NH_3ClO_4 gave 33.0 mg (96%) of 98% optically pure D-$C_6H_5CH(CO_2CH_3)NH_2$. When 2.4 M methanolic HCl solution was used, a 95% recovery of 96% optically pure ester was recovered. When 0.1 M methanolic HCl was employed, only a 27% recovery of ester was realized.

An extraction was carried out as in run 10 except that host was absent and the organic phase was 0.45 mole fraction in CD_3CN. The initially used 98% optically pure D-$C_6H_5CH(CO_2H)NH_3ClO_4$ was converted to its ester as in run 10 to give D-$C_6H_5CH(CO_2CH_3)NH_2$ of 98% optically pure material. Esterification of 100 mg of 70% optically pure $C_6H_5CH(CO_2H)NH_3ClO_4$ was carried out as in run 10 to give 62.0 mg (95%) of $C_6H_5CH(CO_2CH_3)NH_2$ of 68% optical purity. When further dried at 0.1 mm at 25 °C for 2, 3, and 12 h, the material volatilized to 59.5, 57.3, and 42.4 mg, respectively. The material finally obtained was 64% optically pure. This experiment suggests that optically active ester is slightly more volatile than racemic, and that the drying period should be minimized.

Procedure B for Determination of Enantiomer Distribution Constants (EDC). The procedure is exemplified by run 8 of Table I. The extraction involved 731.0 mg (0.987 mmol) of (*SS*)-$(CH_3)_2D(OEOEO)_2D$ of maximum rotation dissolved in 5.0 mL of 0.45 mole fraction CD_3CN in $CDCl_3$ (0.2 M solution) and 753.5 mg of racemic $C_6H_5CH(CO_2H)NH_3ClO_4$ dissolved in 3.0 mL of D_2O, 2.0 M in $LiClO_4$. The solutions were shaken at 0 °C and the layers separated as in procedure A. The organic layer aliquot (3.3 mL) was evaporated, and the residue was treated as in procedure A to separate the amino acid perchlorate from host. The final white solid from the lyophilized aqueous extract was dried at 40 °C for 1 h at 0.1 mm to give 135.5 mg of $C_6H_5CH(CO_2H)NH_3ClO_4$ (equivalent of 81.4 mg of free amino acid) which was transferred in its entirety into a 10.0-mL volumetric flask with 5 N aqueous HCl (*c* 0.81) which gave the tabulated rotations and CRF* values and an average CRF* value of 9.3. The procedure for the aqueous layer was identical with procedure A and gave an average CSF value of 1.51 to provide an EDC of 13.9.

λ, nm	α_{obsd}	$[\alpha]^{25}$	$[\alpha]_{max}^{25}$	% ee	CRF*
589	1.100°	135°	168°	80.5	9.3
578	1.143°	140°	175°	80.1	9.1
546	1.317°	162°	201°	80.4	9.2
436	2.372°	291°	362°	80.5	9.3

When the material from the organic layer was recovered and esterified as in procedure A, the average CRF* was 6.84, which gave an EDC of 10.3 (run 7 of Table I). Whenever compared, procedure B always provided a slightly higher EDC value.

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(1) This work was supported by a grant from the National Science Foundation, CHE 72-04616 A04, and by the U.S. Public Health Service, Grant GM-12640 from the Department of Health, Education, and Welfare.
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(9) The authors warmly thank Mr. Paul Cheng for this preparation.
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Catalysis of the Reversible Elimination Reactions of Substituted *N*-(β-Phenylethyl)quinuclidinium Ions in Aqueous Solution[1]

Sergio Alunni† and William P. Jencks*

Contribution No. 1295 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154.

Received August 20, 1979

Abstract: The rate constants for elimination reactions of substituted *N*-(β-*p*-nitrophenylethyl)quinuclidinium ions induced by hydroxide ion in water at 25 °C show only a small sensitivity to the pK_a of the leaving quinuclidine, with $\beta_{lg} = -0.18$. The primary isotope effect is $k_H/k_D = 8.5$ and the secondary solvent isotope effect is $k_{OD}/k_{OH} = 1.55$ for the quinuclidine derivative. The rates of these elimination reactions are comparable to or faster than that of 2-*p*-nitrophenylethyl bromide. The reaction is readily reversible in quinuclidine buffers and the rate constants of the addition reaction to *p*-nitrostyrene show a large dependence on the pK_a of substituted quinuclidines with $\beta_{nuc} = 0.69$; the equilibrium constants in the elimination direction follow $\beta_{eq} = -0.89$. The addition reaction shows general acid catalysis by protonated quinuclidines and the elimination reaction shows general base catalysis, with a Brønsted coefficient of $\beta = 0.68$ for elimination from the diazabicyclooctane derivative. Elimination reactions from the corresponding phenyl compounds are ~10^3 slower and show a more negative value of $\beta_{lg} = -0.35$ in water at 40 °C; in EtONa/EtOH the value of β_{lg} is −0.28. The change in β_{lg} for the phenyl compounds corresponds to a negative structure-reactivity coefficient $p_{yy'} = \partial\beta_{lg}/-\partial\sigma = \partial\rho/-\partial pK_{lg}$, consistent with the expected E2 mechanism for the phenyl compounds. However, it is uncertain whether the *p*-nitrophenyl compounds react by an E2 or an irreversible E1cB mechanism.

We report here a study of the effects of changing structure of the leaving group and the base catalyst for elimination reactions of substituted β-phenylethylammonium salts in aqueous solution. There is evidence that the mechanisms of a number of carbonyl and imine-forming elimination reactions are determined by the lifetimes of intermediates along the reaction coordinate and it would be of interest to know the extent to which this holds also for olefin-forming eliminations.[2-5] It has been shown that a concerted mechanism is enforced by the negligible lifetime of the carbanion "intermediate" in the decomposition of cyclopropanols through a carbonyl-forming elimination reaction[6] and it is likely that a

† On leave from the Department of Chemistry, University of Perugia.

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Table I. General Acid-Base Catalysis for the Addition of Quinuclidine Derivatives to *p*-Nitrostyrene[a]

amine	pK_a[b]	10^4k_H, M^{-1} s^{-1}	k_B, M^{-2} s^{-1}
quinuclidine[c]	11.45	9.7	0.025
3-hydroxyquinuclidine[d]	10.02	0.8	0.0051
1,4-diazabicyclo[2.2.2]octane[e]	9.22	0.37	0.002 19
3-chloroquinuclidine[f]	9.03	0.15	0.001 58

[a] In water at 25 °C, ionic strength 1.0 M (KCl), with buffer ratio [B]/[BH⁺] = 2.5. [b] Determined at ionic strength 1 M and 25 °C (Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963-6970; ref 13). [c] pH 11.91. [d] pH 10.56. [e] pH 9.6. [f] pH 9.5.

similar situation holds for reactions that would generate extremely unstable carbonium ions.[7] Structure-reactivity parameters and their interactions have been utilized extensively to characterize the transition states of elimination reactions[2,8-11] and it appeared useful to approach this problem by examining these reactions in aqueous solution, in order to compare the properties of these transition states to those for carbonyl and imine-forming eliminations.[12-14] In particular, we wished to examine directly the proton-transfer component of the elimination reaction by determining the Brønsted coefficient for general base catalysis.

There is strong evidence, particularly from heavy atom isotope effects, that many elimination reactions in the β-phenylethyl series proceed through a concerted E2 mechanism with a large amount of carbanionic character.[2,10,15,16] These reactions display a wide spectrum of transition-state structures, as shown by changes in isotope effects and structure-reactivity parameters with changing reactant structure.[2,9-11,15] These structure-reactivity interactions provide a method for examining the coupling between different reacting groups in the transition state.[14] We would like to understand better what happens when this spectrum of transition-state structures is extended to stabilize a β-carbanion species and, eventually, to cause a change or "merging" of mechanism to an E1cB mechanism. We have examined reactions of this class in both the elimination and addition directions using a series of substituted quinuclidines as leaving groups and catalysts. This series permits the evaluation of substituent effects for a group of compounds with constant steric effects and the same reacting atoms. Although a change of mechanism has not been established, we find that the structures of the transition states for the *p*-nitrophenyl compounds show little, if any, difference from those expected for an E1cB mechanism.

