Chromosorb W. The amounts of bromobenzene produced in the reactions with bromotrichloromethane were determined gas chromatographically with another portion of the reaction mixture weighed out with *t*-butylbenzene as the internal standard using a 12 ft by 1/4 in. column packed with 15% Ucon polar on acid washed Chromosorb W. In the carbon tetrachloride reactions, the amount of chlorobenzene produced was determined in a similar manner using *m*-chlorotoluene as the internal standard.

A 10^{-3} to 10^{-4} *M* solution of galvinoxyl in N,N-dimethylformamide was prepared. To ~5 ml of this solution in a test tube was added 3 drops of bromotrichloromethane and 3 drops of phenylhydrazine, and the tube immediately stoppered and placed in a dark cabinet. Within 3 min the color of the galvinoxyl had disappeared. Similar treatment of 5 ml of the galvinoxyl solution with 5 drops of bromotrichloromethane yielded a solution in which the characteristic color of galvinoxyl was present after 30 min but had disappeared when allowed to stand overnight. Treatment of 5 ml of the galvinoxyl solution with 5 drops of phenylhydrazine gave a solution in which the purple color of galvinoxyl persisted after being allowed to stand overnight.

Rate Determinations.—Solutions of bromotrichloromethane in N,N-dimethylformamide were placed in a three necked, round bottomed flask. The reaction flask was connected through a condenser and to a gas buret. After thoroughly flushing the system with nitrogen for 20 min, a solution of phenylhydrazine in N,N-dimethylformamide was added to the bromotrichloromethane solution. The flask was immediately immersed in a constant temperature oil bath. After a 5 min induction period the reading on the gas buret was taken as the initial reading of the gas in the system. The volume of nitrogen produced was read periodically from the gas buret, and the extent of reaction was calculated from the amount of nitrogen produced. In the case of the light-induced reaction, a 270-W G.E. sun lamp was employed as the source of the radiation, and the flask was thermostated in a water bath.

Determination of Relative Reactivities of Bromotrichloromethane and Carbon Tetrachloride toward Benzoyl Peroxide.—A mixture consisting of benzoyl peroxide (0.1634 g, 0.7 mmol), bromotrichloromethane (1.3220 g, 6.7 mmol), and carbon tetrachloride (20.52 g, 133.40 mmol) was evenly divided and placed in two Pyrex tubes. The tubes were then sealed and immersed in a constant temperature oil bath at 79.5° for 21 hr. The reaction mixtures were analyzed by glpc using an 8 ft × 1/4 in. column packed with 12% diethylene glycol succinate on Chromosorb P using *m*-chlorotoluene as the internal standard for the glpc determinations of the amounts of bromobenzene and chlorobenzene formed in the reaction. Two runs were carried out, and the ratios of bromobenzene to chlorobenzene found were 12.17 and 10.86 indicating reactivity ratios of $BrCCl_3$ with respect to CCl_4 toward phenyl radicals of 244 and 217, respectively.

Determination of Relative Reactivities of Bromotrichloromethane and Carbon Tetrachloride toward Phenylhydrazine.—A mixture consisting of phenylhydrazine (0.4365 g, 4.00 mmol), bromotrichloromethane (1.9830 g, 10.00 mmol), and carbon tetrachloride (30.77 g, 200.00 mmol) was evenly divided and placed in three Pyrex tubes. The same procedure and method of analysis as described above were followed. The relative reactivity ratios of $BrCCl_3$ with regard to CCl_4 toward attack by phenyldiimide, as determined from the relative amounts of the halobenzenes, were 132, 123, and 123 for the three separate runs.

Registry No.—Phenylhydrazine, 100-63-0; bromotrichloromethane, 75-62-7; carbon tetrachloride, 56-23-5; benzoyl peroxide, 94-36-0; bromobenzene, 108-86-1; chlorobenzene, 108-90-7.

Effects of Hydrogen-Bond Formation by Phenols on the Conformational Equilibrium of *trans*-1,2-Dimethyl-3-isopropylaziridine[1,2]

ROBERT L. VANETTEN AND JOHN J. DOLHUN[3]

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received May 2, 1968

The conformational equilibrium for inversion about nitrogen of *trans*-1,2-dimethyl-3-isopropylaziridine in cyclopentane was studied as a function of temperature in the presence and absence of equimolar substituted phenols. Hydrogen-bond formation is shown to occur between the amine and the phenols. The inversional equilibrium is shifted by the presence of phenols, and these shifts are particularly pronounced at low temperature or in the presence of a highly bulky phenol. The shifts are attributed to stereoselective hydrogen-bond formation between the phenol and the less stable invertomer.

