A Darzens Aziridine Synthesis[1]

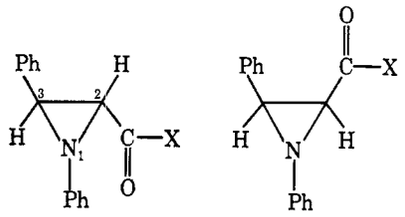
JAMES A. DEYRUP

Department of Chemistry, University of Florida, Gainesville, Florida 32601

Received January 30, 1969

A procedure has been developed which allows successful extension of the Darzens synthesis to the preparation of aziridine esters and amides. The stereochemical course of the condensation yields the unexpected result of preferential formation of *trans* ester and *cis*-amide. The significance and a possible explanation of this result are discussed. The chemistry of these aziridines has been briefly investigated and found to be dominated by the ease with which these compounds form azomethine ylides.

The unexpected reactions and stereochemical behavior which we encountered in our studies of 2-chloro-1,3-diphenylaziridines have focused our interest on exploring the chemistry of related functionally substituted aziridines.[2,3] Although a number of precursors to functionally substituted aziridines were considered, aziridine esters appeared to offer the greatest versatility. In order to correlate our results with our previous work, we chose to prepare *cis*- and *trans*-1,3-diphenyl-2-aziridinecarboxylic acid derivatives (**1** and **2**).

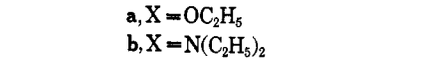


1 **2**

a, X = OC_2H_5
b, X = $N(C_2H_5)_2$

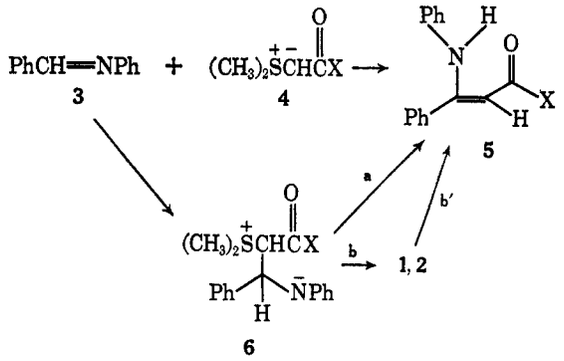
Attempts to extend conventional procedures for aziridine synthesis were unsuccessful when applied to the preparation of **1** and **2**. Our search for alternative routes to these compounds has resulted in the discovery that the Darzens condensation[4] can be extended to the synthesis of **1** and **2**.

Reaction of benzalaniline (**3**) and ethyl chloroacetate in ether (sodium methoxide as base) or in benzene (potassium *t*-butoxide as base) failed to yield the desired product. The combination of dimethoxyethane as solvent and potassium *t*-butoxide as base, however, resulted in the formation of **1a** in 29% yield. Examination of the crude reaction mixture by nmr spectroscopy showed that no more than 10% of the isomeric *cis* adduct (**2a**) was formed. In a similar manner, 2-chloro-N,N-diethylacetamide could be condensed with **3** to give *cis* amide **2b** as the major product in 58% yield. A second product was also isolated in 7% yield and identified as the *trans* isomer **1b**. Analysis of the crude reaction mixture showed a similar ratio (approximately 9:1) of *cis* to *trans* products. The failure of these aziridines to isomerize under the reaction conditions (see Experimental Section) indicates that these product ratios are kinetically controlled. This rather remarkable change in the stereochemistry of the major product from *trans* to *cis* will be discussed below. The structure and stereochemistry of these products were established by their elemental analyses and nmr spectra (Table I).



3

The isolation of aziridines **1a**, **2a** and **2b** is interesting in view of a recent publication concerning the reaction of benzalaniline (**3**) with sulfonium ylides (**4**).[5] The main product of these reactions were cinnamic acid derivatives **5**. Careful inspection (see Experimental Section) revealed that **5** was not formed as a by-product in the aziridine synthesis. Conversely, aziridines **1b** and **2b** were not detected in the synthesis of **5b**.



3 **4** **5** **6**

It was concluded by the authors that the initially formed betaine (**6**) underwent initial closure (b) to aziridine (**1**, **2**) which rapidly opened (b′) to the observed product. An alternative mechanism (a) which bypassed the aziridine ring was excluded by means of an alternative (carbenoid) reaction with **3** which also yielded **5**.

