

rophenyl)-3-thiosemicarbazide in 50 ml of dry DMF was treated with 0.5 g (0.010 mol) of sodium hydride as a 50% mineral oil dispersion. After heating to reflux for 126 hr, the solution was poured into water and washed with hexane. The product was extracted with ethyl acetate to yield 3-methyl-*s*-triazolo[3,4-*b*]benzothiazole (13), mp 152–154°. *Anal.* Calcd for C<sub>9</sub>H<sub>7</sub>N<sub>3</sub>S: C, 57.12; H, 3.73; N, 22.21. Found: C, 56.84; H, 3.79; N, 22.23.

**Method C.** A solution of 5 g (0.019 mol) of 4-(2,4-dichlorophenyl)-5-methyl-1,2,4-triazole-3-thiol (20) in 100 ml of dry DMF was treated with 1 g (0.020 mol) of sodium hydride as a 50% mineral oil dispersion. The solution was heated to reflux for 24 hr and, after cooling, poured into water. The aqueous solution was washed with hexane and the product was extracted with ethyl acetate to yield 7-chloro-3-methyl-*s*-triazolo[3,4-*b*]benzothiazole (21), mp 186–188°. *Anal.* Calcd for C<sub>9</sub>H<sub>6</sub>ClN<sub>3</sub>S: C, 48.33; H, 2.70; N, 18.79. Found: C, 48.32; H, 2.89; N, 18.96.

**Method D.** A solution of 2.0 g (0.0083 mol) of potassium 4-(2-chlorophenyl)-1,2,4-triazole-3-thiolate in 100 ml of dry DMF was heated to reflux for 24 hr. The solution was concentrated to a residue in *in vacuo* and washed with hexane. The resulting solid was extracted with ethyl acetate. The ethyl acetate solution yielded 1 g of *s*-triazolo[3,4-*b*]benzothiazole (5), mp 174–176°. *Anal.* Calcd for C<sub>8</sub>H<sub>5</sub>N<sub>3</sub>S: C, 54.84; H, 2.88; N, 23.98. Found: C, 53.83; H, 2.90; N, 23.33.

**Registry No.**—1, 2740-81-0; 2 (R = H), 624-84-0; 2 (R = CH<sub>3</sub>), 1068-57-1; 3 (R = H), 52747-49-6; 3 (R = CH<sub>3</sub>), 52747-50-9; 3 (R = C<sub>7</sub>H<sub>15</sub>), 52747-51-0; 4 (R = H), 52747-52-1; 5 (R = H), 247-92-7; 6,

52747-53-2; 7, 52747-54-3; 8, 52747-55-4; 9, 52747-56-5; 10, 52747-57-6; 11, 52747-58-7; 12, 52747-59-8; 13, 41814-60-2; 14, 52747-60-1; 15, 52747-61-2; 16, 52747-62-3; 17, 52747-63-4; 18, 52747-64-5; 19, 52747-65-6; 20, 52747-66-7; 21, 52747-67-8; 22, 52747-68-9; 23, 52747-69-0; 1-acetyl-4-(2-chloro-5-methylphenyl)-3-thiosemicarbazide, 52768-72-6; 2-chloro-5-methylphenyl isothiocyanate, 52747-70-3; 4-(2-fluorophenyl)-1-formyl-3-thiosemicarbazide, 52747-71-4; potassium 4-(2-chlorophenyl)-1,2,4-triazole-3-thiolate, 52747-72-5; 1-acetyl-4-(3-chloro-4-methylphenyl)-3-thiosemicarbazide, 52747-76-9; 1-acetyl-4-(2-chloro-4-methylphenyl)-3-thiosemicarbazide, 52747-73-6; 1-acetyl-4-(2,6-dichlorophenyl)-3-thiosemicarbazide, 52747-77-0; 1-acetyl-4-(2-chloro-5-trifluoromethylphenyl)-3-thiosemicarbazide, 52747-74-7; 1-acetyl-4-(2,5-dichlorophenyl)-3-thiosemicarbazide, 52747-75-8; 1-acetyl-4-(2,4-dichlorophenyl)-3-thiosemicarbazide, 52795-85-4.

