No. 1, 15096-03-4; No. 2, 15096-04-5; No. 3, 15096-05-6; No. 4, 15096-06-7; No. 5, 2652-91-7; No. 6, 15096-14-7; No. 7, 6134-57-2; No. 8, 15096-16-9.

Acknowledgments.—The authors are indebted to Elizabethtown College for the use of their nmr spectrometer.

Solvent Effects on *cis–trans* Equilibria of Some Aziridine Ketones[1]

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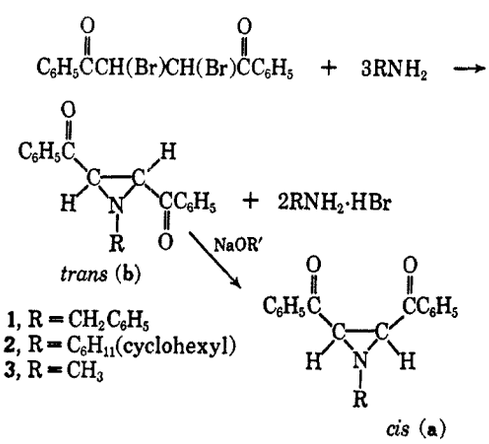
Received August 18, 1967

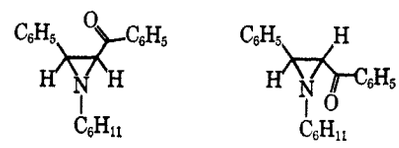
The *cis–trans* isomer ratios of 1-benzyl- and 1-cyclohexyl-2,3-dibenzoylaziridines and 1-cyclohexyl-2-phenyl-3-benzoylaziridine, when equilibrated by base catalysis in seven alcohols and the aprotic solvent dimethyl sulfoxide, have been determined. These equilibria are expressed as constants, K, which range from 5.25 in DMSO to 0.32 in *t*-butyl alcohol and which approximately parallel the dielectric constants of the solvents used. The effects on K of amounts of base and of added salt used are delineated.

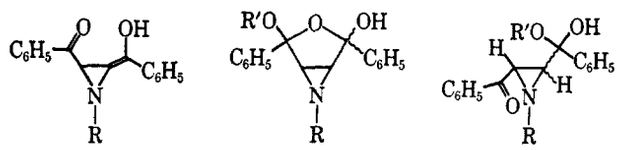
trans-1-Alkyl-2,3-dibenzoylaziridines, **1**, **2**, and **3**, the products of reactions of the primary benzyl-, cyclohexyl-, and methylamines, respectively, with *meso*- and *dl*-dibenzoylethylene dibromides,[2a,b] undergo epimerization upon treatment with strong base in ethanol solution from which the *cis* isomers crystallize exclusively.[2b] *trans*-1-Alkyl-2-aryl-3-aroylaziridines[2b] **4** and



certain *trans*-2-aryl-3-aroyloxiranes[3a] behave similarly. From these data the conclusion has been drawn recently that the *cis*-aziridines are thermodynamically the more stable forms[4] in contrast to the analogous *cis*-dibenzoylcyclopropanes, which unquestionably are the labile forms.[5] However, the actual *cis–trans* stability relationships of the benzoyl aziridines necessary for understanding these phenomena have not been determined and are the subject of this paper.

Our interest in this problem stemmed in part from an earlier study of anomalies in the *cis–trans* stability relations in basic solutions of the dibenzoylstilbenes





5a = anion 6a = anion 7a = anion

where *cis* cyclic dihemiketal and sesquiketal anions similar to **6a** had been believed to be involved.[6] The existence of *cis* cyclic α,β-disubstituted dibenzoylethylene sesquiketals, which are olefin analogs of **6**, has been demonstrated by isolation of unstable compounds of this type in a few instances.[7] Such anions as **6a** might conceivably be formed from dibenzoylaziridines **1**, **2**, and **3** but not from the monobenzoylaziridines **4**.