In view of this reported instability of aziridines **1** and **2**, we undertook a brief examination of their thermal stability and sensitivity toward base. Although no reaction occurred at room temperature in carbon tetrachloride, *trans*-aziridine **1a** underwent isomerization in this solvent at 80°. After 10 hr, equilibrium (50:50) was established between **1a** and a new substance which could not be obtained in pure crystalline form. Structure **2a** was assigned to this compound on the basis of its nmr spectrum (Table I). In a similar manner, **1b** could be equilibrated in carbon tetrachloride at 80° to a 52:48 mixture of **1b** and **2b** respectively.

These isomerizations in the absence of base are most reasonably explained in terms of intermediate azo-

(1) Acknowledgement: Support of this research by National Science Foundation Grants GP-5531 and GP-8044 is gratefully acknowledged.

(2) J. A. Deyrup and R. B. Greenwald, *J. Amer. Chem. Soc.*, **87**, 4538. (1965).

(3) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 5091 (1966).

(4) M. S. Newman and B. J. Magerlein, *Org. Reactions*, **5**, 413 (1949); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, 1965, p 240.

(5) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).

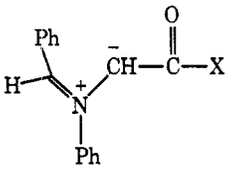
TABLE I

NMR SPECTRA OF CONDENSATION PRODUCTS[a]

Compd	ArH	C-3 H[b]	C-2 H[b]	CH_2	CH_3
1a	6.7–7.4	3.72 (2.0)	3.08 (2.0)	4.07	1.08
2a	6.7–7.6	3.44 (7.0)	3.04 (7.0)	3.80	0.92
2b	6.8–7.5	3.42 (7.5)	3.07 (7.5)	2.9–3.5	4–1.1
1b	6.7–7.4	3.90 (2.0)	3.07 (2.0)	3.0–3.8	0.8–1.4

[a] Chemical shifts are expressed in δ, ppm, with respect to internal TMS. Values in parantheses are for $J_{2,3}$. [b] The assignment of C-2 and C-3 is tentatively based on the greater deshielding effect of a C_6H_5 over a CO_2R group. [c] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 53.

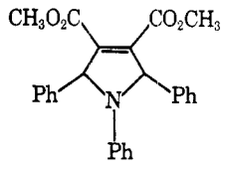
methine ylide **7**.[6] In order to confirm the intermediacy of this dipolar species, aziridines **1a**, **1b**, and **2b** were



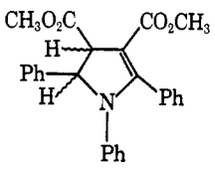
7

heated in carbon tetrachloride in the presence of a twofold excess of a dipolarophile (dimethyl acetylenedicarboxylate). In each case a single 1:1 adduct was obtained.

Previous reactions of aziridines with alkynes (*via* azomethine ylides) have produced 2-pyrrolines,[7] 3-pyrrolines,[6b,8] and mixtures of both.[6a] Especially relevant to this work is the adduct formed from 1,2,3-triphenylaziridine and dimethyl acetylenedicarboxylate.[8] This symmetrical adduct has been definitely assigned the 3-pyrroline structure (**8**) on the basis of the single OCH_3 and ring proton peaks in its nmr spectrum. The unsymmetrical 2-pyrroline isomer (**9**) would be expected



