1,3-Dipolar Cycloaddition Reactions of the Geometrical Isomers of Some Methyl 1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates[1]

PAUL B. WOLLER[2] AND NORMAN H. CROMWELL[3]

Avery Laboratory of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received August 14, 1969

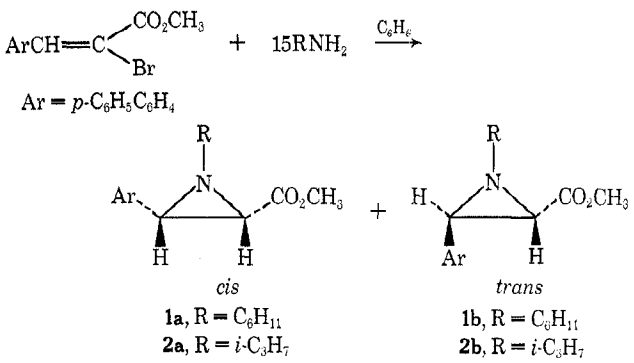
The *cis* and *trans* forms of methyl 1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate and methyl 1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate react stereospecifically with activated alkenes and dimethyl acetylenedicarboxylate in refluxing benzene to produce pyrrolidines and Δ^3-pyrrolines, respectively. The base-catalyzed tautomerization of the Δ^3-pyrrolines to Δ^2-pyrrolines and the extremely facile epimerization of the kinetically favored H_2,H_5-*trans*-Δ^3-pyrrolines to the thermodynamically more stable H_2,H_5-*cis* isomers in methanol, chloroform, or refluxing benzene are described and a possible explanation of these results is presented. In benzene at 80° the aziridine esters equilibrate to a mixture containing 68–70% *cis*-aziridine and 30–32% corresponding *trans* isomer.

In a previous publication[4] we reported the thermolysis of methyl *cis*- and methyl *trans*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1a,b**) in refluxing benzene and methanol. The products of these cleavage reactions were believed to arise *via* a 1,3-dipolar intermediate (azomethine ylide) resulting from heterolytic scission of the C–C bond of the aziridine ring.[5] When aziridines **1a** and **1b** were heated to 80° in a benzene solution containing dimethyl fumarate, trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,-4-tricarboxylate (**3a**) was produced in good yield. Reports of similar 1,3-dipolar cycloaddition reactions of aziridines with activated alkenes and alkynes have appeared in the literature.[6–10]

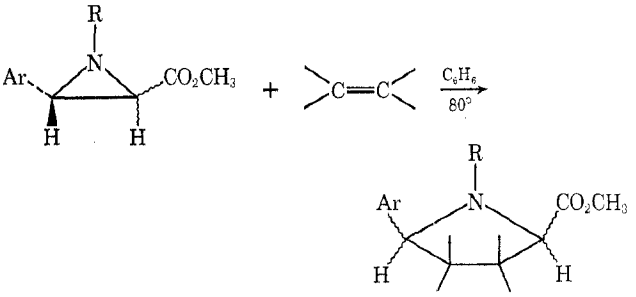
We now wish to report in detail the reaction of two pairs of *cis–trans*-aziridine esters (**1a,b** and **2a,b**) with several activated olefins and with one activated alkyne, the thermal equilibration of these aziridines, and the salient features of the ^1H nmr spectra of the cycloaddition products. Stereochemical assignment of the cycloadducts was made on the basis of pmr spectroscopy; the observed coupling constants are consistent with the Karplus correlation.[11]

Results

The aziridine esters **1a,b** and **2a,b** employed in this study were synthesized by reaction of a 15-fold excess of the primary amine with methyl α-bromo-*p*-phenylcinnamate in benzene. Stereochemical assignment of the *cis* and *trans* isomers are consonant with pmr, ir, and uv spectral data[12] (Table I).



In general, benzene solutions of equimolar quantities of the aziridine and the olefin were heated at reflux for 24–48 hr. After evaporation of the solvent the crude material was chromatographed to yield substituted pyrrolidines (Chart I).