Results and Discussion

In order to establish the actual *cis–trans* stability relationships, *i.e.*, equilibrium constants, $K = [cis]/[trans]$, the equilibrations of aziridines **1**, **2**, and **4** were carried out using both a trace and a large amount of base. That equilibrations under the various conditions had been achieved in each case was demonstrated by obtaining the same value of K starting both from the pure *cis* isomer and from the pure *trans* isomer, respectively. These equilibrations using seven different alcohols and dimethyl sulfoxide were determined by

(1) Supported by Grant GP-5453 from the National Science Foundation.

(2) (a) R. E. Lutz, T. Amacker, S. M. King, and N. H. Shearer, *J. Org. Chem.*, **15**, 181 (1950). (b) A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, Jr., *J. Am. Chem. Soc.*, **87**, 1050 (1965). (c) A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Letters*, 4369 (1965). (d) N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J. Vanderhorst, F. W. Olson, and J. H. Anglin, Jr., *J. Am. Chem. Soc.*, **73**, 1044 (1951). (e) P. L. Southwick and D. R. Christman, *ibid.*, **74**, 1886 (1952).

(3) (a) N. H. Cromwell and R. A. Setterquist, *ibid.*, **76**, 5752 (1954). (b) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *ibid.*, **75**, 96 (1953). (c) H. O. House and R. S. Ro, *ibid.*, **80**, 2428 (1958).

(4) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967), footnote 6.

(5) (a) G. W. Griffin, E. J. O'Connell, and H. A. Hammond, *ibid.*, **85**, 1001 (1963). (b) W. W. Kastenmeyer, M. S. Thesis, University of Virginia, Charlottesville, Va., 1966. (c) D. W. Boykin, Jr., A. B. Turner, and R. E. Lutz, *Tetrahedron Letters*, 817 (1967).

(6) (a) R. E. Lutz and W. J. Welstead, Jr., *J. Org. Chem.*, **27**, 2763 (1962). (b) An attractive alternative explanation for the effect of increasing base concentrations on this *cis–trans* equilibrium position is a medium effect such as is described below, and further study will be required to elucidate this point.

(7) *E.g.*, (a) *cis* cyclic hydroperoxy sesquiketals of dibenzoylstilbenes: O. W. Ridgon and R. E. Lutz, Abstracts, 18th Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966, p A45. (b) The unstable cyclic sesquiketal of *cis*-1,2-dibenzoyldichloroethylene: E. L. Anderson, M. S. Thesis, University of Virginia, Charlottesville, Va., 1964. (c) *Cf.* also the ready formation of a cyclic diketal from *cis*-dibenzoylstilbene oxide: R. E. Lutz, W. J. Welstead, Jr., R. G. Bass, and J. I. Dale, *J. Org. Chem.*, **27**, 1111 (1962).

quenching the heated solutions and by nmr analysis of the products which had precipitated in quantitative yields. The results are shown in Table I.

TABLE I

BASE-INDUCED *cis–trans* EQUILIBRIUM RATIOS *K* OF SUBSTITUTED AZIRIDINES (0.06 *M*)

Solvent	ϵ[a,b]	Base concentration: 0.00087 *M* *K*	0.00087 *M* % *cis*	0.17 *M* *K*	0.17 *M* % *cis*	Δ[c]
1-Benzyl-2,3-dibenzoylaziridine (1)[d]						
DMSO	48.9	5.25	84	*e*	*e*	
CH_3OH	32.6	1.63	62	3.00	75	13
C_2H_5OH[f]	24.3	0.82	45	1.38	58	13
$CH_3(CH_2)_2OH$	20.1	0.75	43	1.06	52	9
$(CH_3)_2CHOH$	18.3	0.56	36	*g*	*g*	
$CH_3(CH_2)_3OH$	17.1	0.67	40	3.39	77	37
$CH_3(CH_2)_4OH$	13.9	0.46	32	1.02	51	19
$(CH_3)_3COH$	10.9	0.32	24	0.47	32	8
1-Cyclohexyl-2,3-dibenzoylaziridine (2)[d]						
CH_3OH	32.6	1.70	63	4.07	80	17
C_2H_5OH	24.3	0.96	49	2.84	74	25
$CH_3(CH_2)_3OH$	17.1	0.54	35	1.59	61	26
$(CH_3)_3COH$	10.9	0.44	30.5	0.46	31.5	1
1-Cyclohexyl-2-phenyl-3-benzoylaziridine (4)[h]						
C_2H_5OH	24.3	1.85	65	2.45	71	6
$(CH_3)_3COH$	10.9	*e*	*e*	1.32	57	