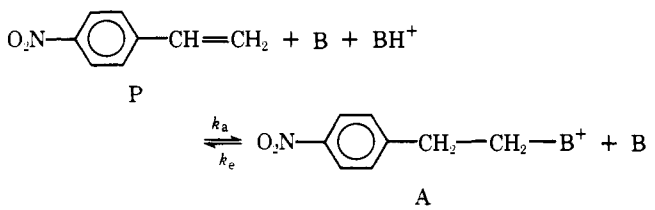
Results

Reversible Addition of Substituted Quinuclidines to *p*-Nitrostyrene. In the presence of buffers prepared from substituted quinuclidines, *p*-nitrostyrene undergoes the reversible addition-elimination reaction with general acid-base catalysis shown in Scheme I. In the presence of a large excess of amine the addition reaction approaches an equilibrium position with the pseudo-first-order rate constant k_{obsd}, which is equal to the sum of the pseudo-first-order rate constants k_a and k_e for the addition and elimination reactions, respectively. The equilibrium position was measured from the absorbance of the remaining *p*-nitrostyrene and the rate constant for addition was determined as described in the Experimental Section. This rate constant, k_a, shows upward curvature in a plot against buffer concentration, indicating that a component of the buffer acts as a catalyst as well as a reactant. The addition reaction can be described by the rate law

$$v = k_H[P][B] + k_{BH}[P][B][BH^+] \quad (1)$$

and a plot of $k_a/[B]$ against $[BH^+]$ gives k_H as the intercept and k_{BH} as the slope, as illustrated in Figure 1 for the reaction with quinuclidine. The rate constants k_H and k_{BH} describe the addition reactions with water and the protonated quinuclidine, respectively, as the proton donors of Scheme I. The rate constants for the reactions of four quinuclidines are reported in Table I.

Scheme I



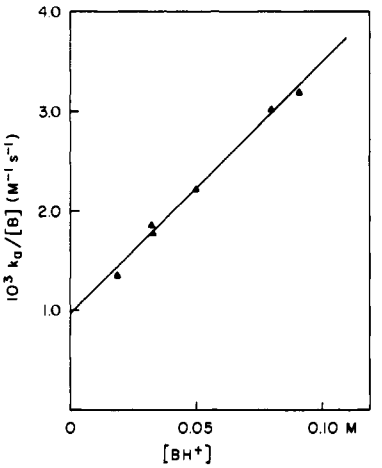


Figure 1. Dependence on the concentration of BH^+ of the second-order rate constants, $k_a/[B]$, for the addition of quinuclidine to *p*-nitrostyrene at 25 °C, ionic strength 1.0 M (KCl).

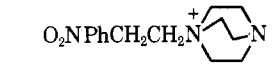
Table II. Rate Constants for the Elimination Reaction of HX from $O_2NPhCH_2CH_2X$ Induced by Potassium Hydroxide[a]

X	10^3k_{OH},[b] M^{-1} s^{-1}	10^3k_{OH},[c] M^{-1} s^{-1}	10^4k_Q, M^{-1} s^{-1}	K_{eq}
quinuclidine	0.86	1.23 0.144[d] 1.90[e]	1.33	0.88
3-hydroxyquinuclidine	1.31	1.29	3.0	16.4
3-chloroquinuclidine	2.17	3.5		145
1,4-diazabicyclo[2.2.2]-octane	2.26	3.5	6.7	122
4-methyl-1,4-diazabi-cyclo[2.2.2]octanium ion bromide	23.8 2.69	36.4 3.47	61.4	

[a] In water at 25 °C, ionic strength 1.0 M (KCl). [b] $[OH^-]$ = 0.08 M. [c] $[OH^-]$ = 0.80 M. [d] For the deuterated compound, *N*-(β-*p*-nitrophenyl-β,β-dideuterioethyl)quinuclidinium ion. [e] Catalyzed by 0.8 M KOD in D_2O.

Rate constants for the elimination reactions induced by hydroxide ion, to form *p*-nitrostyrene, are reported in Table II. The increase in the second-order rate constants with 0.8 M compared with 0.08 M hydroxide ion, at ionic strength 1.0 M, is attributed to a specific salt effect. The absence of an increase with the 3-hydroxyquinuclidine derivative is probably caused by partial ionization of the 3-hydroxyl group in 0.8 M potassium hydroxide to give the less reactive zwitterion; the pK_a of choline is 13.9.[17] For the quinuclidine derivative the deuterium isotope effect, determined with the β-dideuterio compound, is k_H/k_D = 8.5 and the solvent isotope effect in deuterium oxide solution is k_{OD}/k_{OH} = 1.55. The latter value is similar to the value of k_{OD}/k_{OH} = 1.62 for the elimination reaction

Table III. Rate Constants for the Elimination Reaction of i Induced by Four Amines[a]



i

amine	$10^5 k_B$, M^{-1} s^{-1}
quinuclidine	67
3-hydroxyquinuclidine	7.5
3-chloroquinuclidine	1.92
1,4-diazabicyclo[2.2.2]octane	2.22

[a] In water at 25 °C, ionic strength 1.0 M (KCl).

of p-$(CH_3)_3NPhCH_2CH_2N(CH_3)_3^{2+}$ at 60 °C.[11] The second-order rate constant for the elimination reaction from N-(β-p-nitrophenylethyl)quinuclidinium ion induced by 7×10^{-4} M sodium ethoxide in ethanol at 25 °C was found to be 27 M^{-1} s^{-1}.

Rate constants for the elimination reaction, k_e, catalyzed by substituted quinuclidines were determined directly in quinuclidine buffers of increasing concentration at constant pH, as described in the Experimental Section. The reaction is described by the rate law

$$v = k_e[A] = k_{OH}[OH^-][A] + k_Q[B][A] \quad (2)$$

The second-order rate constants k_Q were determined from the slopes of plots of k_e against free amine concentration; the intercepts agreed well with the expected values for the elimination reaction catalyzed by hydroxide ion. Values of k_Q for catalysis by quinuclidine of the elimination reaction from four different N-(β-p-nitrophenylethyl)quinuclidinium derivatives are given in Table II. The rate constants k_B for catalysis by four quinuclidines of the elimination reaction from N-(β-p-nitrophenylethyl)-1,4-diazabicyclo[2.2.2]octanium ion are given in Table III.

Catalysis of elimination from N-(β-p-nitrophenylethyl)-quinuclidinium ion was also observed with buffers of the less basic substituted quinuclidines but rate constants are not reported for this catalysis because of curvature in the plots of k_e against [B] at concentrations >0.1 M, both with and without the correction for the back reaction described in the Experimental Section. It is unlikely that this curvature is caused by complexation with the buffer, because no curvature was observed with quinuclidine buffer nor with the other buffers in the reaction of the 1,4-diazabicyclo[2.2.2]octane derivative. Although a detailed kinetic analysis was not carried out, the curvature was found to be consistent with a change in rate-determining step with increasing buffer concentration to a limiting rate constant of $\sim 4.6 \times 10^{-3}$ M^{-1} s^{-1} for a buffer-independent, hydroxide ion catalyzed reaction of N-(β-p-nitrophenylethyl)quinuclidinium ion; this rate constant is five times larger than the observed rate constant for elimination catalyzed by hydroxide ion in the absence of buffer (Table II).

Equilibrium constants for the elimination reaction, as described by Scheme I from right to left with B = HO^-, were calculated from k_{OH}/k_H using the values of k_{OH} determined at 0.08 M hydroxide ion concentration and are given in Table II.

