# Synthesis of Arylaziridines[1]

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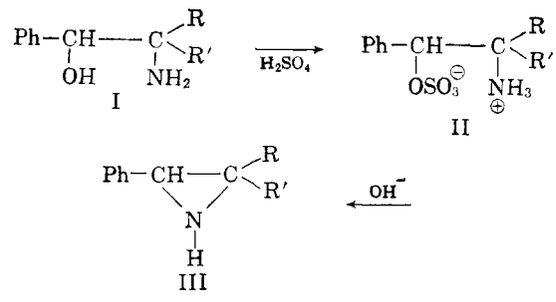
Contrary to several reports in the chemical literature, the Wenker method has been successfully employed in the synthesis of 1- and 2-arylaziridines. Thus, four typical 1-phenyl-2-amino-1-alkanols and 2-anilinoethanol were readily esterified with sulfuric acid in quantitative yields. Cyclization of the intermediary sulfate esters with alkali gave the desired phenyl-substituted ethylenimines which were assayed for purity by gas chromatography and characterized by n.m.r. and infrared spectroscopy. The n.m.r. data for 2-phenylaziridine (styrenimine) and styrene oxide strongly suggest that *geminal* couplings in three-membered heterocycles depend not only on angular factors but also on the heteroatom.

In conjunction with a chemical radioprotection study, a convenient synthetic route to 1- and 2-phenylaziridines was sought. Although several methods for preparing ethylenimines are available,[3] the Gabriel[4] and the Wenker[5] procedures are particularly suitable for preparing both the 1- and 2-substituted imines. A preference for the Wenker method was based primarily on convenience and the excellent yields of alkylaziridines previously[6] obtained *via* this synthetic pathway.

The chemical literature[7] however, discloses that the Wenker method is not applicable to the preparation of aryl-substituted aziridines (ethylenimines). These reports[7] indicate that aryl-substituted amino alcohols (I) fail to undergo esterification with sulfuric acid, but instead, are dehydrated to the corresponding vinylamine derivatives. This generally accepted idea appears to be based on the work of Krabbe and Schmidt[8] which demonstrated that 1,1-diphenyl-2-amino-1-ethanol was readily dehydrated by cold, concentrated sulfuric acid to form 2,2-diphenylvinylamine[9] in approximately 60% yield. On the other hand, earlier reports[10] indicated that treatment of arylcarbinols with cold sulfuric acid gave benzyl sulfate esters. In view of the latter studies, it seemed plausible that, under suitable conditions, the sulfate esters of 1-phenyl-2-amino-1-alkanols could be formed[11] with sulfuric acid and then cyclized to the desired phenylaziridines.

## Results and Discussion

In contrast to previous reports,[7] it was found that the 1-phenyl-2-amino-1-alkanols, Ia–Id, were converted to the sulfate esters in excellent yields by heating equimolar solutions of the amino alcohols




a. R = R′=H; b. R = H, R′=Me;
c. R = H, R′ = Et; d. R = R′ = Me

and sulfuric acid under reduced pressure and at temperatures not exceeding 130°. Incomplete esterification occurred when lower temperatures were used. The sulfate esters were cyclized to the

(1) A preliminary account of this work appeared in the USAF Radiation Laboratory Quarterly Progress Report No. 32, The University of Chicago, July 15, 1959, p. 81. Presented before the Division of Organic Chemistry at the 142nd Meeting of the American Chemical Society, Atlantic City, New Jersey, September 13, 1962.

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(3) J. S. Fruton in "Heterocyclic Compounds," Vol. I, edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 2.

(4) S. Gabriel, *Ber.*, **21**, 1049 (1888); S. Gabriel and C. F. Hirsch, *ibid.*, **29**, 2747 (1896); S. Gabriel and R. Stelzner, *ibid.*, **28**, 2929 (1895).

(5) (a) H. Wenker, *J. Am. Chem. Soc.*, **57**, 2328 (1935); (b) P. A. Leighton, W. A. Perkins, and M. L. Renquist, *ibid.*, **69**, 1540 (1947).

