-C ₆ H ₅); 6.54 [4H, broad signal, NH ₂ , NH, -CH-I, on addition of deuterium oxide, the signal is converted into a multiplet (1H) centered at 5.71 (-CH-I)]; 7.04-7.80 (2H, m, AB part of a ABX sys.).

(a) On addition of deuterium oxide the signal disappears.

solution (a, d, g, i)] or the free bases (IIb, h, j) in an excess of aqueous sodium hydroxide leads to a completely different result from that obtained with a stoichiometric amount of base, *i.e.* the formation of the original aminoaziridine (I); although in case (b) this is afforded only by heating. In every case, only the original diastereoisomer is formed, that is, also the ring closure to give the starting aziridine is stereospecific.

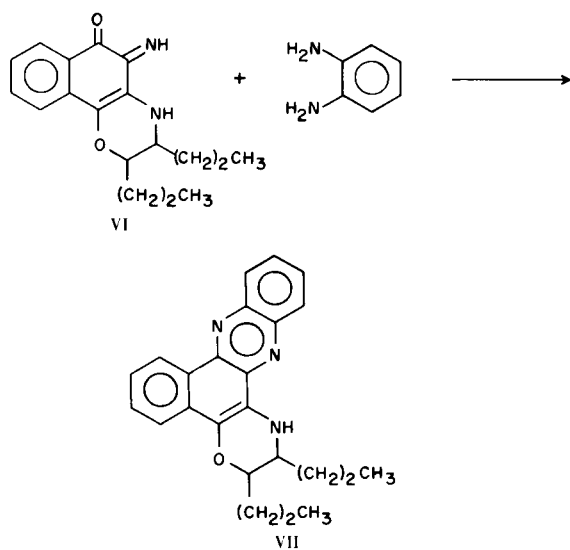
The different behavior of the hydriodides (either isolated or in solution) when reacting with a stoichiometric quantity or with an excess of dilute sodium hydroxide can be interpreted as follows. The neutralization with dilute sodium hydroxide leads to the liberation of the iodobase, which contains two amine functions with different nucleophilic characteristics. In a neutral medium, attack by the primary amino group predominates, with

Scheme II



formation of the benzo[*g*]quinoxaline. In alkaline media on the other hand, the excess of base would remove a proton from the secondary amino group [this amino group being more acidic because of the inductive effect of the iodine (13)], with formation of a strongly nucleophilic anion that is capable of regenerating the aziridine ring (Scheme II).

The reaction of the aminoaziridines (I) with sodium iodide in acetone, *i.e.* in neutral medium, also occurs with gradual differences in reactivity and, when relevant with stereospecificity, as can be seen by an inspection of reaction times and yields in Table III. Again the most reactive aziridine seems to be the phenyl substituted Ie, followed by *trans*-dimethyl (If), which both give high yields of the corresponding benzoquinoxalinedione (III) at room temperature. *Trans*-di-*n*-propyl (Ig) and the monosubstituted aziridines (Ic, d) require reflux conditions to give the same result, which in case of (Ig) is complicated by the formation of an isomeric by product for which spectroscopic evidence speaks for the naphtho-[1,2-*b*]-1,4-oxazine dione imine structure (VI). This is supported by the formation of a benzo[*a*][1,4]oxazino-[2,3-*c*]phenazine derivative (VII) on reaction of VI with *o*-phenylenediamine, a reaction that does not occur with the benzoquinoxalinediones (III).



Cis-alicyclic condensed aziridines (Ia, b) show an even lower reactivity, (Ia) giving only a low yield of (IIIa) on prolonged refluxing and (Ib) forming only the iodobase (IIb) which, as we have seen before, seems unable to cyclize even by prolonging the reaction time. Finally the *cis* disubstituted aziridines (Ih, i, j) do not react at all with sodium iodide in acetone, this being one of the few examples of resistance of aziridine rings to this reagent (14,15).

The above results are in agreement with the general statement that acid catalysed and iodide catalysed isomerization of aziridine derivatives proceed by two subsequent S_N2 steps (16) which, in the case of the most reactive (Ie) may have a certain S_N1 character. In some instances thermodynamic control prevails, as in the formation of the same benzoquinoxalinedione (IIIf) from both diastereoisomers (If) and (Ih).