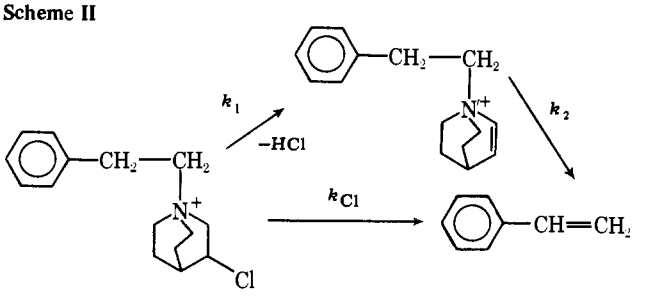
Elimination Reactions from Derivatives of N-(β-Phenylethyl)quinuclidinium Ions and from 2-Phenylethyl Bromide. Rate constants for the elimination reactions with different quinuclidine leaving groups catalyzed by hydroxide ion in water and by ethoxide ion in ethanol at 40 °C are reported in Table IV. The reactions were generally followed by the method of initial rates in water and for the complete reaction as well as by the method of initial rates in ethanol. Good agreement

Table IV. Rate Constants for the Elimination Reactions of HX from $PhCH_2CH_2X$ Induced by KOH (H_2O) or EtONa (EtOH)[a]

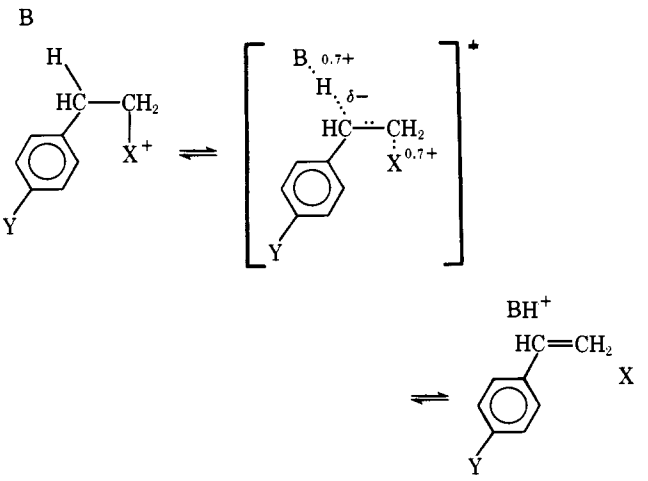
X	$10^8 k_{OH}$,[b] M^{-1} s^{-1}	$10^4 k_{OEt}$,[c] M^{-1} s^{-1}	$10^4 k_{OEt}$,[d] M^{-1} s^{-1}
quinuclidine	4.39	1.47	1.30
1,4-diazabicyclo-[2.2.2]octane	34.7	5.98	5.43
3-chloroquinuclidine	30.9[e]	3.2	6.2[e]
2,3-dehydroquinuclidine	8.35	3.2	2.9
4-methyl-1,4-diazabicyclo-[2.2.2]octane bromide	3700[f]	310	
	30 150[f]		

[a] At 40 °C. In water the ionic strength was maintained at 1.0 M (KCl). [b] The base-solvent system was KOH/H_2O (initial rates 0-1%). [c] The base-solvent system was EtONa/EtOH and the total reaction was followed. [d] The base-solvent system was EtONa/EtOH (initial rates 0-2%). [e] Initial rates 0-0.5%. [f] The total reaction was followed.

Scheme II



Scheme III



was found between the results with the two methods in ethanol except for the 3-chloroquinuclidine compound, which underwent competitive elimination of HCl to give the 2,3-dehydroquinuclidine derivative (Scheme II). The rate constant for the chloro compound was determined by measuring the initial rate of styrene release over 0-0.5% reaction and the rate constant for the dehydro compound was determined from the observed rate constants for the complete reaction course and for the isolated compound, which was prepared from the chloro derivative (Table IV).

Discussion

The observed elimination-addition reactions may be described according to Scheme III. The transition state for a concerted E2 mechanism is shown; the transition state for a stepwise irreversible E1cB mechanism would be the same but without C-X bond cleavage. The numbers indicate the approximate "effective charges" on the catalyzing base and the leaving group in the transition state, based on the observed effects of polar substituents on the reaction rate. In the elimi-

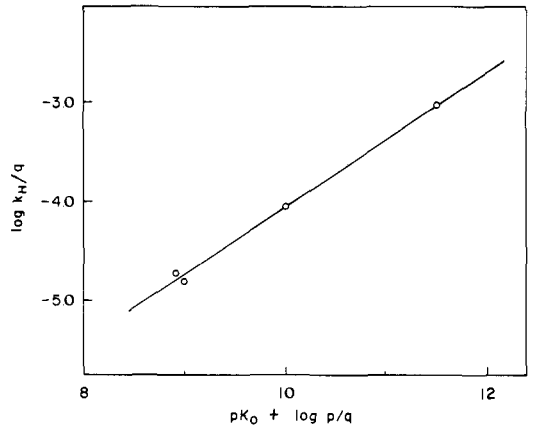


Figure 2. Dependence of the rate constant k_H for the addition of substituted quinuclidines to *p*-nitrostyrene on the pK_a of the quinuclidine at 25 °C, ionic strength 1.0 M (KCl).

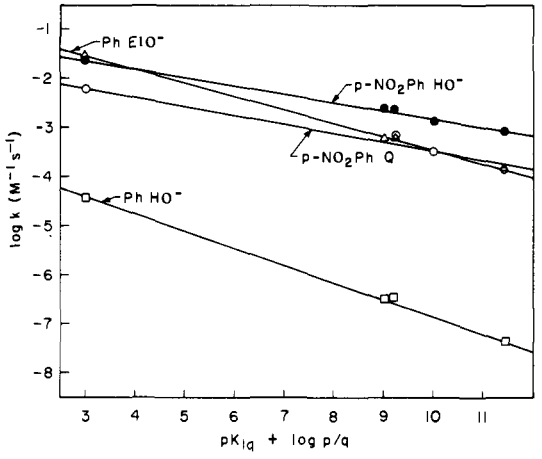


Figure 3. Dependence on the pK_a of the leaving quinuclidine of the rate constants for elimination to form *p*-nitrostyrene catalyzed by hydroxide ion (●) and quinuclidine (○) in water at 25 °C and to form styrene catalyzed by hydroxide ion in water (□) and by ethoxide ion in ethanol (△) at 40 °C.

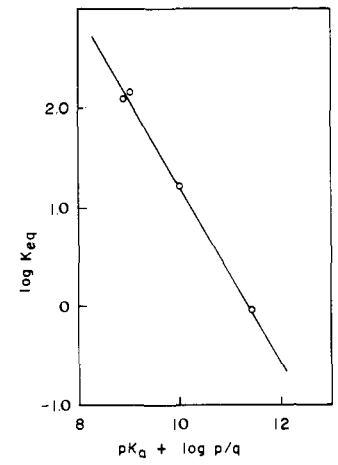


Figure 4. Dependence of the equilibrium constant for elimination to form *p*-nitrostyrene on the pK_a of the leaving quinuclidine at 25 °C, ionic strength 1.0 M (KCl).

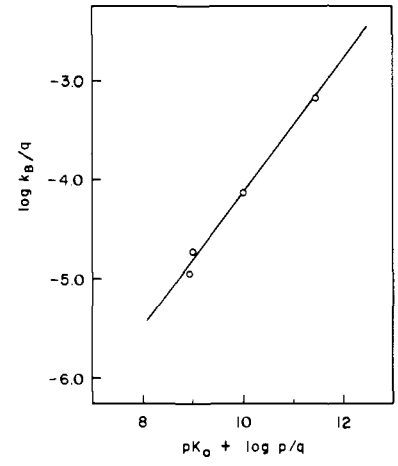


Figure 5. Brønsted plot for catalysis by substituted quinuclidines of the elimination reaction from *N*-(β-*p*-nitrophenylethyl)-1,4-diazabicyclo[2.2.2]octanium ion in water at 25 °C, ionic strength 1.0 M.

nation direction lyoxide ion or substituted quinuclidine can act as the base, B, and in the addition direction the solvent or a protonated quinuclidine can act as the acid, BH^+. The latter process gives a term second order in total buffer concentration for the addition reaction in quinuclidine buffers, because the base acts as a nucleophile to attack the α carbon atom and its conjugate acid acts as a general acid catalyst to protonate the β carbon atom.