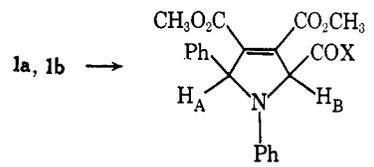
8



9

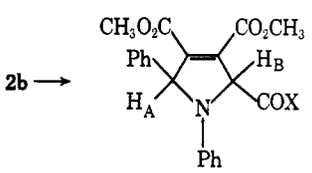
to show two separate OCH_3 peaks as well as different (and coupled) ring protons. Similar nmr spectral symmetry arguments can not be extended to the adducts from **1a**, **1b**, and **2b**. The difference in the chromophoric systems of N-phenyl-2- and 3-pyrrolines allows ultraviolet spectral comparison of these adducts with **8**. The great similarity of the uv spectra of **8** (λ_{max}^{EtOH} 242 mμ, log ϵ 4.29; 288 mμ, log ϵ 3.26), the adduct from **1a** (λ_{max}^{EtOH} 240 mμ, log ϵ 4.37; 284 mμ, log ϵ 3.27), and the adduct from **2b** (λ_{max}^{EtOH} 242 mμ, log ϵ 4.35; 288 mμ, log ϵ 3.25) thus allows assignment of the 3-pyrroline structure to them.[9] The stereospecificity of adduct formation also suggests that the initial adduct has not undergone 1,3-hydride migration to a 2-pyrroline isomer. A concerted 1,3 shift is not thermally allowed, and stereospecific two-step isomerization seems unlikely.

The verification by Huisgen that aziridines open *via* a conrotatory process in thermal reactions[6b] allows assignment of structures **10** and **11** to the products of the reactions described in this paper. An unusual feature of the nmr spectra of these compounds in the magnitude (3.5–7 Hz) of the long range coupling constants J_{AB}.



$J_{AB} = 3.5$ Hz

10



$J_{AB} = 7$ Hz

11

Although efficient coupling does not normally occur through four σ bonds,[7,11] the presence of the nitrogen atom[12] and possible contributions of the homoallylic type[13] could contribute to the size of J_{AB}.[14]

Both the esters and the amides were unaffected by base in ethanol and dimethoxyethane at 25°. At higher temperatures (80°), alcoholic base converted ester **1a** into benzaldehyde and ethyl 2-anilinoacetate. These products were presumably formed in the reaction of **7** with trace amounts of water present in the solvent.[15] A solution of potassium *t*-butoxide and **1b** or **2b** in *t*-butyl alcohol at 82° produced an equilibrium mixture of **2b** and **1b** (65:35). Although no attempts were made to ascertain the role (if any) of base in this latter equilibrium, it is clear that aziridines **1** and **2** are not precursors of **5**. We conclude, therefore, that the reaction of sulphonium ylides with imines proceeds *via* path a and does not involve intermediacy of aziridine (path b). The details of the mechanism by which the unsaturated product **5** is formed is an interesting but as yet unsettled question. A number of possible mechanisms can be considered.[16]

The stereochemical course of these Darzens condensations is unusual and deserves further comment. The

(6) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *Tetrahedron Lett.*, 397 (1966); (b) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

(7) A. Padwa and L. Hamilton, *J. Heterocyclic Chem.*, **4**, 118 (1967).

(8) H. W. Heine and R. Peavy, *Tetrahedron Lett.*, 3123 (1965).

(9) The position and relative intensities of these maxima are in qualitative agreement with models for similar aniline chromophores.[10]

(10) A. T. Bottini and C. P. Nash, *J. Amer. Chem. Soc.*, **84**, 734 (1962).

(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden Day, Inc., San Francisco, Calif., 1964, pp 115.

(12) *Cf.* reference 11, p 121.

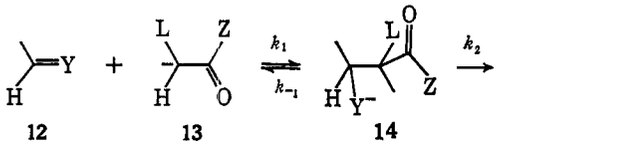
(13) Reference 11, p 110.

(14) Professor R. Huisgen has kindly informed us of his observation of similar long range coupling constants in 3-pyrrolines.

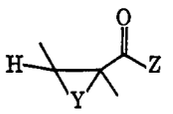
(15) Similar reactions and conclusions have been observed in the chemistry of the N-alkyl aziridine esters; P. B. Woller and N. H. Cromwell, *J. Heterocyclic Chem.*, **5**, 579 (1968).