Solvent effects on conformational equilibria are a matter of considerable interest when attempting to compare physical and chemical properties obtained under different conditions. Extensive work by Eliel and his colleagues clearly established that the conformational energy of amino and of hydroxyl groups differs in protic and aprotic solvents.[4,5] This seemed to us to be a most significant result because of the implication that a hydrogen-bond interaction could markedly change the conformational equilibrium of a molecular system. We have been interested in examining cases based on relatively simple molecular systems in which conformational equilibria are significantly shifted as the result of complexation phenomena. Such a system would thus constitute a model for the introduction of conformational strain energy in a substrate such as might occur in an enzyme–substrate complex.

It appeared that the conformational equilibrium of *trans*-1,2-dimethyl-3-isopropylaziridine[6] (**1**), shown in Scheme I, might be affected by the presence of hydrogen-bond donors such as alcohols or phenols. This follows from the fact that in conformer **1a** the potential donor would experience greater steric repulsion (as shown in **2a**) than would a hydrogen-bonding reagent interacting with conformer **1b** (as shown in **2b**). The result of such a preferential hydrogen-bonding interaction would be to lead to a net stabilization of conformer **1b** and consequently a shift in K_{eq}. The hydrogen-bonded conformers shown in **2a** and **2b** represent only one form present in an effectively infinite distribution of hydrogen-bonded species, and our hypothesis requires that such forms constitute an experimentally observable proportion of the average

(1) This investigation was supported in part by a Frederick Gardner Cottrell grant from the Research Corporation and by Public Health Service Research Grant No. CA-10585 from the National Cancer Institute.

(2) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31–April 5, 1968.

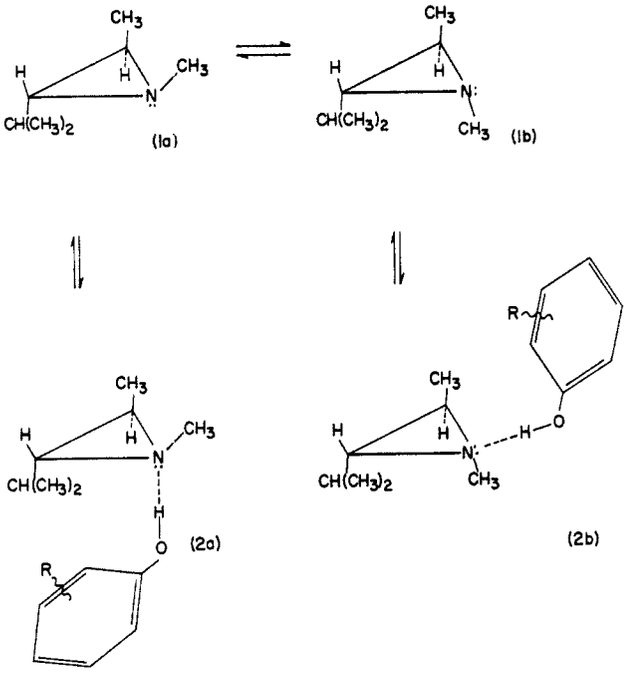
(3) National Science Foundation Undergraduate Research Participant, 1967.

(4) E. L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(5) E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Lett.*, 831 (1963); E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).

(6) A. T. Bottini, R. L. VanEtten, and A. J. Davidson, *ibid.*, **87**, 755 (1965).

SCHEME I



molecular population. To test this hypothesis we have examined the conformation equilibrium K_{eq} ([**1a**]/[**1b**]) of *trans*-1,2-dimethyl-3-isopropylaziridine in the presence of a variety of substituted phenols using cyclopentane as an effectively inert solvent.

Results and Discussion

As predicted, the presence of phenols in cyclopentane solutions of *trans*-1,2-dimethyl-3-isopropylaziridine cause marked changes in the conformational equilibrium of the aziridine (Table I). The aziridine alone in cyclopentane exhibits nearly the same K_{eq} values (Table I) as those observed for the case of chloroform solutions.[6] However, the addition of equimolar phenol causes the value of K_{eq} to change from 4.1 to 2.1 (at $-60°$). An even larger change is noted in the case of more bulky phenols such as the *t*-butylphenols, which change the value of K_{eq} to 1.6 (at $-60°$).