The rate constants for the addition reaction with *p*-nitrostyrene have a large dependence on the basicity of the quinuclidine, with a slope of $\beta_{nuc} = 0.69$ in a plot of log k_H against pK (Figure 2). This suggests a late transition state for the addition reaction with a large development of positive charge on the attacking amine. The value of β_{nuc} is larger than the values of 0.43 and 0.56 for the addition of amines to acrylonitrile[18] and methyl vinyl ketone,[19] respectively, and the small values that are suggested by the rate constants for addition of amines to phenyl vinyl sulfone[21] and cyclohexen-2-one.[22]

The complementary result is found in the elimination direction, for which an early transition state for leaving-group expulsion is indicated by the small dependence of the rate on the pK of the leaving quinuclidine (Figure 3). The same values of $\beta_{lg} = -0.18$ are found for the reactions catalyzed by hydroxide ion (closed circles) and by quinuclidine (open circles). The dependence on the leaving group is twice as large for the phenylethyl compounds, with a value of $\beta_{lg} = -0.35$ (squares, Figure 3); a similar value of $\beta_{lg} = -0.28$ is found for the elimination induced by ethoxide ion in ethanol (triangles, Figure 3). The phenyl compounds were studied at 40 rather than 25 °C, but this increase in temperature would not be expected to cause a large change in β_{lg}. Similar values of $\beta_{lg} = -0.26$ to -0.31 are found for the closely related elimination reactions of *N*-(β-phenylethyl)dimethylanilinium salts in ethanol.[23] The nitrogen isotope effects for this reaction also suggest a small amount of C–N cleavage in the transition state[15] which, according to a recent calculation,[25] may be as little as 10–20%.

The equilibrium constants for the reaction in the direction of elimination to form *p*-nitrostyrene give a slope of $\beta_{eq} = -0.89$ for a plot of log K_{eq} against pK (Figure 4). This is close to the value of -1.0 that would be expected if the "effective charge" on the quinuclidine nitrogen atom of the addition compound were the same as on protonated quinuclidine.

Proton Transfer. The Brønsted coefficient for catalysis of the elimination reaction by substituted quinuclidines is 0.68 (Figure 5); the rate constant for hydroxide ion falls below this line by a factor of 300. This may be compared with approximate values of $\beta = 0.67$ and 0.54 for catalysis by phenolate ions of the elimination reactions in ethanol of 2-*p*-nitrophenylethyl bromide and 2-phenylethyl bromide, respectively.[26] The secondary solvent isotope effect of $k_{OD}/k_{OH} = 1.55$ gives a value of $\beta = 0.63$ from the relationship $2.0^{\beta} = 1.55$.[11] These two measurements were made on compounds with different quinuclidines as leaving groups, but the constant ratio of the rate constants for elimination induced by hydroxide ion and by quinuclidine with different leaving groups (Figure 3)

suggests that there is no significant change in β with changing leaving group. Thus, these two measures of the amount of proton transfer are in agreement and indicate that the proton is approximately two-thirds transferred to the base in the transition state. This supports the generally accepted conclusion that proton transfer has proceeded more than halfway in elimination reactions of quaternary β-phenylethylammonium ions.

The primary deuterium isotope effect of $k_H/k_D = 8.5$ shows that a large deuterium isotope effect can be maintained in a moderately asymmetric transition state; this isotope effect is only slightly smaller than the value of $k_H/k_D = 9.4$ for the elimination of 2-*p*-nitrophenylethyl bromide in 0.06 mole fraction dimethyl sulfoxide.[27] The isotope effect is larger than a recent calculated value for a concerted elimination reaction with 0.7 proton removal in the transition state, possibly because of a structure-independent contribution of tunneling.[25] Different calculations have predicted differing sharpness of the isotope-effect maximum[28] and there is experimental evidence that the maximum can be broad.[29]

A less accurate estimation of the position of the proton can be made by comparing the values of $\beta_{nuc} = 0.69$ for k_H (Figure 2) and $\beta = 0.52$ for k_{BH} (plot not shown). If it is assumed that these structure-reactivity parameters are independent of the nature of the leaving group and catalyst, a value of $\alpha = 0.17$ for proton donation to the β carbon atom in the addition reaction is obtained from the difference between these two β values. The value of β for the addition reaction in quinuclidine buffers includes the effect of changing structure of both the amine nucleophile and the proton donor, BH^+, so that $\beta_{obsd} = \beta_{nuc} - \alpha$. The assumption of independent structure-reactivity parameters receives some support from the constant value of $\beta_{lg} = -0.18$ with hydroxide ion and quinuclidine as bases in the elimination direction (Figure 3). In any case, the result supports the conclusion that the amount of proton donation in the transition state of the addition reaction is small. A small value of $\alpha = 0.15$ has been observed directly for the intramolecular addition of a tertiary amine to give a 1,2-diarylethylammonium ion; however, this reaction shows a much smaller deuterium isotope effect of $k_H/k_D = 1.7$-1.9.[30]

A large rate increase of ~3000-fold is observed upon changing the base-solvent system from KOH/H_2O to $EtONa/EtOH$ for elimination of substituted quinuclidines from the β-phenyl compounds (Figure 3) and there is an even larger increase of 21 000-fold for the β-(*p*-nitrophenylethyl)quinuclidinium compound. These large solvent effects suggest that there is a large amount of proton removal and a decrease in net charge in the transition state that are favored by the strongly basic ethoxide ion in ethanol, which is a poorer ion-solvating medium than water.

Structure–Reactivity Interactions. The change in β_{lg} from -0.18 for the *p*-nitrophenyl to -0.35 for the phenyl compounds (Figure 3) means that there is a change in the structure of the transition state for the elimination reaction with changing substituents on the β-phenyl group that corresponds to a larger amount of C–N bond cleavage for the unsubstituted compound. This change can be described by the coefficient[14]

$$p_{xy'} = \partial\beta_{lg}/-\partial\sigma = \partial\rho/-\partial pK_{lg} \quad (3)$$

with $p_{xy'} = -0.14$.[31] Equation 3 shows that there is a complementary change in ρ with changing pK of the leaving group that corresponds to a larger ρ with the more basic leaving group. A negative $p_{xy'}$ coefficient has also been demonstrated by the observation of a progressive increase in the nitrogen leaving group isotope effect from 0.88 to 1.37% as the β-phenyl substituent is changed from *p*-CF_3 to *p*-CH_3O in the elimination reactions of 2-arylethyltrimethylammonium ions induced by ethoxide ion,[10] and directly by changes in structure–reactivity parameters for the elimination reactions of $ZArEtOSO_2ArY$ in *tert*-butyl alcohol.[32] There is evidence for negative $p_{xy'}$ coefficients in other elimination reactions, based on several criteria,[33-35] but a positive coefficient has been reported for the elimination reactions of substituted fluorene derivatives with trimethylamine as the leaving group; this may reflect steric or other special properties of this system.[36]

A negative $p_{xy'}$ coefficient is consistent with a transition state for a concerted reaction mechanism that has a large component of horizontal motion corresponding to proton transfer in a three-dimensional reaction coordinate–energy diagram (Figure 6), in agreement with earlier conclusions.[2,9-11] The electron-withdrawing *p*-nitro substituent on the β-phenyl group will have the predominant effect of lowering the energy of the carbanion intermediate so that the position of the transition state will tend to shift perpendicular and parallel to the reaction coordinate in such a way as to decrease the amount of C–N cleavage (Figure 6), in agreement with the less negative value of β_{lg}. The net shift can be regarded as an "anti-Hammond" effect (perpendicular) shift for cleavage and formation of the C–N bond. The negative $p_{xy'}$ coefficient is inconsistent with a predominantly vertical reaction coordinate. An electron-withdrawing substituent on the β-phenyl group will have the opposite effect on the amount of C–N breaking and β_{lg} for a reaction coordinate that is predominantly vertical, corresponding to a positive $p_{xy'}$ coefficient and to a major component of C–N cleavage in the transition state (Figure 7A). This shift represents a Hammond (parallel) effect for C–N bond cleavage and formation. The point is made more explicitly by a transformed reaction coordinate diagram in which the horizontal and vertical axes are defined by ρ and β_{lg}, respectively[14] (Figure 7B). For the latter diagram negative and positive $p_{xy'}$ coefficients correspond to reaction coordinates that are rotated clockwise and counterclockwise from the vertical, respectively.