(16) *Cf.* E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

Darzens condensation between halo esters and carbonyl compounds has been investigated by Zimmerman.[17] He concluded that the aldol intermediate **14** (Y = O, Z = OR) is formed rapidly and reversibly prior to rate-determining cyclization ($k_{-1} > k_2$). The stereochemistry of the product **15** is, therefore, determined by the k_2 (*trans*)/k_2 (*cis*) ratio. This ratio for Y = O, Z = OR was



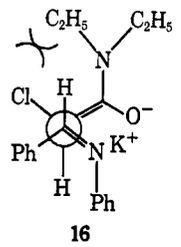
12 **13** **14**



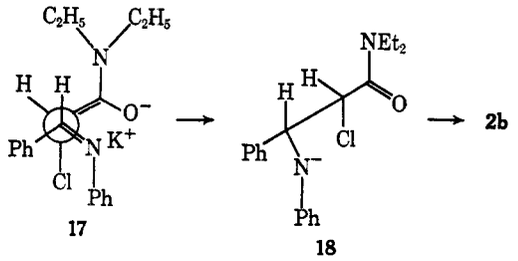
15

observed to be greater than unity. In order to explain this result, Zimmerman noted that overlap of the C–O π orbital with the departing halide is greatest in the transition state which leads to the *trans* product ("overlap control").

The preferred formation of *trans*-aziridine **1a** is in agreement with Zimmerman's picture of the Darzens condensation. In contrast, there is no reason to expect overlap control of k_2 to favor the *trans* ester (**1a**) and the *cis* amide (**2b**). The stereochemistry of **2b** must, therefore, be determined in the condensation of **12** and **13** to give **14**. In other words, k_2 is greater than k_{-1} and k_1 (*cis*) is greater than k_1 (*trans*). The suggested inversion in magnitude of rate constants k_2 and k_{-1} is not unreasonable in view of the decreased stability of enolate anion (**9**)[18] and the increased nucleophilicity of the heteroatom in **14**. In order to understand the stereochemical control of this reaction, it is necessary to consider the transition state leading to the aldol intermediate (as opposed to the relative stability of these intermediates). We would like to suggest that the preferred geometry for the reaction between enolate anion **13** (Z = NR_2) and imine (Y = NR') will find the cation more or less symmetrically disposed between the developing (on nitrogen) and dispersing (acyl oxygen) negative charge. This restriction allows two possible arrangements (**16** and **17**) which have minimal incipient eclipsing interactions. The bulk of the diethylamino group and its probable coplanarity with the enolate anion π system stands in opposition to the bulk of the chloro group. For this reason, **17** would appear to be the preferred arrangement. Bond formation from **17** would produce **18**, which is the diastereomeric precursor to **2b**. The extent to which these considerations are applicable to the Darzens and similar condensations is under further study.[19]



16



17 **18**

Experimental Section

cis- and *trans*-**1,3-Diphenyl-2-azairidinecarboxylic Acid Diethylamide.**—A mixture of 9.05 g (0.05 mol) of benzaldehyde anil and 7.87 g (0.07) mol) of potassium *t*-butoxide in 200 ml of dimethoxyethane was cooled to −40° under nitrogen. This mixture was stirred and maintained at this temperature while a solution of 10.47 g (0.07 mol) of 2-chloro-N,N-diethylacetamide in 125 ml of dimethoxyethane was added over a 2-hr period. The reaction was allowed to warm to room temperature over a 30-min period and concentrated to a small volume *in vacuo* at 35°. The residue was diluted with water and ether. After removal of the ether layer, the aqueous fraction was extracted with two portions of ether, and the combined extracts were dried ($MgSO_4$). Filtration and evaporation of the ether yielded 16.32 g of crude material.[21] This material was chromatographed on deactivated alumina with initial elution by petroleum ether followed by benzene. In this way two pure fractions were obtained which, after recrystallization from benzene–petroleum ether, were identified as the *trans* isomer, mp 90–92° (7%), and the *cis* isomer, mp 80.5–82.5° (58%).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53; N, 9.52. Found: C, 77.76; H, 7.60; N, 9.61 (*trans*); C, 77.41; H, 7.73; N, 9.30 (*cis*).

Inspection (nmr spectral and thin layer) of the other fractions did not reveal any 3-anilino-N,N-diethylcinnamamide.

Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate.—A mixture of 42.5 g (0.25 mol) of benzaldehyde anil and 39.2 g (0.35 mol) of potassium *t*-butoxide in 250 ml of dimethoxyethane was cooled to −40° under nitrogen. To this stirred mixture at −40° was added, over a 3-hr period, a solution of 45.3 g (0.35 mol) of ethyl chloroacetate. The reaction was allowed to warm to room temperature for 1 hr, and then evaporated *in vacuo*. The residue was diluted with water and extracted several times with ether. The ether extracts were dried and concentrated to give 66.85 g of an oil.[22] This oil was diluted with petroleum ether and cooled; yield 19.4 g (29%) of solid, mp 80–83°. Recrystallization from ethanol gave colorless prisms: mp 82–84°; ir (Nujol) 1730 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.62; H, 6.29; N, 5.45.

Preparation of 3-Anilino-N,N-diethylcinnamamide.—This compound was prepared in 48% yield (mp 90–92°), 91–92°)[5] according to the previously published procedure. Careful chromatographic investigation of the mother liquors failed to reveal either of the isomeric aziridines.

Stability of Products to Reaction Conditions.—A solution of 40 mg (0.35 mmol) of potassium *t*-butoxide and 74 mg (0.25 mmol) of *trans*-amide **1b** in 5 ml of dimethoxyethane was allowed to stand at room temperature for 2 hr. The solution was then evaporated, diluted with water, and extracted with chloroform. The thin-layer chromatogram of these extracts showed **1b** and no other products. The chloroform was then evaporated. The weight of the residue and its nmr spectrum demonstrated that **1b** had been recovered quantitatively.

(17) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **82**, 5459 (1960).

(18) A. J. Spezialle and H. W. Frazier, *J. Org. Chem.*, **26**, 3176 (1961).

(19) In contrast to our observed k_1 (*cis*)/k_1 (*trans*), a recent report of the Darzens condensation between **12** (Y = O) and **3** (Z = NR_2) explained the approximately equal (isolated) yields of *cis* and *trans* in terms of an expectation that k_1 (*cis*) ≈ k_1 (*trans*) (ref 20). Alternatively, their result could reflect a fortuitous combination of almost equally rapid aldolization and cyclization steps.

(20) C. C. Tung, A. J. Speziale, and H. W. Frazier, *J. Org. Chem.*, **28**, 1514 (1963).

(21) The nmr spectrum of this crude material revealed none of the *trans* isomer. The complexity of the spectrum in the region of the ring protons might (conservatively) prevent detection of less than 10% *trans* isomer.

(22) The nmr spectrum of this crude product showed no detectable amount (less than 10%) of the *cis* isomer.

A solution of *trans* ester **1a** (125 mg, 0.5 mmol) and potassium *t*-butoxide (112 mg, 1 mmol) in 10 ml of ethanol was allowed to stand at room temperature for 3 hr. Thin layer analysis of this solution indicated that no change had occurred.

Ring Opening of Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate (CCl_4).—A solution of 268 mg (1 mmol) of the aziridine ester and 4 mg of NaOEt in 20 ml of ethanol was refluxed for 3 days. The solution was then evaporated, diluted with water, and extracted with ether. The ether extracts were dried and concentrated to give 250 mg of oil which had a strong odor of benzaldehyde. The nmr spectrum of this oil was identical to the nmr spectrum of a 50:50 mixture of benzaldehyde and ethyl 2-anilinoacetate. This assignment was confirmed by isolation of the latter compound.

Equilibration of *cis*- and *trans*-Diethylamides (*t*-BuOH).—A solution of 235 mg of the *cis* amide was heated at reflux with 10 mg of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol. After 3 days, tlc analysis revealed no further change. The solution was evaporated, diluted with water, and extracted with ether. The residue was examined by nmr spectroscopy, which indicated *cis* and *trans* isomer in an 65:35 ratio, respectively. A solution of 160 mg of the *trans*-amide and 8 mg of potassium *t*-butoxide in 8 ml of *t*-butyl alcohol was treated in a similar manner and produced the same 65:35 distribution.

Equilibration of Ethyl *trans*-1,3-Diphenyl-2-aziridinecarboxylate.—A solution of 1 g of this ester in 25 ml of CCl_4 was refluxed for 10 hr. An nmr spectrum of an aliquot was identified as a 50:50 mixture of *cis*- and *trans*-aziridine esters. This ratio had not changed after 9 hr of additional reflux. The solvent was then removed and the residue was diluted with petroleum ether. The majority of the *trans* isomer could be removed by filtration. The nmr spectrum of the residue was in agreement (see Table I) with that expected for the *cis* isomer. All attempts to obtain this material in a crystalline form have been unsuccessful.