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## Studies on the Isomerization of 4-(1-Aziridinyl)quinazolines to 2,3-Dihydroimidazo[1,2-*c*]quinazolines

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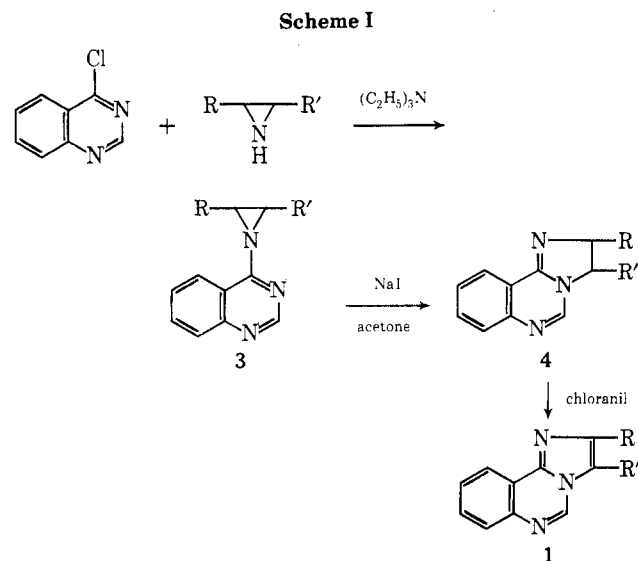
Received April 17, 1974

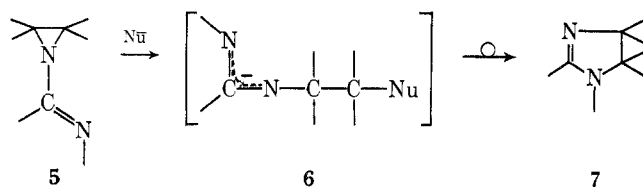
The iodide ion catalyzed isomerization of several 4-(1-aziridinyl)quinazolines to 2,3-dihydroimidazo[1,2-*c*]quinazolines has been investigated in relation to the stereochemical outcome of the reaction. The rearrangement of *cis*- and *trans*-2,3-disubstituted aziridines is quite stereoselective; the selectivity is greater when the aziridine ring is disubstituted with methyl rather than phenyl groups. In any case the stereoselectivity of the isomerization varies with the iodide ion concentration. Oxidation of 2,3-dihydroimidazo[1,2-*c*]quinazolines with chloranil yields good amounts of imidazo[1,2-*c*]quinazoline and its derivatives.

The imidazo[1,2-*c*]quinazoline ring system (1) has been little explored and only a few derivatives are described in the chemical literature.<sup>1-6</sup> Two of us have recently reported a synthesis of 1 based on the manganese dioxide oxidation of the 5,6-dihydroimidazo[1,2-*c*]quinazoline (2) obtained in low yield by treatment of 2-(*o*-nitrophenyl)-1-hydroxyimidazole 3-oxide with zinc powder and formic acid.<sup>7</sup>

This paper describes a novel three-step synthetic route to 1 by chloranil oxidation of 2,3-dihydroimidazo[1,2-*c*]quinazoline (4), which is easily prepared by iodide ion catalyzed isomerization of 4-(1-aziridinyl)quinazoline (3) (Scheme I).

Through the isomerization of suitable aziridines, a wide variety of five-membered heterocyclic ring compounds is obtained.<sup>8</sup> While the rearrangement of *N*-acylaziridines to the isomeric 2-aryl- or 2-alkyl- $\Delta^2$ -oxazoline ring system by some nucleophilic ions has been the subject of a number of studies,<sup>8a,9</sup> the opposite is true for the nucleophile-catalyzed isomerization of aziridine derivatives such as 5, which, probably through the intermediate ambident anion