(6) S. J. Brois, Ph.D. thesis, University of Chicago, 1960.

(7) (a) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, New York, N. Y., 1953, p. 729; (b) V. Migrdichian, "Organic Synthesis," Reinhold Publishing Corp., New York, N. Y., 1955, p. 475; (c) Ref. 3, Vol. I, p. 63; (d) K. N. Campbell, B. K. Campbell, J. F. McKenna, and E. P. Chaput, *J. Org. Chem.*, **8**, 103 (1943).

(8) W. Krabbe and K. H. Schmidt, *Ber.*, **72**, 381 (1939).

(9) Recent work [B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956)] discloses that the alleged "2,2-diphenylvinylamine" (m.p. 142° after recrystallization) reported by Krabbe and Schmidt[8] [see also W. Krabbe, A. Seher, and E. Polzin, *Ber.*, **74**, 1892 (1941)] is an erroneous formulation. Witkop noted that 2,2-diphenylvinylamine was unstable in solution and tautomerized to diphenylacetaldimine (m.p. 89°, C=N at 6.01 μ). Since the latter aldimine (m.p. 89°) and the alleged "2,2-diphenylvinylamine" (m.p. 142°) obviously differ, the actual structure of the dehydration product obtained by Krabbe and Schmidt[8] remains in doubt.

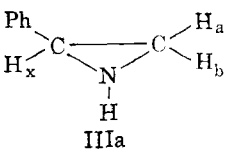
(10) E. Schmidt, *Arch. Pharm.*, **252**, 89 (1914); H. Emde, *Helv. Chim. Acta*, **12**, 399 (1929).

(11) It should be noted that sulfate esters of aryl-substituted amino alcohols have been prepared by other sulfation techniques. For example, 1-phenyl-2-amino-1-ethyl sulfuric acid is formed by the action of silver sulfate on 2-phenyl-2-chloroethylamine [F. Wolfheim, *Ber.*, **47**, 1440 (1914)]. Moreover, the reaction of 1-phenyl-2-methylamino-1-propanol (VII) with chlorosulfonic acid was reported [T. Taguchi and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **7**, 103 (1959)] to give the "supposed" O-sulfate ester. According to Taguchi and Kojima, treatment of the alleged sulfate ester of VII with aqueous potassium hydroxide followed by picric acid, afforded the picrate of 1,2-dimethyl-3-phenylaziridine.

aziridines by treatment with hot, aqueous sodium hydroxide.

The infrared spectra of the 2-phenylaziridines disclose an N—H stretching frequency at 3200 cm.$^{-1}$, an absorption which appears to be very characteristic for a wide spectrum of alkyl-substituted ethylenimines.[6,12] Other prominent absorption bands for IIIa–IIId are presented in the Experimental.

The n.m.r. spectrum of 2-phenylaziridine (styrenimine) in chloroform discloses an unsymmetrical three spin (abx)[13] system where the absolute $J$ values are $J_{ax}$ (*trans*) = 3.1, $J_{bx}$ (*cis*) = 6.0, and

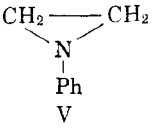


IIIa

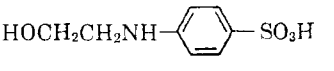
$J_{ab}$ (*geminal*) = 0.6 c.p.s. The assignment of peaks is based on the assumption that $J_{cis} > J_{trans}$ by analogy with styrene oxide,[14] the oxygen analog of styrenimine (IIIa). Of particular interest are the $J_{geminal}$ values observed for styrenimine and styrene oxide. According to valence-bond theory,[14a] the *geminal* coupling constant is a sensitive function of the HCH angle and changes in this angle should be reflected in the value of $J_{geminal}$. Thus, if one assumes that the HCH angles in styrenimine and styrene oxide are essentially equivalent[15] then the *geminal* couplings in these molecules should be very similar in magnitude. In fact, the $J_{geminal}$ values of 0.6 c.p.s. for styrenimine and 5.65 c.p.s.[14b] for styrene oxide differ considerably and indicate that *geminal* couplings in three-membered heterocycles depend not only on angular factors but also on the heteroatom. Complete details of the n.m.r. studies concerning couplings in three-membered heterocycles will appear in a future publication.