In this manner both **1a** and **1b** afforded the pyrrolidines **3a,b** and **4a,b** when treated with dimethyl fumarate and dimethyl maleate, respectively. The stereochemical relationship of the protons at C_4 and C_5 in these adducts is readily ascertained by an examination of the pmr spectra. In both **3a** and **4a** one of the methoxycarbonyl proton resonance signals appears at 0.6 ppm higher field than those of the remaining two (δ 3.6–4.0). An inspection of models reveals that only the methyl group of the C_4 substituent can be oriented in the shielding cone of the phenyl nucleus, and this can occur only when the C_4 and C_5 substituents are *cis*. The observed couplings of 8.3–9.5 Hz are in good agreement with reported

(1) (a) Presented in part by N. H. Cromwell at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 1969. (b) This work was supported in part by an ACS-PRF Graduate Fellowship held by P. B. W. and in part by a U. S. Public Health Service Grant CA-02931.

(2) Petroleum Research Foundation Fellow, 1968–1969.

(3) To whom inquiries should be addressed.

(4) P. B. Woller and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 579 (1968).

(5) For other examples of aziridine rearrangements involving C–C bond scission of the aziridine ring, see (a) G. H. Coleman and G. P. Waugh, *Proc. Iowa State Acad. Sci.*, **40**, 115 (1933); **49**, 286 (1942); *Chem. Abstr.*, **29**, 2527 (1935); **37**, 5707 (1943); (b) A. Padwa and W. Eisenhardt, *Chem. Commun.*, **7**, 380 (1968); (c) S. V. Zovota, G. V. Loza, and M. Y. Lukina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 432 (1967); *Chem. Abstr.*, **67**, 21278 (1967); (d) B. K. Campbell and K. N. Campbell, *J. Org. Chem.*, **9**, 178 (1944).

(6) (a) H. W. Heine and R. E. Peavy, *Tetrahedron Lett.*, 3123 (1965); (b) H. W. Heine, R. E. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966); (c) H. W. Heine, A. B. Smith, III, and J. D. Bower, *ibid.*, **33**, 1097 (1968); (d) H. W. Heine and R. Henzel, *ibid.*, **34**, 171 (1969).

(7) (a) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); (b) A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1967).

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

(9) The authors kindly thank Dr. J. A. Deyrup, University of Florida, for sending us a preprint of a paper submitted for publication.

(10) (a) F. Texier and R. Carrier, *Tetrahedron Lett.*, 823 (1969); (b) S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 764 (1968); (c) J. W. Lown, R. K. Smalley, and G. Dallas, *Chem. Commun.*, 1543 (1968).

(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

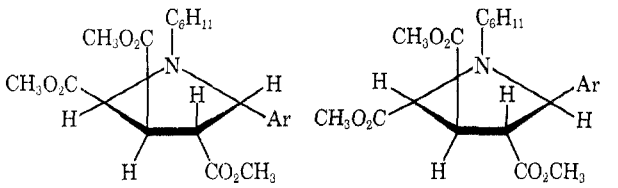
(12) A. E. Pohland, R. D. Badger, and N. H. Cromwell, *ibid.*, 4369 (1969).

TABLE I

SPECTRAL DATA OF METHYL 1-CYCLOHEXYL-2-(p-BIPHENYL)-3-AZIRIDINECARBOXYLATE, *cis* (1a) AND *trans* (1b)

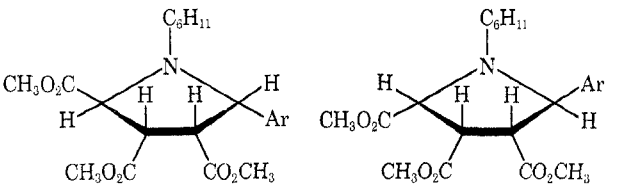
	Nmr (CDCl3)			Ir $\gamma_{C=O}$ cm^{-1}		Uv (CH3OH)	
Compd	H_2, δ	H_3, δ	J, Hz	CCl_4	Nujol	λ, mμ	ε
1a	2.88	2.49	7.0	1757, 1730	1747	257	23,900
1b	3.26	2.73	2.5	1734	1727	257	26,600