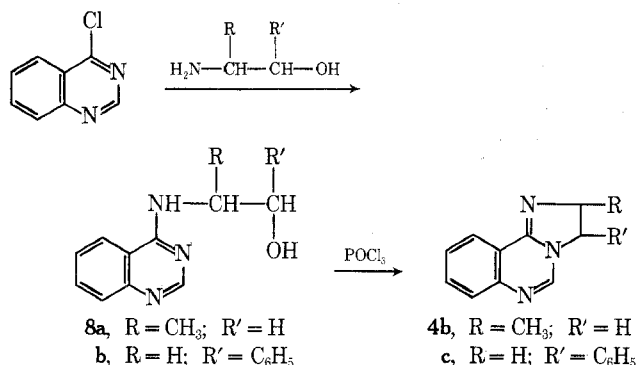


6, gives  $\Delta^2$ -imidazolines (7).<sup>8a</sup> For this reason we have investigated, also from a steric standpoint, the iodide-catalyzed isomerization of 3 to 4.

### Results and Discussion

In Table I are listed the 4-(1-aziridinyl)quinazolines (3) selected for this study which were prepared by the reaction of the appropriate aziridine with 4-chloroquinazoline. The isomerization of 4-(1-aziridinyl)quinazoline (3a) with sodium iodide in refluxing acetone gave 2,3-dihydroimidazo[1,2-*c*]quinazoline (4a) in nearly quantitative yields. The structure of compound 4a was confirmed by comparison with an authentic sample prepared through a different route;<sup>3</sup> 4a was converted into imidazo[1,2-*c*]quinazoline by chloranil oxidation in boiling xylene.

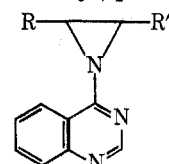
The monosubstituted aziridines 3b,c were also isomerized to 2,3-dihydroimidazo[1,2-*c*]quinazolines. However, while 3b is converted into 2-methyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4b), 3c gives 3-phenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4c), indicating a different site of the initial nucleophilic attack. Similar differences in the orientation of products from the nucleophilic attack of the 2-phenylaziridines had been already observed by other authors.<sup>10</sup> The structures of compounds 4b and 4c were determined by comparison with authentic samples obtained by a different synthetic route. By reaction with 2-amino-propanol and 1-phenyl-2-aminoethanol, 4-chloroquinazoline yields the amino alcohols 8a and 8b which were converted into 2,3-dihydroimidazo[1,2-*c*]quinazolines (4b,c) on reaction with  $\text{POCl}_3$  in chloroform.



Like 4a, compounds 4b,c were converted into imidazo[1,2-*c*]quinazolines (1b,c) by chloranil oxidation.

The rearrangement products of *cis*- and *trans*-dimethylaziridine (3d,e) were a mixture of the two geometric isomers, 4d and 4e, which were separated by chromatography on a silica gel column. The assignment of the configuration with respect to the 2,3-methyl groups is based on the comparison between the chemical shifts at the 2 and 3 positions. The 2- and 3-methyl groups in the compounds 4d,e absorb at  $\sim 0.06$  ppm higher field in the *cis* compound than in the corresponding *trans* isomer. On the other hand, the 2- and 3-methine protons absorb at  $\sim 0.6$  ppm lower field in *cis*-2,3-dimethyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4d) than in the *trans* isomer 4e. This effect is due to the diamagnetic anisotropy of the C-methyl bond and is found in many *cis*-*trans* isomer pairs of five-membered ring compounds.<sup>8c,11</sup> In this case we have not been able to apply the criterion frequently used for the assignment of the *cis* or

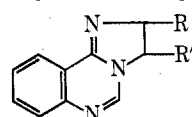
Table I  
4-(1-Aziridinyl)quinazolines



Compd	Time, hr	Stereo-chemistry	R	R'	Yield, %	$n_D^{20}$
3a <sup>c</sup>	15		H	H		
3b	6		CH <sub>3</sub>	H	91	1.6000 <sup>a</sup>
3c	12		C <sub>6</sub> H <sub>5</sub>	H	52	1.6058 <sup>a</sup>
3d	12	Cis	CH <sub>3</sub>	CH <sub>3</sub>	83	1.5950 <sup>a</sup>
3e	12	Trans	CH <sub>3</sub>	CH <sub>3</sub>	85	1.5842 <sup>a</sup>
3f	720	Cis	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	25	b

<sup>a</sup> Undistillable oil. <sup>b</sup> Solid (mp 114–116° from *n*-hexane). <sup>c</sup> Reference 17.