Diamagnetic shifts between 0.3–0.4 p.p.m. were observed for the resonances of ring and methyl protons *cis* to the adjacent phenyl group[16] in IIIa, IIIb, and IIId. Accordingly, two methyl resonances at 8.98 and 9.34 $\tau$ are observed in the n.m.r. spectrum of 2,2-dimethyl-3-phenylaziridine (IIId). Moreover, in the proton spectrum of IIIb, the double methyl proton signals at 9.47 and 9.17 $\tau$ were assignable to the *cis* and *trans* forms of this molecule. The *cis/trans* isomer ratio of 1:1.25 estimated from the relative signal intensities was in good agreement with the gas chromatographic analysis. Because the methyl and methylene proton resonances in the n.m.r. of 2-phenyl-3-ethylaziridine (IIIc) overlapped, no firm conclusion about the *cis/trans* isomer distribution could be drawn. The gas chromatogram of IIIc however, does indicate a 1:2 isomer ratio. The n.m.r. and infrared spectral studies (see Experimental for details) conclusively support the structures assigned to IIIa–IIId.

A previous publication[17] claimed that treatment of 2-anilinoethanol (IV) with sulfuric acid followed by strong alkali, gave N-(2-hydroxyethyl)sulfanilic acid (VI) in place of the desired 1-phenylaziridine (V). In contrast we found that V was obtained from IV in high yield *via* the typical Wenker procedure.



V



VI

The n.m.r. spectrum of V disclosed two resonance signals corresponding to phenyl (multiplet at 3.44 $\tau$) and ring (sharp singlet at 8.58 $\tau$) protons in the expected ratio.

In summary, the present study demonstrates conclusively that 1- and 2-arylaziridines can be conveniently prepared *via* the Wenker method.

## Experimental[18]

**Amino Alcohols.**—Samples of 1-phenyl-2-amino-1-ethanol (Ia), 1-phenyl-2-amino-1-propanol (Ib), 1-phenyl-2-amino-1-butanol (Ic), and 1-phenyl-2-amino-2-methyl-1-propanol (Id) were provided by the Commercial Solvents Corp., Terre Haute, Indiana. The 2-anilinoethanol (IV) was purchased from Distillation Products Industries, Rochester, New York, and used without further purification.

**2-Phenylaziridine (IIIa).**—An aqueous solution of one-half mole of Ia was neutralized to a methyl red end point with 50% aqueous sulfuric acid, followed by addition of an equal volume of acid solution. Water was removed by heating the solution at 10–15 mm., finally at 130°. The product crystallized and was coarsely ground and heated at 120–130° under reduced pressure to constant weight. Completion of the reaction was demonstrated by loss of the calculated weight of water to give a quantitative yield of product. An aqueous solution of the sulfate IIa was neutral to methyl red.