CHART I



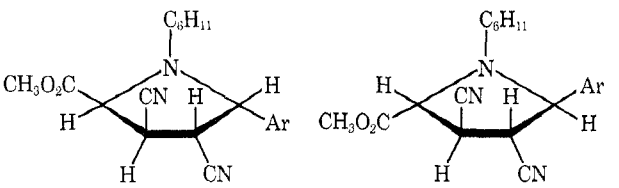
3a

3b



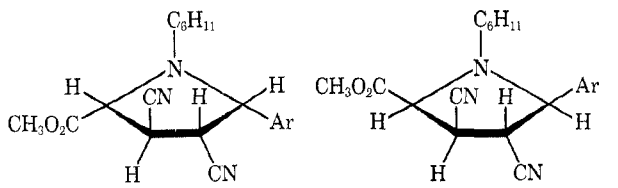
4a

4b



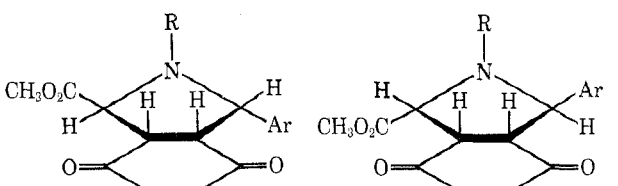
5a

5b



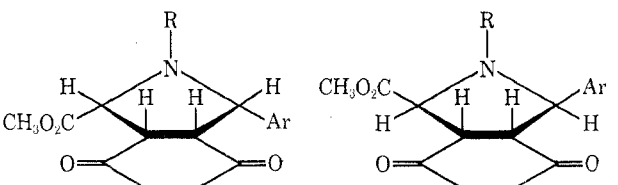
5c

5d



6a, R = C_6H_{11}; X = NPh
7a, R = *i*-C_3H_7; X = NPh
8a, R = C_6H_{11}; X = NH
9a, R = C_6H_{11}; X = O

6b, R = C_6H_{11}; X = NPh
7b, R = *i*-C_3H_7; X = NPh
8b, R = C_6H_{11}; X = NH
9b, R = C_6H_{11}; X = O



6c, R = C_6H_{11}; X = NPh

6d, R = C_6H_{11}; X = NPh

Ar = *p*-$C_6H_5C_6H_4$

values for *cis* vicinal couplings in pyrrolidines.[5b] On the other hand, adducts **3b** and **4b** exhibit three distinct signals for the methoxycarbonyl protons in the range δ 3.6–4.0; coupling constants ($J_{4,5}$) of 5.7 and 3.9 Hz for **3b** and **4b**, respectively, indicate C_4 H and C_5 H to be *trans* in these isomers. The pertinent chemical shifts and coupling constants (Table II) are consonant with the assigned stereochemistry.

The *cis*-aziridine **1a** and fumaronitrile afforded two isomeric adducts which were assigned the gross structure methyl 1-cyclohexyl-5-(*p*-biphenyl)-3,4-dicyanopyrrolidine-2-carboxylate (**5a,b**). Adducts **3a** and **5a** both exhibited unexpectedly large *trans* vicinal coupling constants for C_3H and C_4H ($J_{3,4}$ = 11.0–11.5 Hz). These values were confirmed by deuterium labeling, spin-decoupling experiments, and computer simulation.[13] Presumably in **3a** and **5a** steric repulsion between the substituents at C_2 and C_3 and at C_4 and C_5 distorts the skeleton in such a manner as to cause the C_3H–C_4H angle to increase to well above 120°. Attainment of this particular conformation is aided by relief of eclipsing of the protons and substituents at C_2 and C_5 with those at C_3 and C_4, respectively.[14] In the all-*trans* **3b** and **5b**, the steric interactions are minimized and *trans* vicinal couplings in these compounds are restored to their normal magnitude.[11]

N-Phenylmaleimide was found to react with the *cis*-aziridines **1a** and **2a** in refluxing benzene to produce the isomeric adducts **6a,b** and **7a,b**, respectively. Cycloadducts of the same stereochemistry were obtained from **1a** when it was allowed to react with maleimide and maleic anhydride.