Significant $p_{xy'}$ coefficients can also be caused by simple electrostatic interactions between polar substituents on the β-phenyl group and the amine without changes in transition-state structure,[14,37] but the negative sign of the observed $p_{xy'}$ coefficient is opposite to that expected for an electrostatic effect in the elimination direction. For example, an electron-donating substituent on the amine (increased pK_{lg}) will give a favorable electrostatic interaction with an electron-withdrawing substituent on the β-phenyl group to stabilize the reactant; to the extent that this is lost in the transition state the compound will react more slowly (decreased ρ). In the addition direction the electrostatic effect gives a negative $p_{xy'}$ coefficient, from the favorable electrostatic interaction of an electron-donating substituent on the amine (increased pK_{nuc}) with an electron-withdrawing substituent on the β-phenyl group (giving an increased ρ). This difference in the direction of the electrostatic effect in the two directions of an addition–elimination reaction may provide a useful means of distinguishing electrostatic effects from interaction coefficients that reflect changes in transition-state structure, which have the same sign for both directions (there is no such difference for electrostatic effects involving the catalyst, which is present in the transition state but not the reactant or product).

The closely related elimination reactions of 2-phenylethyldimethylanilinium salts in ethanol show a small increase in the nitrogen isotope effect with electron-withdrawing substituents in the leaving aniline that provides evidence for an increase in C–N bond cleavage and for motion of the transition state perpendicular to the reaction coordinate.[15] This effect represents a negative coefficient $p_y = \partial\beta_{lg}/-\partial pK_{lg}$ and provides further support for a significant component of C–H cleavage in the diagonal reaction coordinate, which slides downward as the energy of the cationic nitrogen atom at the top of the diagram in Figure 6 is increased by electron-withdrawing

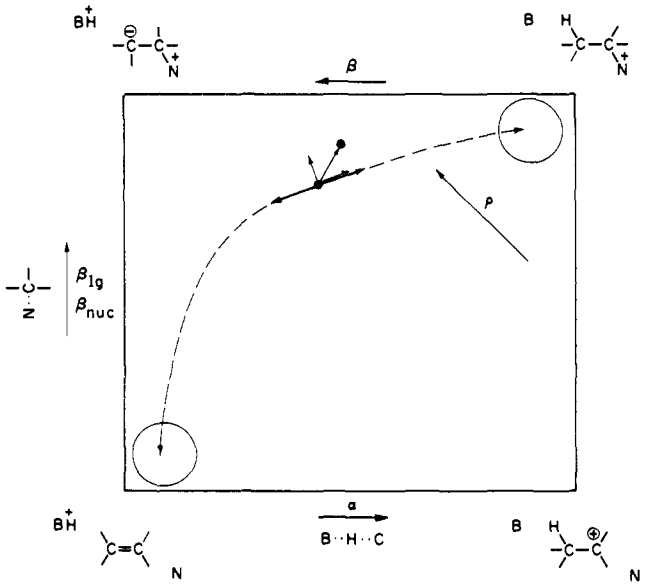


Figure 6. Reaction coordinate-energy diagram for elimination reactions of β-phenylethylammonium derivatives. The horizontal and vertical axes describe the amounts of proton removal and C–N cleavage as measured by the Brønsted β and β_{lg}, respectively; charge development on the central β carbon atom is measured by ρ along a diagonal axis. The effect on the position of the transition state of an electron-withdrawing substituent on the β carbon atom is shown for a predominantly horizontal reaction coordinate. The energy contour lines are omitted.

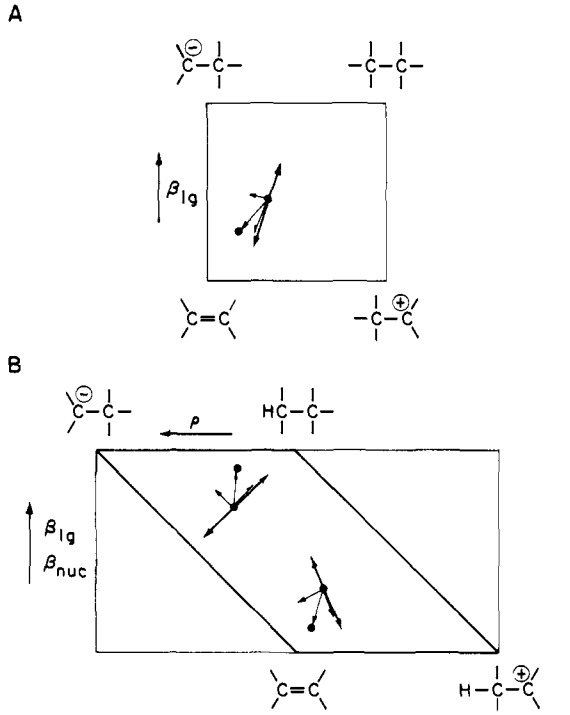


Figure 7. (A) Reaction coordinate-energy diagram, as in Figure 6, to show the effect on the position of the transition state of an electron-withdrawing substituent on the β carbon atom for a predominantly vertical reaction coordinate. (B) Transformed, rectangular reaction coordinate-energy diagram[14] to evaluate structure-reactivity interactions of polar substituents on the β carbon atom and on the leaving group. The change from a negative to a positive coefficient $p_{yy'} = \partial\beta_{lg}/-\partial\sigma = \partial\rho/-\partial pK_{lg}$ corresponds to the change from a clockwise to a counterclockwise rotation of the reaction coordinate from the vertical.[14]

substituents; a predominantly vertical reaction coordinate would be expected to give the opposite behavior.[14] The same conclusion is supported by the increased primary isotope effect with electron-withdrawing substituents on the phenyl group of 2-arylethyltrimethylammonium salts, from $k_H/k_D = 2.64$ for *p*-OCH_3 to 4.16 for *p*-CF_3; this corresponds to a negative coefficient $p_{xy'} = \partial\beta/\partial\sigma = \partial\rho/\partial pK_{BH}$ and to the decrease in carbanion character with increasing carbanion stability that is expected for a predominantly horizontal reaction coordinate.[10] A similar result has recently been obtained for $ArCH_2CHPhCl$.[34] The large primary isotope effect of $k_H/k_D = 8.5$ for the *N*-(β-*p*-nitrophenylethyl)quinuclidinium ion reaction may be regarded as an extension of this trend.