The conversion of the sulfate ester, 1-phenyl-2-amino-1-

(12) G. L. Closs and S. J. Brois, *J. Am. Chem. Soc.*, **82**, 6068 (1960).
(13) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *ibid.*, **79**, 4596 (1957).
(14) (a) H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959); (b) C. A. Reilly and J. D. Swalen, *ibid.*, **32**, 1378 (1960).
(15) This assumption is based on the fact that the HCH angles in both ethylenimine and ethylene oxide are equal within a fraction of a degree [See ref. 14a and F. S. Mortimer, *J. Mol. Spectroscopy*, **5**, 199 (1960)].
(16) Recent work shows that the resonance of a proton *cis* to the vicinal phenyl group in 1,2-diphenylcyclopropanes is also diamagnetically shifted [D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind.* (London), 1205 (1958)].
(17) K. Furukawa, S. Yamanaka, and R. Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **54**, 664 (1951).
(18) Boiling points are uncorrected. Infrared spectra of neat liquid samples were determined with a Perkin-Elmer Model 21 spectrophotometer with sodium chloride optics. The n.m.r. spectra were run at room temperature employing a Varian Model A-60 spectrometer. External tetramethylsilane was used as reference for neat liquid samples and chemical shifts are given on the "tau" ($\tau$) scale [G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)]. Gas chromatographic analyses were obtained with an F&M Scientific Corp. Model 500 linear programmed temperature gas chromatograph. Microanalyses were performed by William Saschek, the University of Chicago, and Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

ethyl sulfate, to IIIa was carried out by dissolving one-half mole of IIa in 1 l. of 2 *N* sodium hydroxide at 0°, and then slowly heating the resulting solution in an oil bath. At approximately 90°, the imine product separated from solution as an upper layer. The basic material was steam distilled into a cooled receiver until a fresh portion of the distillate gave a neutral reaction. The imine product was separated and dried over potassium hydroxide pellets.

Fractional distillation through a 24-in. Podbielniak tantulum spiral column afforded a 90% yield of the desired 2-phenylethylenimine, b.p. 94–95° (10 mm.), $n^{20}D$ 1.5588. Gas chromatographic analysis of IIIa through a 10-ft. column packed with 20% Carbowax 20M revealed a single peak.

In addition to phenyl (multiplet at 2.80 $\tau$) and imine (sharp singlet at 8.86 $\tau$) protons in 5:1 ratio, the n.m.r. spectrum of 2-phenylaziridine shows an unsymmetrical three-spin (abx) system in which the a, b, and x multiplets are centered at 8.52, 8.14, and 7.34 $\tau$, respectively. Careful measurements indicate that the absolute $J$ values in the abx spectrum ($CHCl_3$) are $J_{ax}$ (*trans*) = 3.1 ± 0.1, $J_{bx}$ (*cis*) = 6.0 ± 0.1, and $J_{ab}$ (*geminal*) = 0.6 ± 0.05 c.p.s. The x-proton multiplet exhibited as expected, splittings corresponding to $J_{ax}$ (*trans*) and $J_{bx}$ (*cis*). The infrared spectrum of IIIa disclosed prominent absorption bands at 3200, 3008, 2970, 1604, 1495, 1467, 1452, 1398, 1227, 1198, 1090, 1068, 1027, 925, 863, 750, and 695 cm.$^{-1}$.

*Anal.* Calcd. for $C_8H_9N$: C, 80.62; H, 7.61; N, 11.76. Found: C, 80.75; H, 7.79; N, 11.50.

**2-Phenyl-3-methylaziridine (IIIb).**—In the same manner, 0.1 mole of Ib was quantitatively esterified with sulfuric acid. Ring closure of the inner salt, 1-phenyl-2-amino-1-propyl sulfate, was accomplished with 4 equivalents of aqueous sodium hydroxide. Repeated fractional distillation of the basic product gave an 84% yield of IIIb, b.p. 96–97° (10 mm.), $n^{20}D$ 1.5455. Gas chromatography shows two slightly overlapping peaks which correspond to a 45:55 mixture of *cis*/*trans* isomers.

The proton spectrum of IIIb discloses phenyl (multiplet centered at 3.22 $\tau$), imine (7.86 $\tau$), ring (broad resonances at 7.38 and 8.38 $\tau$) and methyl (two doublets at 9.17 and 9.47 $\tau$) protons signals in the expected ratio of 5:1:2:3. The *cis* (9.47 $\tau$) and *trans* (9.17 $\tau$) methyl resonances (each split by the $\beta$-ring hydrogen, $J$ = 5.4 c.p.s.) show relative signal intensities of 1:1.25, respectively. The infrared spectrum of pure IIIb exhibits prominent bands at 3200, 2950, 1600, 1495, 1453, 1420, 1380, 1343, 1218, 1073, 1029, 985, 835, 732, and 695 cm.$^{-1}$.