In contrast to the reaction of the *trans*-aziridine **1b** with the maleate and fumarate esters, this same aziridine, on reacting with N-phenylmaleimide afforded, in addition to **6a** and **6b**, two additional products which were found to be isomeric with **6a,b**. Only one of the two new isomers could be obtained as a pure compound and was assigned the all-*cis* stereochemistry (**6c**). The fourth isomer was believed to have the H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*trans* configuration (**6d**). The pmr spectrum of cycloadduct **6c** did not exhibit the expected doublets for C_2 H and C_5 H, but rather a series of three evenly spaced resonance signals was observed for each proton with the outer two signals of greater intensity than the center signal. This type of splitting pattern is attributed to virtual coupling[15] arising from the fact that the chemical shifts of C_3 H and C_4 H are nearly identical.

The reaction of **1b** with fumaronitrile was followed by pmr spectroscopy and found to give a mixture of four isomeric adducts. The pmr spectrum of the crude material exhibited four distinct methyl ester resonance signals, two of which had chemical shifts identical with those resonances in **5a** and **5b**, respectively. The products from this reaction could not be separated by the conventional means but, by analogy

(13) A. A. Bothner-By and A. Castellano, LAOCN 3, Program III, Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind., 1968.

(14) A similar result has been observed in 2,3-disubstituted indoles: see C. Lagercrantz and M. Yhland, *Acta Chem. Scand.*, **16**, 1799 (1963); A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 205 (1965).

(15) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1968).

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF METHINE PROTONS[a]

Adduct	δ, ppm from $(CH_3)_4Si$				J, Hz		
	H_2	H_3	H_4	H_5	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
3a	4.50	3.95	4.13	4.89	6.9	11.5	9.5
3b	4.57	3.55[b]	3.70[b]	4.91	1.0	...[b]	5.7
4a	4.63	3.39	3.88	5.00	3.5	9.0	8.3
4b	4.28	3.53	3.16	5.07	6.3	10.0	3.9
5a	4.43	3.50	4.25	4.89	6.5	11.0	9.4
5b	4.44	3.46	3.24	4.81	0.8	3.0	6.6
6a	4.63	3.29	3.80	5.11	0.0	8.0	9.5
6b	4.53	3.77	3.32	4.92	8.7	10.0	5.4
6c	4.11	3.50[b]	3.65[b]	4.56	7.6	...[b]	8.8
7a	4.63	3.33	3.83	5.03	0.0	8.4	9.8
7b	4.53	3.75	3.36	4.85	8.7	10.3	5.4
8a	4.45	3.10	3.58	4.98	0.0	8.0	9.6
8b	4.49	3.70	3.26	4.86	8.8	10.0	5.4
9a	4.59	3.48	3.88	5.13	0.0	8.7	9.6
9b	4.44	...[c]	...[c]	4.80	8.3	...[c]	5.0
10a	5.17	...	...	5.60	...	$J_{2,5}$ = 7.0	...
10b	4.81	...	...	5.31	...	$J_{2,5}$ = 4.6	...
11a	5.15	...	...	5.58	...	$J_{2,5}$ = 7.0	...
11b	4.81	...	...	5.31	...	$J_{2,5}$ = 4.5	...
13a	...	...	3.73	5.00	...	...	5.4
13b	...	...	3.70	4.93	...	...	6.0
14a	...	...	4.43	5.26	...	...	13.0
14b	...	...	4.39	5.19	...	...	13.4

[a] Pmr spectra were determined at *ca.* 35° on a Varian Associates Model A-60 spectrometer as deuteriochloroform solutions with tetramethylsilane as internal standard (δ 0.0); decoupling experiments were performed on a Varian Associates Model A-60D spectrometer equipped with a Model V-6058A field sweep spin decoupler. [b] Chemical shifts of H_3 and H_4 were nearly identical, giving rise to complex multiplets; coupling constants were not determined. [c] Resonance signals for H_3 and H_4 were masked by those of **9a**.