The effects of added phenols on K_{eq} are much less pronounced at elevated temperatures. In agreement with a previous report,[6] K_{eq} for the aziridine is observed to decrease with increasing temperature corresponding to a small positive enthalpy change (+0.24 kcal/mol) for the conversion **1a** → **1b**. However, in the presence of a phenol there is noted a reversal of this temperature dependence (Table I). Clearly, a transformation having a much larger enthalpy change must be occurring in the case of the phenol–aziridine mixtures so as to reverse the temperature dependence of K_{eq}. This process is almost certainly the increasing dissociation of a hydrogen-bonded complex as the temperature is raised.

The formation of *t*-amine–phenol hydrogen-bonded complexes is known[7-10] to be an exothermic process

TABLE I

CONFORMATION EQUILIBRIUM OF *trans*-1,2-DIMETHYL-3-ISOPROPYLAZIRIDINE IN CYCLOPENTANE SOLVENT WITH ADDED PHENOLS[a,b]

	K_{eq} at various temperatures, °C					
Phenol	−60	−40	−20	0.0	20	40
None	4.1	4.0	4.0	3.8	3.5	—
Phenol	2.1	2.4	3.1	3.1	3.2	3.3
o-*t*-Butylphenol	1.6	2.0	2.8	3.0	3.1	3.2
m-*t*-Butylphenol	1.6	2.1	2.9	3.0	3.0	3.1
p-*t*-Butylphenol	—	2.0	2.8	2.9	2.9	3.1
2,6-Di-*t*-butylphenol	—	—	—	1.6	2.5	—
o-Phenylphenol	—	1.7		2.0		2.5
m-Phenylphenol	—	—	—	2.3	2.4	2.4
p-Phenylphenol	—	—	—	2.3	2.5	2.7
o-Bromophenol	1.5	1.7	2.7	3.0	3.0	3.5
m-Bromophenol	1.6	2.0	2.4	2.4	2.6	2.7
p-Bromophenol	1.6	2.1	2.4	2.8	2.9	3.0

[a] The aziridine and the phenols were present as 1 *M* solutions in cyclopentane. [b] The values of K_{eq} were calculated by graphical integration of the areas under the two N-methyl bands and are reproducible to ±0.2 units. A dash indicates that the two bands overlapped too much to permit accurate graphical integration.

with $\Delta H°$ typically ranging from −4 to −8 kcal/mol. For example, the thermodynamic parameters accompanying hydrogen-bond formation between phenol and triethylamine in cyclohexane solution are[7] $\Delta G°$ = −2.6 kcal/mol, $\Delta H°$ = −5.8 kcal/mol, and $\Delta S°$ = −10 cal/mol/deg. This is consistent with the present observations in that hydrogen-bond formation is expected to be increasingly favored at lower temperature and the greatest changes in K_{eq} produced by added phenols occur at lower temperature.

These results cannot be satisfactorily explained as due to ion-pair formation caused by complete proton transfer to the amine. The pK'_a of the aziridine is 9.2 ± 0.1 as determined titrimetrically in aqueous solution. The dissociation constant of the protonated amine would not be expected to differ greatly in an organic solvent.[11,12] On the other hand, the pK_a of phenol changes from 10.0 in water[13] to 12.8 in 95% ethanol,[14] and should be even further increased in cyclopentane solution. Accepting that the pK_a's of phenol and the aziridine must differ by more than three pK units it follows that proton transfer from phenol to the amine is negligible. This point can be given further support by noting that 2,6-di-*t*-butylphenol would be expected to have a pK_a at least two pK units greater[15] than phenol. This effect together with that caused by the different solvent would mean that the amine and 2,6-di-*t*-butylphenol have pK_a's differing by over five orders of magnitude. Since the effects of this phenol on the conformational equilibrium must be produced by hydrogen-bond formation rather than ion-pair formation, it appears reasonable to ascribe all the effects apparent in Table I to hydrogen bonding.[16]

More direct proof of the importance of hydrogen bonding in this experimental system has been obtained