The absence of a difference in β_{lg} for the elimination reactions induced by hydroxide ion and by quinuclidine, which differ in basicity by 4 p*K* units (Figure 3), means that the interaction coefficient $p_{xy} = \partial\beta_{lg}/\partial pK_{BH+} = \partial\beta/\partial pK_{lg}$ is not detectably different from zero. This could be a consequence of a large component of proton transfer in a predominantly horizontal reaction coordinate, which would not be expected to give a large p_{xy} coefficient,[10,11,14] or of imbalance between the effects of different structural changes on the transition state.[38]

Conclusions

The increase of ca. twofold in the negative β_{lg} for elimination from the phenyl compared with the *p*-nitrophenyl compound, representing a negative $p_{yy'}$ coefficient, is consistent with a concerted E2 mechanism with an increased amount of C–N bond cleavage for the phenyl compound and a major component of proton transfer in the reaction coordinate. The 7000-fold faster elimination with bromide than with quinuclidine as the leaving group shows that the departure of the leaving group contributes a significant driving force to the reaction and that there is significant bond breaking in the transition state. For the *p*-nitrophenyl compound this rate ratio is only 3 and there is an intermediate ratio of $k(Br)/k(NMe_3^+) = 24$ when the para substituent on the phenyl group is $-NMe_3^+$ (at 60 °C).[11] Bromide ion is a better leaving group than a tertiary amine and is a poorer activator of proton removal to form a carbanion, as indicated by values of $\sigma_I = 0.44$ and 0.92 for Br and $N(CH_3)_3^+$, respectively.[39,40] An E2 mechanism is also indicated by analogy with other 2-phenylethylammonium compounds, for which a concerted mechanism is supported by a large body of evidence including structure-reactivity interactions[10,11,15] and leaving group isotope effects.[10,15,41,42]

The primary process in elimination from the *N*-(β-*p*-nitrophenylethyl)quinuclidinium compounds is proton transfer; there is little if any driving force from expulsion of the leaving group. The bond to the leaving group behaves as if it is in a potential well in the transition state so that it responds passively to the driving force from carbanion development on the β carbon atom. This kind of situation appears to hold even for 2-phenylethyldimethylanilinium ions, which show an increase in nitrogen isotope effect and C–N bond cleavage with electron-withdrawing substituents on the leaving group.[15] The values of $\beta = 0.68$, $k_{OD}/k_{OH} = 1.55$, and $k_H/k_D = 8.5$ for the *N*-(β-*p*-nitrophenylethyl)quinuclidinium series suggest that proton transfer is a major component of the reaction coordinate and that the proton is approximately two-thirds removed in the transition state. The value of $\beta_{lg} = -0.18$ shows that there is essentially no lengthening of the bond to the leaving quinuclidine group beyond that which is to be expected for the formation of a carbanion on the β carbon atom in the transition state. The values of β_{lg} are −0.4 and −0.2 for the formation of a carbanion from $PhCH_2SO_2OAr$ and $CNCH_2CH_2N(Me)_2Ar^+$, respectively.[4,43] There is a smaller value of $\beta_{lg} = -0.092$ for carbanion formation from $CH_3COCH_2CH_2OAr$,[44] but this is comparable to the value of $\beta_{lg} = -0.18$ if account is taken of the different amounts of proton removal that are indicated by the Brønsted coefficients of 0.29 and 0.68 for the two reactions. A small or zero component of bond breaking to

the leaving quinuclidine is also suggested by the faster elimination of the less basic quinuclidines than of bromide ion and the rate ratio of only 3 for bromide compared with quinuclidine itself in the 2-*p*-nitrophenylethyl compounds. In ethanol the expulsion of quinuclidine (k_{OEt} = 27 M^{-1} s^{-1} at 25 °C) is even faster than that of bromide ion ($k_{OEt} \sim 7.3$ M^{-1} s^{-1} at 60 °C).[26]

Further experimental work is necessary to establish whether the different behavior of the phenyl and *p*-nitrophenyl quinuclidinium compounds represents a change in mechanism as well as a change in transition-state structure. All of the data, including the change in β_{lg} that is described by a negative $p_{yy'}$ coefficient, are consistent with a concerted E2 mechanism for the phenyl compound, but none of the results reported here is inconsistent with an E1cB mechanism for the *p*-nitrophenyl compound. Such a carbanion mechanism was suggested in 1933 by Hughes, Ingold, and Patel for the decomposition of *N*-(β-*p*-nitrophenylethyl)trimethylammonium ion to *p*-nitrostyrene.[45] The leveling of the rate at high buffer concentrations with the quinuclidine compound and weakly basic catalysts, but not with strongly basic catalysts or with better leaving groups, could be explained by a change in rate-determining step from an irreversible E1cB mechanism at low buffer concentration to a reversible E1cB mechanism at high buffer concentration. Such a change in rate-determining step would be favored by relatively poor leaving groups and by strong acids, BH^+, which would increase the rate of carbanion reprotonation relative to leaving-group expulsion.[44] A change in mechanism is also consistent with evidence that benzyl carbanions have only a very short or no lifetime in hydroxylic solvents, so that protonation occurs faster than diffusion, whereas *p*-nitrobenzyl carbanions are much more stable and have a lifetime that is sufficient to permit diffusion and equilibration with the solvent.[6,46] However, we do not know the rate constant for expulsion of an amine from the adjacent carbon atom for either of these carbanions and it is possible that a concerted mechanism is enforced by a negligible lifetime of the carbanion with respect to this elimination step. Furthermore, the quinuclidine compound would be expected to react by the same mechanism as *N*-(β-*p*-nitrophenylethyl)-trimethylammonium ion, which undergoes elimination only 4.6 times faster.[47] An E2 mechanism for the latter compound is supported by the reported lack of hydrogen exchange into starting material during elimination in phosphate buffer at pH 7, 100 °C[48] and by heavy atom isotope effects for the leaving nitrogen[49] and α carbon atoms.[50,51] This evidence appears to be conclusive, but some uncertainty is raised by the poor agreement between the α-^{14}C isotope effects reported from different laboratories[52] and the possibility that these isotope effects could result from a reversible E1cB or an $(E1cB)_{ip}$ mechanism. If the E2 mechanism is indeed correct, the value of $\beta_{lg} = -0.18$ means that a small sensitivity of the rate to substituents on the α carbon atom or to the nucleofugic ability of the leaving group does not provide a valid criterion to distinguish between E2 and E1cB mechanisms.

Experimental Section

Materials. Quinuclidines and their hydrochlorides were recrystallized commercial materials (Aldrich). Reagent grade potassium chloride was used without further purification. Glass-distilled and freshly boiled water was used throughout. Ethanol was purified following the Manske[53] procedure. Solutions of sodium ethoxide in ethanol were prepared by dissolving clear cuts of sodium in purified ethanol under nitrogen. 2-*p*-Nitrophenylethyl bromide was recrystallized (Aldrich) or was prepared by nitration of 2-phenylethyl bromide followed by recrystallization from benzene–petroleum ether (mp 68 °C). *p*-Nitrostyrene was prepared from 2-*p*-nitrophenylethyl bromide with sodium hydroxide in aqueous ethanol followed by extraction with ether and crystallization from petroleum ether at 0 °C; the NMR spectrum agreed with the literature.[54]

***N*-Methyl-1,4-diazabicyclo[2.2.2]octanium Iodide.** Methyl iodide (0.8 g) was added to 6 g of 1,4-diazabicyclo[2.2.2]octane (Dabco) in methanol. After 15 h the product was precipitated with ether and recrystallized twice from ethanol–ether, mp 60–100 °C dec. Anal. Calcd for $C_7H_{15}N_2I$: C, 33.07; H, 5.90; N, 11.02. Found: C, 33.02; H, 5.97; N, 10.98.

***N*-(β-Phenylethyl)quinuclidinium Bromide.** A solution of 2.6 g of quinuclidine hydrochloride and 1.13 g of potassium hydroxide in 15 mL of water was extracted with ether and the ether was evaporated under nitrogen. 2-Phenylethyl bromide (4.5 g) was then added to the free amine in 5 mL of methanol. After 15 h at room temperature and heating for 1 h at 50 °C the salt was precipitated with ether and recrystallized from ethanol–ether, mp 276–278 °C. Anal. Calcd for $C_{15}H_{22}NBr$: C, 60.81; H, 7.43; N, 4.73; Br, 27.03. Found: C, 60.94; H, 7.28; N, 4.56; Br, 27.13.