[a] Dielectric constant of pure alcohol at 25° and of pure dimethyl sulfoxide (DMSO) at 20°. [b] R. C. Weast, Ed., "Handbook of Chemistry and Physics," 46th ed, The Chemical Rubber Co., Cleveland, Ohio, 1965, p E-50; "Dimethyl Sulfoxide Technical Bulletin," Crown Zellerbach Corp., Camas, Wash., 1966, p 2. [c] Increase in per cent of *cis* content using large amount of base relative to trace amount of base. [d] See ref 2b. [e] Decomposition involved. [f] In 93% C_2H_5OH using 0.00087 *M* NaOH solution, K = 1.13; using 0.17 *M* NaOH solution, K = 1.32. [g] New compound; see Experimental Section. [h] See ref 2d, e.

The column of data representing the equilibrations produced by trace amounts of base and long heating shows a strikingly high *cis–trans* species equilibrium ratio for **1a–1b** in DMSO, namely K = 5.25, which progressively decreases to the relatively low value of 0.32 in *t*-butyl alcohol. Generally speaking, cooling these solutions to room temperature, instead of quenching, caused crystallization in 50–60% yields of mixtures of **a** and **b** in ratios which are close to the equilibrium ratios as determined by quenching, and which are close to the ratios of the isomers remaining in the filtrate. These latter ratios represent the solubility ratios of the two isomers in the presence of each other in the reaction medium. In methanol the ratio of the isomers **1a** and **1b** remaining in the filtrate is 1.56 or 61% *cis* isomer, which is in close agreement with the separately determined solubility ratio of **1a** and **1b** in the presence of each other but with no base present, namely [*cis*]/[*trans*] = 1.50 or 60% *cis* isomer. This close agreement of the ratios of the solubilities of the isomers with their equilibrium constant is a new example of a long recognized phenomenon.[8]

The marked decrease in K for the dibenzoylaziridine **1** in the seven alcohols and one aprotic solvent, dimethyl sulfoxide (DMSO), using the trace amounts of base, follows the decrease in the dielectric constants of the eight pure solvents near 25° and at the elevated temperatures, and the presumed concomitant decrease in their solvating abilities. The more polar[2b] *cis*-aziridine is the more stable isomer in the most polar and least sterically hindered alcohol; the reverse is true for the *trans* isomer. The same principles are applicable to the benzoylaziridines **2** and **4**.

Equilibrations of alcoholic solutions of **1a** and **1b** using a large amount of base require only short heating, and upon quenching gave higher values of K than when the trace amount of base had been used. In accord with earlier experiments,[2b] and in contrast to those above, slow cooling, instead of quenching, of the methanol and ethanol solutions equilibrated in this way, gave 50–60% yields of pure *cis* isomer as the solid phase. The solution phase on quenching gave the same value for K as had been determined by quenching the refluxing solutions. Thus the *cis* and *trans* isomers remain in continuous solution equilibrium down to and at room temperature, whereupon the solid phase $\rightleftharpoons$ solution phase equilibrium becomes established upon standing. This is in contrast to *cis–trans* equilibrations by trace amounts of base where the speed is negligibly slow at room temperature. An important conclusion drawn from the above results is that temperature has little effect on K of the solution phase in the range involved.

In two representative experiments the monobenzoylaziridine *cis–trans* pair **4a** and **4b** showed equilibrium positions and solvent effects comparable with those of **1** and **2**.