(7) R. L. Denyer, A. Gilchrist, J. A. Pegg, J. Smith, T. E. Tomlinson, and L. E. Sutton, *J. Chem. Soc.*, 3889 (1955).
(8) D. Neerinck and L. Lamberts, *Bull. Soc. Chim. Belges*, **75**, 473 (1966), and references cited therein.
(9) S. Singh, A. S. N. Murthy, and C. N. R. Rao, *Trans. Faraday Soc.*, **62**, 1056 (1966).
(10) T. D. Epley and R. S. Drago, *J. Amer. Chem. Soc.*, **89**, 5770 (1967).
(11) B. Gutbezahl and E. Grunwald, *ibid.*, **75**, 559 (1953).
(12) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).
(13) E. F. Herington and W. Kynaston, *Trans. Faraday Soc.*, **53**, 138 (1957); A. I. Briggs, *ibid.*, **52**, 35 (1956).
(14) G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **22**, 360 (1939).
(15) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).
(16) It should be pointed out that more highly acidic phenols such as *p*-nitrophenol or 2,4-dinitrophenol would be expected to protonate the amine; *cf. Chem. Abstr.*, **68**, 78114, 87131 (1968).

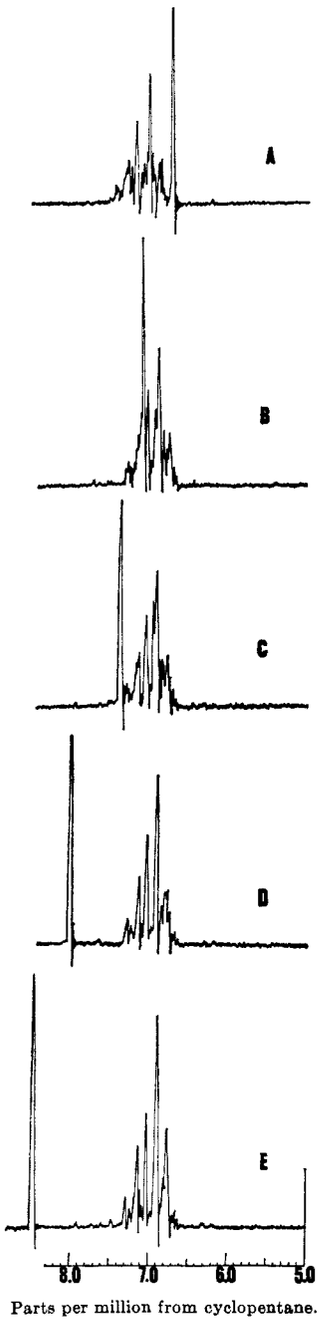


Figure 1.—The 60-Mc nmr spectrum of 1 M phenol in cyclopentane as a function of added *trans*-1,2-dimethyl-3-isopropylaziridine concentration: A, no amine; B, 0.05 M; C, 0.10 M; D, 0.20 M; E, 0.40 M amine. All spectra were recorded at 35°.

by examining the chemical shift dependence of the phenolic hydroxyl resonance as a function of aziridine concentration. In Figure 1 is shown the nmr spectrum of phenol in the presence of increasing concentrations of *trans*-1,2-dimethyl-3-isopropylaziridine. The hydroxyl resonance is superimposed on those of the aromatic hydrogens when the phenol is present as a 1 M solution in cyclopentane. However, the addition of increasing amounts of the tertiary amine causes a marked downfield shift in the hydroxyl resonance, an observation readily explained by hydrogen-bond formation.[17-19]

(17) U. Liddel and N. F. Ramsey, *J. Chem. Phys.*, **19**, 1608 (1951).
(18) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, pp 143–153.
(19) D. P. Eyman and R. S. Drago, *J. Amer. Chem. Soc.*, **89**, 1617 (1966).

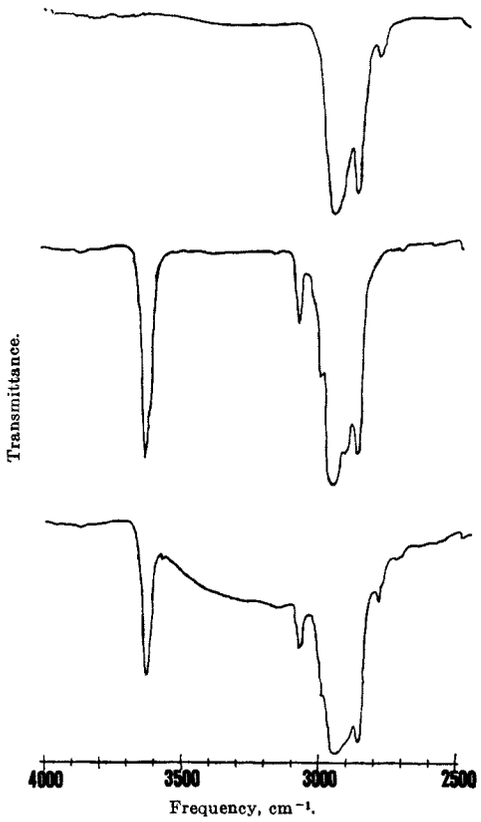


Figure 2.—Infrared spectra of cyclopentane solutions of *trans*-1,2-dimethyl-3-isopropylazirdine (top), 2,6-di-*t*-butylphenol (center), and an equimolar mixture of the two compounds (bottom).