Equilibration of *trans*-Diethylamide 1b (CCl_4).—A solution of 80 mg of **7** in 25 ml of CCl_4 was refluxed for 3 days. The solution was evaporated and the percentages of **2b** and **1b** determined as 52:48 (respectively) by nmr spectroscopy.[23]

Reaction of *cis*-1,3-Diphenyl-2-aziridinecarboxylic Acid Diethylamide with Dimethyl Acetylenedicarboxylate.—A solution of 294 mg (1 mmol) of the aziridine and 282 mg (2 mmol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 24 hr. Evaporation at reduced pressure yielded a solid which was recrystallized from benzene–petroleum ether to give 330 mg (76%) of a solid: mp 139–140°; nmr ($CDCl_3$) δ 6.3–7.5 (m, 10 H), 6.18 (d, 1 H, J = 7 Hz), 6.12 (d, 1 H, J = 7 Hz), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.1–3.8 (m, 4 H), and 0.8–1.4 ppm (m, 6 H).

Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.69; H, 6.47; N, 6.42. Found: C, 68.81; H, 6.46; N, 6.28.

Reaction of *trans*-1,3-Diphenyl-2-aziridine Carboxylic Acid Diethylamide with Dimethyl Acetylenedicarboxylate.—A solution of 294 mg (1 mmol) of the aziridine and 282 mg (2 mmol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 24 hr. Evaporation at reduced pressure yielded a solid which was recrystallized from benzene–cyclohexane to give 350 mg (80%) of a solid: mp 148–149°; nmr ($CDCl_3$) δ 6.3–8.1 (m, 10 H), 5.77 (d, 1 H, J = 4 Hz), 5.40 (d, 1 H, J = 4 Hz), 3.76 (s, 3 H), 3.60 (s, 3 H), 3.1–4.1 (m, 4 H), and 1–1.5 ppm (m, 6H).

Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.66; H, 6.53; N, 6.31.

Examination of the crude reaction mixture from the reaction of the *cis*- and *trans*-aziridines failed to reveal detectable amounts of isomeric contamination.

Reaction of Ethyl *trans*-1,2-Diphenyl-2-aziridinecarboxylate with Dimethyl Acetylenedicarboxylate.—A solution of 500 mg (1.9 mmol) of this aziridine and 530 mg (3.7 mol) of the dipolarophile was refluxed in 30 ml of carbon tetrachloride for 3 days. The solvent was removed and the residue recrystallized from ethanol to give 500 mg (64%) of solid: mp 120–121°; nmr (CCl_4) δ 6.4–7.8 (m, 10 H), 5.70 (d, J = 3.5 Hz, 1H), 5.22 (d, J = 3.5 Hz, 1 H), 4.35 (q, J = 7Hz, 2 H), 3.76 (s, 3 H), 3.60 (s, 3 H), and 1.37 ppm (t, J = 7 Hz).

Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.31; H, 5.56; N, 3.23.

No isomers could be detected in the crude reaction mixture. Another experiment with equimolar amounts of the two reactants produced the same stereochemical result. In contrast, reflux of an equimolar mixture of the two reactants in toluene for 3 hr produced a mixture of two adducts. The second adduct was recognized as isomeric to the first: nmr (CCl_4) δ 6.14 (d, J = 7.5 Hz, 1 H), and 5.81 ppm (d, J = 7.5 Hz, 1 H). This second adduct was not characterized further.

Registry No.—**1a**, 20414-50-0; **1b**, 20414-51-1; **2a**, 20414-52-2; **2b**, 20414-53-3; **10b**, 20414-54-4; **11b**, 20414-55-5; **11a**, 20414-56-6.

Acknowledgments.—The author wishes to express his appreciation to Miss Karyl Barron (National Science Foundation Summer Research Participation Program, 1968) for the preparation of several of the above compounds.

(23) This shift in equilibrium constant **2b/1b** with change in solvent is in qualitative agreement with solvent effects observed in aziridine ketone equilibrations: R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968).