The lack of reactivity of the *cis* disubstituted aziridines (Ih, i, j) toward sodium iodide in acetone, as compared with the *trans* disubstituted aziridines, should be explainable on the basis of a conformational isomerism induced by the different configuration: the difference of configuration might stabilize an unreactive conformer in the case of the *cis*-isomers. An analogous explanation may be invoked also for the lack of reactivity of (IIb) with excess sodium iodide in acetone, and for the relative stability of (IIh, j) as compared with the non-isolable iodobases, deriving from monosubstituted and *trans* disubstituted aminoaziridines.

EXPERIMENTAL

All the melting points were determined with a Büchi apparatus and are uncorrected. The nmr spectra were recorded in deuteriochloroform solution with JEOL JNH-MH-60 and Varian HA-100 spectrometers, using TMS (tetramethylsilane) as an internal standard. The ir spectra were determined in Nujol with a Perkin-Elmer Model 257 spectrometer. The uv and visible spectra were recorded with a Unicam SP 800 spectrometer. The thin layer chromatography was carried out on silica gel GF₂₅₄ (Merck), and the column chromatography on 0.05-0.2 mm silica gel (Merck). Ugo Gulini assisted with the experimental work.

Substituted Aziridines.

Some of the substituted aziridines were commercially available (2-methyl- and 2-ethylaziridine K & K). Some others were prepared (in a sterically pure form, when relevant) by literature methods: cyclopentenimine, cyclohexenimine, *cis*- and *trans*-2,3-dimethyl aziridine (17); *cis*-2-phenyl-3-ethylaziridine, *cis*-2-benzyl-3-phenylaziridine (18); 2-phenylaziridine (19). The *trans*-2,3-di-*n*-propylaziridine is a new compound, and was prepared from *trans*-4-octene by the stereospecific method described by Hassner *et al.* (17) (yield 90%). After redistillation, the *trans*-2,3-di-*n*-propylaziridine has boiling point of 70-72° at 20 mm, $n_D^{20} = 1.429$; ir (film) ν_{\max} (cm⁻¹): 3130 (NH stretching).

Anal. Calcd. for C₈H₁₇N: C, 75.52; H, 13.47; N, 11.01. Found: C, 75.78; H, 13.65; N, 10.83.

2-Chloroacetamido-3-Substituted-Aziridino-1,4-naphthoquinones (IV).

Anhydrous triethylamine (15 ml.) and 0.01 mole of substituted aziridine were added to a suspension of 0.01 mole of 2-chloroacetamido-3-chloro-1,4-naphthoquinone (20) in 50 ml. of anhydrous benzene with stirring. The reaction mixture was stirred at room temperature for several hours. The yellow solid that forms was then filtered off and recrystallized. In some cases, the compound was isolated by evaporation of the filtrate and chromatography of the resulting residue on a silica gel column with a suitable eluent (see Table I).

2-Amino-3-Substituted-Aziridino-1,4-naphthoquinones (I).

A suspension of 0.003 mole of 2-chloroacetamido-3-substituted-aziridino-1,4-naphthoquinone (IV) in 15 ml. of ethanol and 15 ml. of 2*N* sodium hydroxide was stirred at room temperature for several hours; 50 ml. of water was then added to the reaction mixture. The red-violet product that separated out was extracted with ethyl acetate. Evaporation of the solvent yielded a residue, which was crystallized (see Table II). The compounds Ig and Ii were isolated by chromatography of residue on a silica gel column, the eluents being benzene/ethyl acetate (80/20) and methylene chloride respectively.

2,3-Disubstituted-1,2,3,4,5,10-Hexahydrobenzo[*g*]quinoxaline-5,10-diones (III).

Method A.

A solution of 0.002 mole of 2-amino-3-(substituted-aziridino)-1,4-naphthoquinone and 0.006 mole of sodium iodide in 50 ml. of acetone was stirred at room temperature for several hours. Addition of water to the solution obtained by partial evaporation of the solvent yields a blue solid which was filtered off and crystallized (see Table III). This method was suitable for aminoaziridines Ie and If.

Method B.

The procedure was similar to that of Method A, the solution being heated under reflux for several hours. The solvent was evaporated to small volume, and on addition of water, a blue solid separated out; this was filtered off and crystallized. In some cases, the solid was extracted with methylene chloride and chromatographed on a silica gel column with a suitable eluent (see Table III). The method was indicated for aminoaziridines Ia, c, d.

Method C.

Hydriodic acid (0.5 ml. of 57%) was added to a solution of 0.002 mole of 2-amino-3-(2'-phenylaziridino)-1,4-naphthoquinone (Ie) in 15 ml. of ethanol. The acidic solution was stirred for several minutes at room temperature. A solid crystallized out in time, and was filtered off and recrystallized (see Table III). With acids other than hydriodic acid, the aziridine ring of Ie was cleaved as in similar cases (see reference 13a), but a complex reaction mixture was formed in which no trace of IIIe could be found.