Further evidence establishing the importance of hydrogen-bond formation in this experimental system was obtained by examination of the ir spectra of cyclopentane solutions of 2,6-di-*t*-butylphenol, the aziridine, and of an equimolar mixture of the amine and the phenol in cyclopentane. Figure 2 shows portions of the ir spectrum of these compounds in cyclopentane. The appearance of a single, relatively sharp band at about 3620 cm^{-1} due to the hydroxyl stretching of 2,6-di-*t*-butylphenol (Figure 2, center) is consistent with the fact that this compound is known to undergo no significant amount of self-association.[20-24] However, when an equimolar amount of *trans*-1,2-dimethyl-3-isopropylaziridine is present in the cyclopentane solution of the phenol, it may be seen that the intensity of the unbonded hydroxyl stretching absorption at 3620 cm^{-1} is significantly reduced (Figure 2, bottom) and there is a new broad absorption centered in the region of 3200 to 3300 cm^{-1}. This new absorption band has an integrated intensity some 20 times larger than the free phenolic hydroxyl stretching band. This increase in intensity is qualitatively consistent with observations made by Barrow[25] for the case of hydrogen-bond formation between triethylamine and a variety of alcohols.[26] For the case of *n*-butyl alcohol

(20) N. D. Coggeshall, *ibid.*, **69**, 1620 (1947).
(21) W. C. Sears and L. J. Kitchen, *ibid.*, **71**, 4110 (1949).
(22) B. G. Somers and H. S. Gutowsky, *ibid.*, **85**, 3065 (1965).
(23) F. Takahashi and N. C. Li, *J. Phys. Chem.*, **69**, 1612 (1965).
(24) S. Singh and C. N. R. Rao, *ibid.*, **71**, 1074 (1967).
(25) G. M. Barrow, *ibid.*, **59**, 1129 (1955).
(26) The appearance of a similar broad band centered at 3300 cm^{-1} has been noted in carbon tetrachloride solutions of phenol plus excess *p*-methoxybenzene. This absorption was attributed to a phenolic hydroxyl–azo nitrogen hydrogen-bonded species: E. Osawa, T. Kato, and Z.-I. Yoshida, *J. Org. Chem.*, **32**, 2803 (1967).

plus triethylamine in carbon tetrachloride he found that the hydroxyl stretching frequency was shifted to 3240 cm^{-1} by hydrogen-bond formation and the integrated intensity of the new band was approximately seven times larger.

From Table I it may be seen that 2,6-di-*t*-butylphenol causes the largest effect on K_{eq}. From the corresponding values of K_{eq} in the presence and absence of the phenol we may calculate that $\Delta G°$ for the conformational equilibrium is shifted by 0.5 kcal at 0°. The relatively large effect with this phenol is presumably due to the presence of the two bulky *t*-butyl groups which accentuate the steric effects of hydrogen-bond formation. A complicating factor which precludes a more quantitative interpretation of some of these data is the fact that certain of the phenols undergo self-association at these concentrations.[27] However, 2,6-di-*t*-butylphenol does not undergo self-association to any significant extent.[20-24] Thus, the changes in K_{eq} apparent in Table I should be considered to be minimal changes, although it might be argued that the numerical similarity of K_{eq} values at −60° in the presence of the substituted phenols implies that phenol–amine hydrogen-bond formation is essentially complete at this temperature and steric effects due to substituents on monosubstituted phenols are not very important. Presumably the phenol can rotate so as to minimize steric interference between the phenol substituents and the aziridine; this is not possible with 2,6-di-*t*-butylphenol.