Table II  
Substituted 2,3-Dihydroimidazo[1,2-*c*]quinazolines<sup>a</sup>



Compd	Time, hr	Stereo-chemistry	R	R'	Yield, %	Mp, °C
4a	1		H	H	89	62–63 <sup>b</sup> (EtOAc)
4b	3		CH <sub>3</sub>	H	92	57–59 (EtOAc)
4c	3		H	C <sub>6</sub> H <sub>5</sub>	96	118–120 (EtOAc)
4d	16 (from 3d)	Cis	CH <sub>3</sub>	CH <sub>3</sub>	94	85–87 (EtOAc)
	12 (from 3e)				4	
4e	16 (from 3e)	Trans	CH <sub>3</sub>	CH <sub>3</sub>	96	47–49 (EtOAc)
	12 (from 3d)				6	
4f	24 (from 3f)	Cis	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	68	157–158 (EtOAc)
4g	24 (from 3f)	Trans	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	32	110–111 ( <i>n</i> -hexane)

<sup>a</sup> A mole ratio iodide-aziridine 1.0:1 was used. <sup>b</sup> This compound after drying on  $\text{P}_2\text{O}_5$  melts at 121–122°, lit.<sup>3</sup> 119–123°.

*trans* configuration based on the 2-H, 3-H coupling constant<sup>11</sup> since in compounds 4d,e the complex multiplet pattern of the 2- and 3-methine protons prevents evaluation of the coupling constant. The structure of compounds 4d,e was confirmed by their conversion into 2,3-dimethylimidazo[1,2-*c*]quinazoline (1d) by chloranil oxidation.

As apparent from the yields reported in Table II, the isomerization of the isomeric aziridines 3d,e occurs with similar stereoselectivity. We have ascertained that the *cis*:*trans*-2,3-dimethyldihydroimidazo[1,2-*c*]quinazoline ratio is affected by a change in the iodide ion concentration. The stereoselectivity increases and becomes nearly total only at very low concentration of nucleophile (mole ratio iodide/aziridine <0.1:1); in the case of *trans*-dimethylaziridine a greater degree of stereoselectivity was observed.

In order to determine whether the type of substituents on the aziridine ring influences the stereoselectivity of the

reaction, we investigated the isomerization of the *cis*- and *trans*-4-[1-(2,3-diphenyl)aziridinyl]quinazoline. Unfortunately, while the *cis* isomer **3f** was obtained in poor yield from the *cis*-2,3-diphenylaziridine according to Scheme I, the *trans*-2,3-diphenylaziridine did not react at all since in the reaction medium it decomposed before reacting with 4-chloroquinazoline.

The isomerization of **3f** with iodide ion also gave mixtures of the two geometric isomers (**4f,g**), which were separated by column chromatography. The assignment of the *cis* or *trans* configurations is based on the comparison between the 2-H, 3-H coupling constants. *trans*-2,3-Diphenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (**4g**) showed protons 2-H and 3-H as doublets ( $J = 6.8$  Hz) centered at  $\tau$  4.72 and 4.92. In the *cis* isomer **4f** the 2-H and 3-H protons appear as doublets ( $J = 8.5$  Hz) centered at  $\tau$  4.24 and 4.34. In the five-membered ring, which cannot deviate appreciably from planarity, *cis* proton coupling is generally larger than *trans* proton coupling.<sup>11,12</sup> The observed difference in chemical shift of 2-H and 3-H protons and of phenyl groups protons (see Supplementary Material) in the two isomers can be attributed to the shielding effect of the phenyl groups. The structure of compounds **4f,g** was confirmed by their conversion into 2,3-diphenylimidazo[1,2-*c*]quinazoline (**1e**) by chloranil oxidation.

As can be seen from the yields reported in Table II the isomerization reaction of the *cis* isomer **3f** has a lower stereoselectivity; however in this case also the stereoselectivity increases as the concentration of nucleophile decreases.