An explanation was sought for the crystallizing exclusively of the pure *cis* isomer **1a** upon cooling the refluxing solution equilibrated by the large amount of base. When a suspension of equal amounts of both *cis* and *trans* solid isomers **1a** and **1b** in methanol containing the large amount of base was stirred at room temperature for a prolonged period of time, the resulting solid phase was pure *trans* isomer **1b**, not the *cis* isomer **1a**. The value for K of the solution phase again was 3.0, close to the value for the solution equilibration at elevated temperature and in the absence of solid phases **1a** and **1b**. In a separate experiment, pure solid *cis* isomer **1a** was similarly treated with methanol containing the large amount of base at room temperature. The solid phase remained pure *cis* isomer **1a** while the solution phase again had the value of 3.0 for K.

The above results demonstrate that the saturated solution isomer ratio is not dependent upon the composition of the solid phase, but that the final solid phase, pure *cis* or pure *trans* isomer, does depend upon the initial solid phase present. This dependence can be understood by assuming the following: (a) the rate of nucleation is greater for the *cis* than for the *trans* isomer, thus determining product formation when adequate crystalline surface areas of neither isomer are present, and (b) the rate of crystallization is greater for the *trans* isomer than for the *cis*, and this governs the product formation when adequate crystalline surface areas of both isomers are present.

Suspecting that the increase of K when the large amount of base is used is essentially due to a medium effect (*i.e.*, changing the dielectric constant and/or polarity of the medium), sodium chloride and lithium chloride were added in the equilibrations of **1a** and **1b** in ethanol catalyzed by a trace of base. The result was to raise K from 0.82 to 3.0 as is shown in Table II.

(8) (a) O. Dimroth, *Ann.*, **399**, 91 (1913). (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p 89.

TABLE II
VARIATION OF K FOR 1-BENZYL-2,3-DIBENZOYLAZIRIDINE (0.06 M) WITH VARYING BASE AND SALT CONCENTRATIONS IN ETHANOL

Sodium ethoxide, M^{-1}	Salt, M^{-1}	K	% *cis* isomer
0.17	0.00	1.38	58
0.0087	0.00	1.02	51
0.00087	0.00	0.82	45
0.00087	0.0090 NaCl	0.92	48
0.00087	0.20 LiCl	1.51	60
0.00087	2.0 LiCl	3.00	75

This effect is comparable with that of the effect of large amounts of base. Therefore the large amounts of base not only act as catalyst but must also induce a medium effect.

Enolization must be involved in the *cis–trans* interconversion by the action of base, as has been shown by deuterium exchange for the α hydrogens of dypnone oxides[3c] and of certain aroylaziridines.[2c] The possibility was considered that in solutions of the benzoylaziridines containing large amounts of base, the concentration of *cis* species might be enhanced by accumulation of enolate anion of the type **5a**, which would account for the higher value of K. This possibility was excluded by first deuterating **1** and **2** through equilibrations in methanol-d_1 and 1-butanol-d_1. Using these deuterated aziridines in the deuterated solvents in three experiments, no significant proton acquisition at the α carbon was observed upon hydrolytic quenching as would be required if extensive amounts of **5a** had accumulated.

The possibility that the higher value of K caused by the large base concentration was due to accumulation of significant amounts of low-absorbing cyclic sesquiketal or hemiacetal species such as **6**, **7**, and/or their anions was excluded by uv analysis. If such species existed, a diminution in the ϵ_{max} value would have been expected. This was not observed.

The relatively rapid and balanced base-catalyzed equilibrations of the *cis*- and *trans*-benzoylaziridines in the alcohols are in sharp contrast to the relatively slow and extremely unbalanced equilibrations in ethanol of the *cis–trans*-1,2-dibenzoylcyclopropanes and their 3,3-diphenyl derivatives and the 1-phenyl-2-benzoylcyclopropanes, where the *trans* isomers predominate.[5] These differences may be attributed to the effect of the ring nitrogen atom which causes the aziridines to be more polar than the cyclopropanes and therefore better able to participate in solvation and which causes the *cis*-aziridines to be solvated better than the *trans* isomers.