*Anal.* Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.33; N, 10.51. Found: C, 81.30; H, 8.37; N, 10.41.

**2-Phenyl-3-ethylaziridine (IIIc).**—In precisely the same manner, 0.1 mole of Ic was quantitatively converted to 1-phenyl-2-amino-1-butyl sulfate. The inner salt ester (IIc) was not characterized but directly cyclized with concentrated alkali. Fractional distillation of the dried material gave an 88% yield of the desired ethylenimine analog (IIIc), b.p. 107–108° (10 mm.), $n^{20}D$ 1.5352. Two partially overlapping peaks in the gas chromatogram indicates that IIIc contains *cis*/*trans* isomers in a 1:2 ratio.

Phenyl (3.10 $\tau$), imino (7.74 $\tau$) and ring (broad bands centered at 7.25 and 8.40 $\tau$) hydrogens in a 5:1:2 ratio were observed in the proton spectrum of IIIc. The methyl and methylene resonance signals were not sufficiently resolved to permit accurate chemical shift and intensity measurements. Characteristic infrared bands for IIIc appeared at 3200, 2930, 1600, 1495, 1455, 1380, 1310, 1208, 1073, 1032, 840, 730, and 692 cm.$^{-1}$.

*Anal.* Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.69; H, 8.99; N, 9.64.

**2,2-Dimethyl-3-phenylaziridine (IIId).**—The conversion of 0.1 mole of Id to the corresponding sulfate ester (IId) proceeded in quantitative yields. The inner salt ester, 1-phenyl-2-amino-2-methyl-1-propyl sulfate, was treated with excess alkali solution to induce cyclization. Fractional distillation of the basic product afforded an 83% yield of the imine, b.p. 92–93° (10 mm.), $n^{20}D$ 1.5285. Gas chromatographic analysis showed that IIId was homogeneous.

Resonances assignable to phenyl (multiplet centered at 3.02 $\tau$), $\alpha$-ring (sharp singlet at 7.37 $\tau$) and methyl (two sharp peaks of equal intensity at 8.98 and 9.34 $\tau$) protons in the ratio of 5:1:6 were readily discernable in the n.m.r. spectrum of IIId. Prominent bands in the infrared appear at 3200, 3000, 2922, 1600, 1495, 1452, 1380, 1278, 1073, 1026, 788, and 698 cm.$^{-1}$.

*Anal.* Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.54; H, 9.04; N, 9.71.

**1-Phenylaziridine (V).**—Treatment of 0.1 mole of 2-anilinoethanol (IV) with sulfuric acid afforded the desired 2-anilinoethyl sulfate in excellent yield. Cyclization of the inner salt ester was accomplished with 4 equivalents of aqueous sodium hydroxide. Steam distillation of the product was avoided since it was found that prolonged heating with water produced, at the expense of V, a dimeric product, *viz.* N,N'-diphenylpiperazine. Therefore, the upper imine layer was taken up in ether and mechanically separated from the reaction mixture. Distillation of the dried product gave an 81% yield of the N-phenyl-substituted imine, b.p. 71–72° (10 mm.), $n^{20}D$ 1.5538 [lit.,[19] b.p. 70–70.5 (13 mm.), $n^{20}D$ 1.5524].

The proton spectrum of V showed only two resonance signals corresponding to phenyl (multiplet centered at 3.44 $\tau$) and ring (sharp singlet at 8.58 $\tau$) protons in a 5:4 ratio. Prominent infrared bands appeared at 3000, 2960, 1593, 1490, 1314, 1158, 1075, 1023, 895, 755, and 688 cm.$^{-1}$.

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(19) H. W. Heine, B. L. Kapur, and C. S. Mitch, *J. Am. Chem. Soc.*, **76**, 1173 (1954).