***N*-(β-Phenylethyl)-3-chloroquinuclidinium Bromide.** An excess of 2-phenylethyl bromide was added to a solution of 3-chloroquinuclidine (prepared from the hydrochloride as described above). After 15 h the salt was precipitated with ether and recrystallized from ethanol–ether or 2-propanol, mp 177–179 °C. Anal. Calcd for $C_{15}H_{21}NBrCl$: C, 54.46; H, 6.35; N, 4.24; Br, 24.21. Found: C, 54.15; H, 6.51; N, 4.27; Br, 24.34.

***N*-(β-Phenylethyl)-2,3-dehydroquinuclidinium bromide** was prepared by reaction of *N*-(β-phenylethyl)-3-chloroquinuclidinium bromide with sodium ethoxide in ethanol. After 15 h at room temperature, the solution was filtered and the product was precipitated from the solution with ether and recrystallized from 2-propanol, mp 181–182 °C. Anal. Calcd for $C_{15}H_{20}NBr$: C, 61.22; H, 6.80; N, 4.76; Br, 27.21. Found: C, 61.41; H, 6.85; N, 4.73; Br, 27.44.

***N*-(β-Phenylethyl)-1,4-diazabicyclo[2.2.2]octanium Bromide.** 2-Phenylethyl bromide (4 g) was added to a solution of 15 g of 1,4-diazabicyclo[2.2.2]octane in 40 mL of methanol. After 15 h the crystalline product was collected and recrystallized from ethanol, mp 270 °C dec. Anal. Calcd for $C_{14}H_{21}N_2Br$: C, 56.57; H, 7.07; N, 9.43; Br, 26.94. Found: C, 56.60; H, 7.32; N, 9.33; Br, 27.01.

***N*-(β-*p*-Nitrophenylethyl)quinuclidinium bromide** was prepared by the same procedure used for the phenyl analogue and recrystallized from ethanol–ether or 2-propanol, mp 215–217 °C. Anal. Calcd for $C_{15}H_{21}N_2BrO_2$: C, 52.79; H, 6.16; N, 8.21; Br, 23.46. Found: C, 52.50; H, 6.40; N, 8.11; Br, 23.69.

***N*-(β-Phenylethyl)-4-methyl-1,4-diazabicyclo[2.2.2]octanium Bromide Iodide.** To a solution of 600 mg of *N*-(β-phenylethyl)-1,4-diazabicyclo[2.2.2]octanium bromide in 10 mL of MeOH was added 1 g of methyl iodide. After 15 h the product was precipitated with ether and recrystallized from ethanol–ether.

***N*-(β-*p*-Nitrophenylethyl)-3-chloroquinuclidinium bromide** was prepared by the same procedure used for the phenyl analogue and recrystallized from ethanol–ether or 2-propanol, mp 256–260 °C dec. Anal. Calcd for $C_{15}H_{20}N_2BrClO_2$: C, 47.94; H, 5.33; N, 7.46; Br, 21.30. Found: C, 47.83; H, 5.50; N, 7.40; Br, 21.51.

***N*-(β-*p*-Nitrophenylethyl)-1,4-diazabicyclo[2.2.2]octanium Bromide.** A solution of 2-*p*-nitrophenylethyl bromide and an excess of 1,4-diazabicyclo[2.2.2]octane in methanol was allowed to stand overnight and then heated at 50 °C. The product was precipitated with ether and recrystallized from ethanol–ether. The rate constant for the elimination reaction of this substrate with aqueous potassium hydroxide was the same as for the same reaction using a stock solution of the compound prepared by mixing *p*-nitrostyrene and 1,4-diazabicyclo[2.2.2]octane buffer in ethanol–water (method B).

***N*-(β-*p*-Nitrophenylethyl)-3-hydroxyquinuclidinium Bromide.** A solution of 1.5 g of 2-*p*-nitrophenylethyl bromide and 0.83 g of 3-hydroxyquinuclidine in 20 mL of methanol was allowed to stand overnight and heated for 1 h at 50 °C. The product was precipitated with ether and crystallized from ethanol–ether. The rate constant of the elimination reaction of this substrate with aqueous potassium hydroxide was the same as for the same reaction using a stock solution of the compound prepared by mixing *p*-nitrostyrene and 3-hydroxyquinuclidine buffer in ethanol–water (method B).

***N*-(β-*p*-Nitrophenylethyl)-4-methyl-1,4-diazabicyclo[2.2.2]octanium bromide iodide** was prepared by the same procedure used for the phenyl analogue and recrystallized from ethanol–ether, mp 250 °C dec.

Kinetic Measurements. The equilibration of *p*-nitrostyrene with buffers of substituted quinuclidines was studied in water at 25 °C and ionic strength maintained at 1.0 M with potassium chloride. The disappearance of *p*-nitrostyrene was followed spectrophotometrically

at 335 nm after the injection of 3 μL of a stock solution (~0.04 M) into a cuvette containing 2.0 mL of buffer. The equilibration follows pseudo-first-order kinetics with $k_{obsd} = k_e + k_a$, in which k_e and k_a are pseudo-first-order rate constants for elimination and addition of the amine, respectively, under the conditions of a given experiment. The value of k_{obsd} was obtained from the half-times and $k_{obsd} = 0.693/t_{1/2}$, based on linear semilogarithmic plots of $(A_0 - A_\infty)/(A_t - A_\infty)$ against time. Values of k_a were obtained from $k_a = k_{obsd}/(1 + K')$, in which $K' = [P]/[A]$ is a dimensionless equilibrium constant that describes the equilibrium ratio of *p*-nitrostyrene, P, to addition compound, A, under the conditions of a particular experiment. The value of K' was evaluated from $K' = 1/[(A_0\epsilon_p/C) - 1]$, in which A_0 is the initial absorbance of P, $\epsilon_p = 8380$ is the extinction coefficient of P at 335 nm, and $C = [A_\infty - (\epsilon_A/\epsilon_p)A_0]/(\epsilon_p - \epsilon_A)$. Values of ϵ_A, the extinction coefficient of the addition compound at 335 nm, were found to be 658 for *N*-(β-*p*-nitrophenylethyl)quinuclidinium ion, 908 for *N*-(β-*p*-nitrophenylethyl)-3-hydroxyquinuclidinium ion, 640 for *N*-(β-*p*-nitrophenylethyl)-3-chloroquinuclidinium ion, and 713 for *N*-(β-phenylethyl)-4-methyl-1,4-diazabicyclo[2.2.2]octanium ion, based on the compounds obtained by synthesis. The hydroxide ion concentration was obtained from the measured pH and the empirical equation $-\log [OH^-] = 14 - (pH + 0.19)$ for experiments at pH <12.

Pseudo-first-order rate constants for the elimination reactions were determined spectrophotometrically by following the appearance of *p*-nitrostyrene at 335 nm or styrene at 248 nm (ϵ_{248} 12 615 in 0.8 M KOH, 0.2 M KCl). The reactions were initiated by the addition of 0.5 mL of a stock solution of substrate (~6×10^{-4} M) to 2.0 mL of base solution in a cuvette that had been equilibrated in a thermostat; for 2-*p*-nitrophenylethyl bromide 1 μL of a stock solution in ethanol was added to 2.5 mL of base. Some experiments were carried out by adding 0.5–1.0 μL of a stock solution of substrate, prepared by incubating *p*-nitrostyrene in a concentrated buffer of substituted quinuclidine-quinuclidine hydrochloride in aqueous ethanol, to 2.5 mL of potassium hydroxide solution in a cuvette. Rate constants obtained by this procedure were found to agree well with those obtained with synthesized substrates when the size of the aliquot was ≤1 μL. *p*-Nitrostyrene was found to be stable in alkaline solution at the low concentrations used for the experiments. All experiments in water were carried out at ionic strength 1.0 M, maintained with potassium chloride.