Similar solvent and salt effects on the equilibrium position should be observable in certain analogs such as aroyl oxiranes[3] and aroyl ethylenes[6] where base-catalyzed equilibrations exist. One might expect also to observe such effects in various aroylcyclopropanes[5] but here the equilibria are unbalanced and the effects would not be so easily discernible.

Experimental Section

Nmr spectra were measured in $CDCl_3$ solutions (*ca.* 15% w/v) containing tetramethylsilane (TMS) as internal standard and using a Varian Associates, Model A-60, instrument at 60 Mc, near 33°.

***cis–trans* Equilibrations at Elevated Temperature.**—Equilibrations using 1.0 g (*ca.* 0.003 mole) of 1-benzyl- and 1-cyclohexyl-2,3-dibenzoylaziridines and 1-cyclohexyl-2-phenyl-3-benzoylaziridine[2] were all achieved by approach from both the *cis* and the *trans* isomers, respectively, using 50 ml of the dried solvent with the base (the corresponding sodium alkoxide and potassium *t*-butoxide in DMSO) concentration and added salt concentration indicated in Tables I and II. These solutions were heated to reflux (except for those in 1-propanol, 1-butanol, 1-pentanol, and DMSO which were heated to about 70° using an ethanol bath) for 1 to 2 min for the solutions of the higher base concentration and for 0.5 hr in methanol to 6 hr in DMSO for solutions with the trace concentration of base. These were the ideal times required to achieve the closest approximation to the true equilibria because heating for shorter periods gave a mixture of isomers whose percent composition favored the amount of the starting isomer as compared with the equilibrium value, and because heating for prolonged periods of time caused decomposition to occur. The equilibrated solutions were divided in half; one portion upon cooling to room temperature yielded a precipitate in 50–60% yield, and the other portion upon quenching in water gave a quantitative yield of precipitate. The resulting precipitates in each instance were filtered, air dried, and analyzed by nmr spectroscopy using the integrated values (±5%) of the chemical shifts of the aziridine ring protons (**1a**, δ 3.38 ppm; **1b**, 4.10; **2a**, 3.38; **2b**, 4.07; **4a**, 3.22; **4b**, 3.57).[2b,c] The product composition is shown in Tables I and II. Two of the analyses determined by nmr, when checked by chromatographic separation using Florosil and elution with benzene–ethyl ether, conditions which did not cause epimerization, gave excellent agreement.

Equilibration at Room Temperature.—One half gram each of *cis*- and *trans*-1-benzyl-2,3-dibenzoylaziridine[2b] (**1a** and **1b**) was dissolved in 30 ml of hot absolute methanol, and the mixture was cooled rapidly to room temperature. Absolute methanol (20 ml) containing 0.49 g of sodium methoxide was added and the resulting solution was stirred for 36 hr at which time the solid was filtered (0.43 g) and identified as exclusively the *trans* isomer **1b**. The filtrate was quenched in water, and the resulting precipitate was filtered, air dried, and analyzed by nmr: **1a**, 75%; **1b**, 25%.

The same experiment was repeated using 1.0 g of *cis* isomer **1a** and none of **1b**. The solid phase was exclusively **1a** (0.43 g) and the solution phase by quenching and nmr analysis consisted of **1a**, 75%, and **1b**, 25%.

Treatment with Sodium 2-Propoxide Solution.—One gram of either *cis*- or *trans*-1-benzyl-2,3-dibenzoylaziridine[2b] when treated with 50 ml of 0.17 M sodium 2-propoxide solution gave a new compound, mp 143–144°, which analyzed correctly for $C_{26}H_{23}NO_2$ and is currently under investigation.

Registry No.—**1a**, 980-55-2; **1b**, 15287-85-1; **2a**, 802-60-8; **2b**, 15287-87-3; **4a**, 2211-65-6; **4b**, 15287-88-4.

Acknowledgment.—We wish to thank Dr. Thomas I. Crowell for his helpful discussions.