The results of the isomerization of the compounds **3d,f** agree with those obtained by Foglia, *et al.*, relative to the isomerization of *cis*- and *trans*-*N*-acyl-2,3-disubstituted aziridines to  $\Delta^2$ -oxazolines and can be rationalized on the basis of a mechanism similar to that proposed by these authors.<sup>9</sup> The different ratio of *cis*:*trans* isomers formed with different iodide ion concentrations can be attributed to an alternative reaction pathway, more probable at high concentrations of catalyst, for the *threo* and *erythro* intermediates. This alternative reaction consists in an identity reaction (SN2) with another iodide ion to give the corresponding diastereoisomer, which can cyclize to the isomeric 2,3-dihydroimidazo[1,2-*c*]quinazoline.<sup>9,13</sup> The low stereoselectivity in the *cis*-2,3-diphenylaziridine isomerization can be attributed to the greater facility for the *threo* intermediate, a benzylic halide, to undergo the identity reaction.<sup>14</sup>

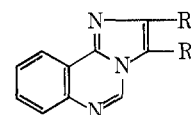
### Experimental Section

**General Procedures.** All the melting points were determined with a Büchi apparatus, and are uncorrected. Nmr spectra were taken with a Varian NV-14 spectrometer. Chemical shifts are reported as  $\tau$  (parts per million) relative to tetramethylsilane (TMS). Unless otherwise stated deuterated chloroform was used as a solvent. In reporting nmr data the following abbreviations are used: s = singlet, d = doublet, dd = double of doublet, t = triplet, m = multiplet. Infrared spectra were obtained on a Perkin Elmer Model 257 spectrophotometer. Uv spectra were obtained with a Unicam SP 800 spectrophotometer. Silica gel GF<sub>254</sub> (Merck) was used for thin-layer chromatography.

**Preparation of Aziridines.** 2-Phenylaziridine, *cis*- and *trans*-dimethylaziridines, and *cis*- and *trans*-diphenylaziridines were synthesized by the  $\beta$ -iodo azides route.<sup>15,16</sup> On the basis of nmr and ir spectra, the isomer aziridines were >99% stereochemically pure.

**Preparation of 4-(1-Aziridinyl)quinazolines (3a-f).** **General Procedure.** To a solution of 4-chloroquinazoline<sup>3</sup> (0.05 mol) and triethylamine (0.08 mol) in 100 ml of benzene was added a solution of aziridine (0.10 mol) in 30 ml of benzene at 0°. The reaction mixture was stirred at room temperature for several hours, then the triethylamine hydrochloride was filtered. The benzene filtrate was evaporated and the residue was chromatographed on a silica gel column eluting with ethyl acetate. In the case of **3f** the compound was eluted with a mixture of benzene-ethyl acetate 80:20; evapora-

**Table III**  
Imidazo[1,2-*c*]quinazoline



Compd	Time, hr	R	R'	Yield, %	Mp, °C (solvent of crystallization)
1a <sup>a</sup>	3	H	H	87	
1b	3	CH <sub>3</sub>	H	78	160–162 (EtOAc)
1c	4	H	C <sub>6</sub> H <sub>5</sub>	56	169–171 (CH <sub>2</sub> Cl <sub>2</sub> )
1d <sup>a</sup>	3	CH <sub>3</sub>	CH <sub>3</sub>	83	
1e	3	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	91	165–167 (EtOAc)

<sup>a</sup> Reference 7.

tion of the third eluate gave a residue which was crystallized from *n*-hexane.

**2,3-Dihydroimidazo[1,2-*c*]quinazolines (4a-c).** A solution of 4-(1-aziridinyl)quinazoline (**3a-c**, 12 mmol) and sodium iodide (12 mmol) in 50 ml of dry acetone was heated at reflux for several hr. The solvent was removed *in vacuo*, and the residue was extracted between water and ethyl acetate. Removal of the organic solvent yielded a residue which was chromatographed on a silica gel column eluting with a mixture of ethyl acetate-methanol (70:30 for **4a,b** and 92:8 for **4c**) (see Table II and the Supplementary Material).