Reactions of the *p*-nitrophenyl compounds with potassium hydroxide were followed to completion, but rate constants for the slower reactions in quinuclidine buffers (buffer ratio $B/BH^+ = 2.5$) were determined by the method of initial rates from the absorbance change at 0–1% reaction. Pseudo-first-order rate constants, k_e, were obtained by dividing the initial rate of change in absorbance by $(A_\infty - A_0)$; the value of A_∞ was obtained from parallel experiments that were carried to completion in potassium hydroxide solution. Second-order rate constants for the buffer-catalyzed elimination reaction of the 1,4-diazabicyclo[2.2.2]octane derivative were obtained from the slopes of linear plots of k_e against the concentration of free amine, based on at least four buffer concentrations at a ratio $[B]/[BH^+] = 2.5$. It was shown that the back reaction from addition of buffer components to *p*-nitrostyrene did not affect the rate constants by calculating k_e from $k_e = (k_aS)/(A_\infty - A_0)$, in which k_a is the experimentally determined rate constant for the addition reaction under the conditions of the experiment, A_∞ is the final absorbance measured in potassium hydroxide solution, and the slope, S, was obtained from a plot of $A_t - A_\infty$) against $(1 - 1/e^{k_at})$. Rate constants obtained from this method were found to agree well with those obtained by the simpler procedure.

The slower reactions of the β-phenylethyl derivatives were followed at 40 °C by following the initial rates for 1–2% reaction in water or by following the complete reaction course in ethanol (ϵ of styrene at 248 nm = 14 800 in ethanol and 12 600 in water). In separate experiments the reactions in ethanol were followed by the method of initial rates and good agreement was obtained with the two methods.

The primary isotope effect for the elimination reaction of *N*-(β-*p*-nitrophenyl-β,β-dideuterioethyl)quinuclidinium ion was determined using a stock solution of this compound that was prepared by incubation of *p*-nitrostyrene and quinuclidine buffer in D_2O/CD_3OD for 3 days at room temperature. This time is sufficient for equilibration, based on the observed rate constants for addition and elimination, and it was shown that the isotope effect was constant with different times of incubation. The reaction was followed spectrophotometrically after injection of 1 μL of this solution into 2.5 mL of 0.8 M potassium hydroxide–0.2 M potassium chloride at 25 °C.

The solvent deuterium isotope effect was measured in 0.8 M KOH or KOD in H_2O or D_2O using a stock solution of *N*-(β-*p*-nitrophenylethyl)quinuclidinium ion prepared similarly in H_2O/CH_3OH.

The pK_a of protonated 4-methyl-1,4-diazobicyclo[2.2.2]octanium iodide was found to be 3.01 at ionic strength 1.0 M, 25 °C, by titration.

References and Notes

(1) Supported by grants from the National Science Foundation (PCM77-08369) and the National Institutes of Health (GM20888 and GM20168).
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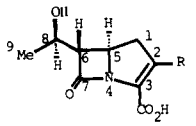
Studies on the Syntheses of Heterocyclic Compounds. 800.[1] A Formal Total Synthesis of (±)-Thienamycin and a (±)-Decysteaminylthienamycin Derivative

Tetsuji Kametani,* Shyh-Pyng Huang, Shuichi Yokohama, Yukio Suzuki, and Masataka Ihara

Contribution from the Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan. *Received August 30, 1979*

Abstract: The synthesis of a key intermediate for the preparation of (±)-thienamycin (**1**) and its derivatives has been developed. By 1,3-dipolar cycloaddition, the nitrile oxide derived from 3-nitropropanal dimethyl acetal (**3**) was added to methyl crotonate to give selectively *trans*-4-methoxycarbonyl-3-(2′,2′-dimethoxyethyl)-5-methylisoxazoline (**5**). Catalytic reduction of **5** yielded a stereoisomeric mixture of the amino esters **7**, hydrolysis of which followed by treatment with dicyclohexylcarbodiimide gave mainly two trans azetidinones **11** and **12**, together with a small amount of the cis isomer. On the other hand, reaction of **7** with methylmagnesium iodide yielded the desired trans azetidinone **11** along with a trace of the cis isomer **15**. The stereochemistry of the 8*S**-trans isomer **12** was confirmed by X-ray analysis of its derivative **21**. The 8*R**-trans compound **11** was protected with the *p*-nitrobenzyloxycarbonyl group and then converted to the alcohol **17** and to the thioacetal **19**, which had already been correlated to (±)-thienamycin. After protection of **12** with the *o*-nitrobenzyloxycarbonyl group, the acetal **24** was converted to the (±)-8*S**-decysteaminylthienamycin derivative **27** in several steps, involving an intramolecular Wittig reaction.

Thienamycin (**1**) was isolated from fermentation broths of the soil microorganism *Streptomyces cattleya* by a Merck research group.[2,3] It is a β-lactam antibiotic with the carbapenem structure having highly desirable antibacterial activity; activity is relatively high against Gram-positive bacteria and extends over the full range of Gram-negative bacteria, including *Pseudomonas aeruginosa*. Four epithienamycins were recently found in broths of *S. flavogriseus*.[4,5] It has also been found that decysteaminylthienamycin (**2**), derived from



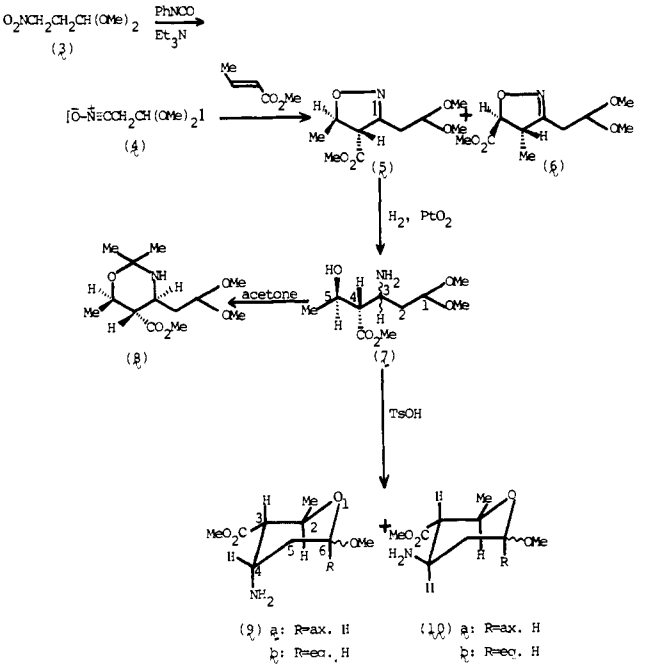
(1) R=SCH$_2$CH$_2$NH$_2$
(2) R=H

thienamycin, has antibacterial activity as potent as that of thienamycin itself.[6] (±)-Thienamycin (**1**)[7] and the derivative **2**[8] have been totally synthesized through the same intermediate by the Merck group. We here report a facile synthesis of the key synthetic intermediate to (±)-thienamycin and the decysteaminylthienamycin derivative, through a trans isoxazoline derivative **5**.

Formal Total Synthesis of (±)-Thienamycin

1,3-Dipolar cycloaddition of the nitrile oxide derived from 3-nitropropanal dimethyl acetal (**3**)[9] and methyl crotonate was carried out in benzene solution[10] as described in the Experimental Section. The product consisted mainly of *trans*-4-methoxycarbonyl-3-(2′,2′-dimethoxyethyl)-5-methylisoxazoline (**5**) together with a small amount of the regioisomer **6**, and these were easily separated by distillation followed by column chromatography. Preferential formation of **5** from 1,3-dipolar cycloaddition of the nitrile oxide **4** and methyl crotonate was expected from Huisgen's report[11] and from application of Houk's molecular orbital perturbation treatment.[12] Because the stereochemical relationship between the C_6 and C_8 positions of thienamycin is already set up in the isoxazoline **5**, it should be possible to synthesize thienamycin with the correct stereochemistry from **5**, if the intervening reaction proceeds with retention of the relative configuration.

Reduction of **5** using Adams' catalyst in acetic acid under 4.5–6 atoms of hydrogen yielded quantitatively a stereoisomeric mixture of the two amino esters **7** in a ratio of 3:2, which



(9) a: R=ax. H
b: R=eq. H
(10) a: R=ax. H
b: R=eq. H

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