Phenols cause significant changes in the inversional equilibria of *trans*-1,2-dimethyl-3-isopropylaziridine, and both ir and nmr spectroscopy provide evidence for the involvement of hydrogen bonds in causing the changes in K_{eq}. The free-energy difference between the conformational equilibrium in the presence and absence of equimolar phenols corresponds to as much as 0.5 kcal at 0°. This system thus constitutes an unusually direct demonstration of a means by which solvation effects may cause changes in conformational equilibria. Moreover, the present study does not involve changes in bulk solvent. Rae has recently interpreted certain solvent effects on the spectral characteristics of *o*-nitroanilines in terms of the steric effects resulting from changes in hydrogen bonding to the aromatic amino group[28] or nitro group.[29] Such studies suffer from the difficulty of interpreting effects of changes in bulk solvent upon possibly highly solvated solute molecules existing in a possibly highly structured solvent. Similarly, previous work by Eliel[4,5] also involved changes in the bulk solvent, and it is difficult to predict the size of complex hydrogen-bonded clusters of water or alcohol molecules. This is consistent with other results reported recently by Eliel and his colleagues where it was shown that the $-\Delta G°$ value for the hydroxymethyl ($-CH_2OH$) group bonded to a cyclohexane ring was significantly increased in going from cyclohexane to isopropyl or *t*-butyl alcohol.[30] The formation of complex hydrogen-bonded clusters due to self-association of the alcohol solvent molecules in the region of the hydroxymethyl group would of course explain why the solvent dependence of the $-\Delta G°$ value was greater for solvents which simultaneously incorporate hydrogen-bond donating and accepting groups as compared to those solvents (such as dimethoxyethane) which contain only hydrogen-bond accepting groups. The present work clearly establishes that steric effects due to stereoselective hydrogen-bonding interactions can be evidenced even when the bulk solvent properties are not greatly changed. In addition it demonstrates that the "size" of lone pairs will be very much a function of the solvent used in carrying out the measurements.

(27) For a variety of experimental approaches see G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.

(28) I. D. Rae, *Aust. J. Chem.*, **20**, 1173 (1967).

(29) I. D. Rae, *ibid.*, **20**, 2381 (1967).

Experimental Section

Phenols were obtained from Aldrich Chemial Co. and Distillation Products Industries. The *o*- and *m*-*t*-butylphenols were distilled before use, whereas *o*-phenylphenol was recrystallized from petroleum ether (bp 30–60°), *m*-phenylphenol was recrystallized from water, and *p*-phenylphenol was recrystallized from dry ethanol. The other phenols were used as obtained from commercial sources. The melting points and boiling points agreed in all cases with the literature values. The solvent employed in this study was Phillips Research Grade cyclopentane.

The conformational equilibrium of *trans*-1,2-dimethyl-3-isopropylaziridine was determined by means of nmr spectroscopy[6] using a 60-mc spectrometer (Varian Model A-60). The value of K_{eq} was calculated by graphical integration of the bands due to the two N-methyl resonances appearing at about δ 2.4. The two bands in many instances were partially merged. The values reported in Table I were found to be reproducible to ±0.2 unit in independent experiments; the major source of experimental error was the difficulty of carrying out an accurate graphical integration. Dashes in Table I indicates that the two bands overlapped too much to permit accurate integration. The nmr spectra were determined using solutions 1 *M* in aziridine and 1 *M* in phenol unless otherwise specified. The majority of the spectra were obtained using fresh solutions but no changes were noted in the course of 24 hr in the spectra of mixtures of phenols plus the aziridine.

Variable temperature nmr spectra studies were conducted using a Varian Model V-6040 temperature controller calibrated before use using ethylene glycol and methanol standards; temperatures are accurate to ±3°. Infrared spectra were determined at 30° using a Perkin-Elmer Model 421 spectrophotometer and sodium chloride cells.

The pK'_a of *trans*-1,2-dimethyl-3-isopropylaziridine was determined by graphical estimation from the curve obtained by titration of a 1.0 *M* solution of the amine with 0.1 *M* hydrochloric acid. The pH values were determined at 30° using a Corning Model 7 pH meter.

Registry No.—**1**, 17392-77-7; phenol, 108-95-2; *o*-*t*-butylphenol, 88-18-6; *m*-*t*-butylphenol, 585-34-2; *p*-*t*-butylphenol, 98-54-4; 2,6-di-*t*-butylphenol, 128-39-2; *o*-phenylphenol, 90-43-7; *m*-phenylphenol, 580-51-8; *p*-phenylphenol, 92-69-3; *o*-bromophenol, 95-56-7; *m*-bromophenol, 591-20-8; *p*-bromophenol, 106-41-2.

Acknowledgments.—The authors gratefully acknowledge the expert technical assistance of Mr. Jack Barnes.

(30) E. L. Eliel, D. G. Neilson, and E. C. Gilbert, *Chem. Commun.*, 360 (1968).