***cis*- and *trans*-2,3-Dimethyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4d and 4e).** A solution of *cis*- or *trans*-4-[1-(2,3-dimethyl)aziridinyl]quinazoline (**3d,e**) in acetone was isomerized with sodium iodide in the manner previously described for **3a-c**. Removal of ethyl acetate yielded a residue which was chromatographed on a silica gel column with a mixture of ethyl acetate-methanol, 90:10. The faster eluting component was identified as *trans*-2,3-dimethyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (**4e**) on the basis of its nmr spectrum.

The slower eluting component was identified as *cis*-2,3-dimethyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (**4d**) by a method similar to the one for the *trans* isomer (see Discussion, Table II, and the Supplementary Material).

***cis*- and *trans*-2,3-Diphenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4f and 4g).** The crude product obtained by isomerization of *cis*-4-[1-(2,3-diphenyl)aziridinyl]quinazoline (**3f**) was chromatographed on a silica gel column. Elution with a mixture of benzene-ethyl acetate, 50:50, gave a first eluate containing a compound which was identified as *trans*-2,3-diphenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (**4g**) on the basis of its nmr spectrum. The slower eluting component was identified as *cis*-2,3-diphenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (**4f**) using a method similar to the one for the *cis* isomer (see Discussion, Table II, and the Supplementary Material).

**Imidazo[1,2-*c*]quinazolines (1a-e).** A solution of 2,3-dihydroimidazo[1,2-*c*]quinazoline (**4a-g**) (5,3 mmol) and chloranil (11.0 mmol) in 400 ml of xylene was heated at reflux for several hours. The solution was extracted several times with diluted NaOH solution until the aqueous extract became colorless. The chloroform was then washed with water and dried with potassium carbonate. After evaporation of the solvent a solid was obtained which was crystallized by a suitable solvent (see Table III).

**4-(1-Hydroxymethylethylamino)quinazoline (8a).** To a solution of 4-chloroquinazoline (68 mmol) and triethylamine (0.1 mol) in 130 ml of dry benzene was added dropwise at 0°, with stirring, a solution of 2-aminopropanol in 40 ml of benzene. After the mixture stood at room temperature for 24 hr, the solid formed was filtered, taken up in water, and filtered again. The solid crystallized from water melts at 160–161° (yield 87%); ir (Nujol) band at 3260 cm<sup>-1</sup> (OH,NH). *Anal.* Calcd for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.13; H, 6.53; N, 20.73.

**4-(2-Hydroxy-2-phenylethylamino)quinazoline (8b).** This compound was prepared from 4-chloroquinazoline and 1-phenyl-2-aminoethanol in 76% yield using the same method as for compound **8a**. The solid obtained, crystallized from methanol-water, melts at 220–222°; ir (Nujol) band at 3225 cm<sup>-1</sup> (OH,NH). *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>H<sub>3</sub>O: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.56; H, 5.88; N, 16.06.

**2-Methyl- and 3-Phenyl-2,3-dihydroimidazo[1,2-*c*]quinazoline (4b and 4c) from 8a and 8b.** A solution of 14.2 mmol of **8a** or

**8b**) in 28 ml of POCl<sub>3</sub> was heated at reflux for 1 hr. Evaporation of the POCl<sub>3</sub> gave a residue which was taken up with iced water; after alkalization with diluted Na<sub>2</sub>CO<sub>3</sub> the oil which separated was extracted several times with ethyl acetate. Removal of the solvent yielded a residue which was crystallized from ethyl acetate-*n*-hexane (**4b**) or ether (**4c**).

**Acknowledgment.** We thank the Italian National Research Council (C.N.R. ROME) for financial support of this research and Professor M. Cardellini for helpful discussions.

**Registry No.**—**1a**, 234-72-0; **1b**, 52747-78-1; **1c**, 52747-79-2; **1d**, 30391-78-7; **1e**, 52747-80-5; **3a**, 27114-97-2; **3b**, 52747-81-6; **3c**, 52747-82-7; **3d**, 52747-83-8; **3e**, 52747-84-9; **3f**, 52747-85-0; **4a**, 1010-62-4; **4b**, 52747-86-1; **4c**, 52747-87-2; **4d**, 52747-88-3; **4e**, 52747-89-4; **4f**, 52747-90-7; **4g**, 52747-91-8; **8a**, 52747-92-9; **8b**, 52747-93-0; 4-chloroquinazoline, 5190-68-1; aziridine, 151-56-4; 2-phenylaziridine, 1499-00-9; *cis*-2,3-dimethylaziridine, 930-19-8; *trans*-2,3-dimethylaziridine, 930-20-1; *cis*-2,3-diphenylaziridine, 1605-06-7; 2-methylaziridine, 75-55-8; 2-aminopropanol, 78-91-1; 1-phenyl-2-aminoethanol, 7568-93-6.