Method D.

The procedure was similar to that of Method C. After 30 minutes, the solution was neutralized with dilute sodium hydroxide and stirred at room temperature for several hours. Partial evaporation of the solvent yielded a blue residue which was extracted with ethyl acetate. Evaporation of the solvent gave a residue which was crystallized or chromatographed on a silica gel column with a suitable eluent (see Table III). This method gave positive results with aminoaziridines Ia, c, d, f, g, i.

Method E.

Sodium iodide (0.002 mole) was added to a solution of 0.001 mole of iodo base (IIh or IIj) in 10 ml. of acetone. The solution was stirred for several hours at room temperature; on partial evaporation of the solvent, a blue solid separated out; this was filtered off and crystallized (see Table III). The nmr spectra of the hexahydrobenzoquinoxalinediones (III) are reported in Table IV.

4*H*-2,3,5,6-Tetrahydro-2,3-di-*n*-propyl-5-iminonaphtho[1,2-*b*]oxazin-6-one (VI).

Application of method B of the preceding paragraph to 2-amino-3-(2',3'-*trans*-di-*n*-propylaziridino)-1,4-naphthoquinone (Ig) gave a reaction mixture which on column chromatography first separated a blue fraction (IIIg) followed by a blue violet solid fraction (yield 25.2%) which melts at 142-143° after crystallization from ethyl acetate (VI); $uv \lambda \text{ max (ethanol): nm (log } \epsilon \text{): 231 (3.88), 290 (4.32), 616 (2.97); ir } \nu \text{ max (cm}^{-1}\text{): 3190 (NH stretching), 1670 (C=O stretching); nmr (deuteriochloroform): } \tau \text{ 2.40 (1H, m, H7); 2.66-3.10 (3H, m, H8, 9, 10); 5.94 (broad 3H, NH, and O-CH-CH-N; on addition of deuterium oxide, the signal changes into a multiplet, 1H); 6.93 (1H, m, O-CH-CH-N); 8.12-9.34 (14H, two m partly overlapping, (CH}_2\text{)}_2\text{CH}_3\text{.}$

Anal. Calcd. for C₁₈H₂₂N₂O₂: C, 72.45; H, 7.43; N, 9.38. Found: C, 72.39; H, 7.73; N, 9.18.

1*H*-2,3-Dihydro-2,3-di-*n*-propylbenzo[*a*][1,4]oxazino[2,3-*c*]phenazine (VII).

Equimolar quantities of VI and *o*-phenylenediamine were heated in ethanol under reflux for 5 hours. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column with benzene/ethyl acetate (80/20) as the eluent. On evaporation of the first red-violet eluate, a residue that melts at 174-175° after crystallization from *n*-hexane was obtained; $uv \lambda \text{ max (ethanol): nm (log } \epsilon \text{): 248 (4.54), 333 (4.45), 506 (3.26); ir } \nu \text{ max (cm}^{-1}\text{): 3290 (NH stretching), 1620 (C=N stretching).}$

Anal. Calcd. for C₂₄H₂₅N₃O: C, 77.60; H, 6.78; N, 11.31. Found: C, 77.51; H, 6.84; N, 11.15.

Hydroiodides V.

Hydriodic acid (0.5 ml. of 57%) was added to a solution of 0.001 mole of aminoaziridine (Ib, c, f, h) in 15 ml. of ethanol. The yellow solid that formed on standing overnight at 0° was filtered off and washed repeatedly with ethyl acetate. No purification of these products could be accomplished by crystallization (see Table V). The open chain structure of these salts is shown not only by the conversion of two of them (Vb, h) into the corresponding iodo bases but also by their uv absorption, which are identical with those of the iodo bases and exhibit a bathochromic shift in relation to the starting aziridines whose uv spectra are also reported in Table V.

Iodo Bases II.

Method A.

Neutralization of the salt (Vb, h) with 0.1 *N* sodium hydroxide solution gives a violet product which was extracted with methylene chloride. Evaporation of the solvent yielded a residue which was crystallized (see Table VI).

Method B.

One g. of sodium iodide was added to a solution of 0.002 mole of aminoaziridine Ib in 50 ml. of acetone. The solution was heated under reflux for 4 hours. On evaporation of the solvent, one obtained a residue which was taken up in a 50/50 ethyl acetate/cyclohexane mixture. The solution was filtered and chromatographed on a silica gel column with the same solvent mixture as the eluent. A residue was obtained from the first violet fraction and crystallized (see Table VI).

Method C.

Concentrated hydriodic acid (0.5 ml.) was added to a solution

of 0.001 mole of amino aziridine Ij in 30 ml. of ethanol. After 18 hours at room temperature and one night at 0°, a violet solid crystallized directly from the acidic solution. This solid was filtered off and crystallized (see Table VI). The open-chain structure of the iodo bases was shown not only by their uv absorption, which showed a bathochromic shift in relation to the starting aziridines, but also by their nmr spectra, which show the non-equivalence of the two groups R and R' that originally formed part of the aziridine ring (IIb, h) and of the protons adjacent to them; moreover, as was to be expected, the latter show (also for IIj) a chemical shift to much lower fields in relation to the starting aziridines (see Table VII).

Regeneration of the 2-Amino-3-Substituted-Aziridino-1,4-naphthoquinones I from the Iodo Bases II or from the Hydroiodides V.

The iodo base II (or salt V) (0.01 mole) in 10 ml. of ethanol was added to 20 ml. of 2N sodium hydroxide solution. After 1 hour, the solution was extracted several times with ethyl acetate. Evaporation of the solvent yielded the corresponding amino-aziridine (Ic, f, h, j) which was crystallized from a suitable solvent (cf. Table II). The amino aziridines Ia, d, g, i were obtained in a similar way from the acidic solutions containing the hydroiodides Va, d, g, i, which could not be isolated.

2-Amino-3-cyclohexenimino-1,4-naphthoquinone (Ib) was obtained by addition of 0.001 mole of iodo base IIb (or salt Vb) to a solution of 1 g. of potassium hydroxide in 60 ml. of ethanol. The solution was refluxed for 4 hours, and evaporation of the solvent then yielded a residue which was taken up in water and extracted several times with ethyl acetate. Evaporation of the solvent gave a residue which was crystallized from ethanol.

REFERENCES

- (1) Work carried out with the support of the Consiglio Nazionale delle Ricerche.
- (2) This work was presented to the VIth National Conference on Organic Chemistry (Taormina, May 28-31 1972).
- (3) H. W. Heine, *Angew. Chem.*, **74**, 772 (1962).
- (4) H. W. Heine, "Mechanism of Molecular Migrations," B. S. Thyagarajan, Ed., Wiley-Interscience, **3**, 145 (1971).
- (5) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).
- (6) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).
- (7) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **31**, 59 (1966).
- (8) P. E. Fanta, R. J. Smat, and J. R. Krikau, *J. Heterocyclic Chem.*, **5**, 419 (1968).
- (9) T. A. Foglia, L. M. Gregory, and G. Maerker, *J. Org. Chem.*, **35**, 3779 (1970).
- (10) H. Otomasu, K. Yoshida, and H. Takahashi, *Yakugaku Zasshi*, **90**, 1391 (1970).
- (11) G. Casini, F. Claudi, M. Felici, M. Ferappi, and M. Grifantini, *Farmaco, Ed. Sci.*, **24**, 732 (1969).
- (12) V. Rosnati, F. Sannicolò, G. Zecchi, *Gazz. Chim. Ital.*, **101**, 344 (1971).
- (13a) F. Claudi, M. Felici, M. Ferappi, M. Grifantini, *Farmaco Ed. Sci.*, **24**, 725 (1969). (b) A. V. Podol'skii, L. S. German, and J. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser Khim.*, 1134 (1967).
- (14) R. K. Smalley, *J. Chem. Soc. (C)*, 80 (1966).
- (15) P. Rajagopalan and C. N. Talaty, *J. Am. Chem. Soc.*, **88**, 5048 (1966).
- (16a) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., p. 206. (b) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958). (c) T. Nishiguchi, H. Tockio, A. Nabeya, and Y. Iwakura, *ibid.*, **91**, 5841 (1969). (d) L. Wartski and C. Wakselman, *Bull. Soc. Chim.*, 1478 (1972).
- (17) A. Hasner, C. J. Matthews, and F. W. Fowler, *J. Am. Chem. Soc.*, **91**, 5046 (1969).
- (18) K. Kotera, S. Miyazaki, H. Takahashi, I. Okada, and K. Kitahonoki, *Tetrahedron*, **24**, 3681 (1968).
- (19) A. Hassner and C. Hethcock, *ibid.*, **20**, 1037 (1964).
- (20) J. R. E. Hoover and A. L. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).