**Supplementary Material Available.** Analytical data for compounds **1b,c,e**, **3b-f**, and **4a-g**, nmr data for compounds **1b,c,e** and **4a-c**, and uv data for compounds **1b,c,e** and **4a-f** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24X reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036.

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## Quinuclidine Chemistry. I. Configuration and Chemistry of 2-Substituted Benzylidene-3-quinuclidinones

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Received July 23, 1973

The base-catalyzed condensation of 3-quinuclidinone with several aromatic aldehydes which gives rise to 2-benzylidene-3-quinuclidinones as single geometrical isomers (kinetic products) is discussed. These isomers rapidly isomerize with HCl in CHCl<sub>3</sub> to the hydrochloride salts of the other geometrical isomers and in the case of 2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone the isomerization is quantitative. The latter also spontaneously isomerizes to the thermodynamic isomer. The configuration of these isomeric 2-benzylidene-3-quinuclidinones was determined from nmr shift reagent [Eu(DPM)<sub>3</sub>] studies and the kinetic products were shown to have the *Z* configuration. Reduction of (*E*)-2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone with NaBH<sub>4</sub> gave a crystalline allylic alcohol which, by catalytic hydrogenation, gave predominantly *trans*-2-(3,4,5-trimethoxybenzyl)-3-quinuclidinol. Aluminum isopropoxide reduction of 2-(3,4,5-trimethoxybenzyl)-3-quinuclidinone under nonequilibrating conditions gave exclusively the *cis* alcohol. Reduction of the same ketone with sodium and isopropyl alcohol gave predominantly *trans*-2-(3,5-dimethoxybenzyl)-3-quinuclidinol, the 4-methoxy group being removed in the process. The *cis*-2-(3,5-dimethoxybenzyl)-3-quinuclidinol was formed by reduction of 2-(3,5-dimethoxybenzyl)-3-quinuclidinone with aluminum isopropoxide under nonequilibrating conditions.

In the course of our work with quinuclidines as medicinal agents we required 2-substituted benzylidene-3-quinuclidinones as intermediates. These ketones were prepared by condensation of aromatic aldehydes with 3-quinuclidinone under base catalysis.<sup>1-3</sup> We wish to report on the nature of this condensation, the configurational assignment of several benzylidenequinuclidinones, and some of the reactions which they undergo.

The reaction of 3-quinuclidinone with 3,4,5-trimethoxybenzaldehyde gave a single isomer, (*Z*)-2-(3,4,5-trimethoxybenzylidene)-3-quinuclidinone (**1**) (see Chart I). The configuration of **1** was established by nmr using a lanthanide shift reagent (discussion to follow) and was confirmed by correlation with an X-ray crystallographic determination<sup>4</sup> of (*Z*)-2-*p*-bromobenzylidene-3-quinuclidinone (**3**). When

a chloroform solution of **1** was treated with hydrogen chloride a facile isomerization occurred to give the hydrochloride salt of **2**, complete isomerization being indicated by a single vinyl proton resonance in the nmr spectrum. Such an isomerization by an acid is easily rationalized as proceeding through a carbonium ion and is indicative of a product formed by a kinetically controlled process isomerizing to the thermodynamically more stable form. Treatment of this salt with base gave **2** which contained 6% **1** (by nmr) as a result of base-induced reverse isomerization and exhibited a vinyl proton resonance at  $\delta$  7.10 compared with 6.93 for **1**. That **1** is the kinetic product was verified by observing its spontaneous isomerization to **2**, using nmr. After 68 hr at room temperature there was no evidence of further change with 12.5% **1** and 87.5% **2** being present. This isom-