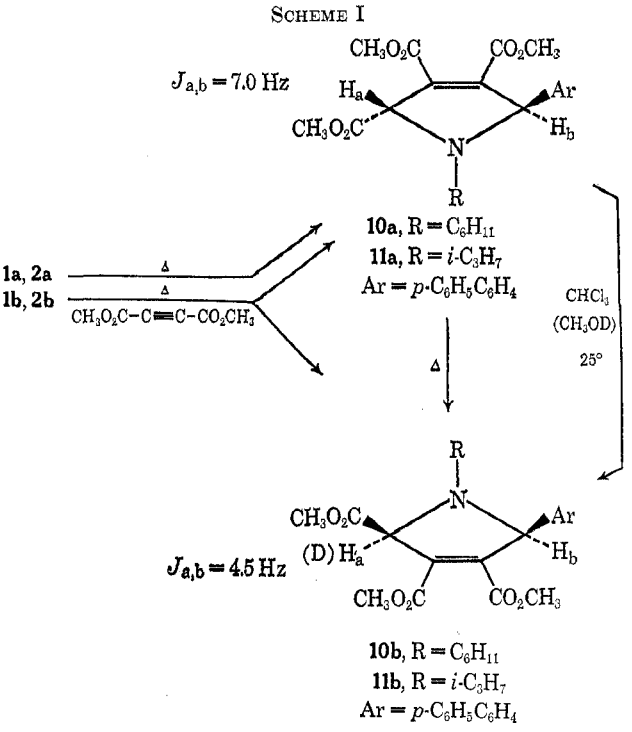
to **1b** and N-phenylmaleimide, were assigned the structures **5a–5d**.

The adducts obtained from reaction of 2 molar equiv of dimethyl acetylenedicarboxylate and 1 mol equiv of aziridines **1a,b** and **2a,b** in refluxing benzene were assigned the gross structure trimethyl 1-alkyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10a,b**, R = C_6H_{11}; **11a,b**, R = *i*-C_3H_7) (Scheme I). The pmr spectra of these compounds are unusual in that C_2 H and C_5 H exhibit long-range coupling constants in the range 4.5–7.0 Hz.[16]

Evidence for the Δ^3-pyrroline structure was obtained from the variety of reactions and rearrangements these compounds undergo (Scheme II). Thus oxidation of **10b** and **11b** with chloranil in boiling xylene produced the corresponding trimethyl 1-alkyl-5-(*p*-biphenyl)-pyrrole-2,3,4-tricarboxylates **12a** and **12b**. In methanol containing a catalytic amount of sodium methoxide, **10b** and **11b** were tautomerized to a mixture of the H_4,H_5-*trans* trimethyl 1-alkyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13a**, R = C_6H_{11}; **13b**, R = *i*-C_3H_7) and the corresponding H_4,H_5-*cis* isomer (**14a**, R = C_6H_{11}; **14b**, R = *i*-C_3H_7). The structure and stereochemistry of compounds **13a,b** and **14a,b** were assigned on the basis of pmr spectroscopy. Just as in the case of adducts **3a** and **4a**, the methoxycarbonyl protons at C_3 in **14a** and **14b** are shielded by *ca.* 0.8 ppm relative to the remaining methyl ester resonance signals (δ 3.81 and 4.00). Furthermore, the chemical shifts of C_4H and C_5H in **14a,b** and **13a,b** are as expected for the anisotropic effects exerted by the aryl and methoxycarbonyl groups on these protons in the two configurations. The observed coupling constants ($J_{4,5}$) of 5.4–6.0 and 13.0 Hz, in **13a,b** and **14a,b**, respectively, are also in support of the assigned stereochemistry. Deuterium was incorporated at C_4 in **13a,b** and **14a,b** when the tautomerization was conducted in methanol-d_1. Aluminum oxide (Woelm, neutral, activity grade I) induced isomerization of **10b** and **11b** to **14a** and **14b**, respectively.

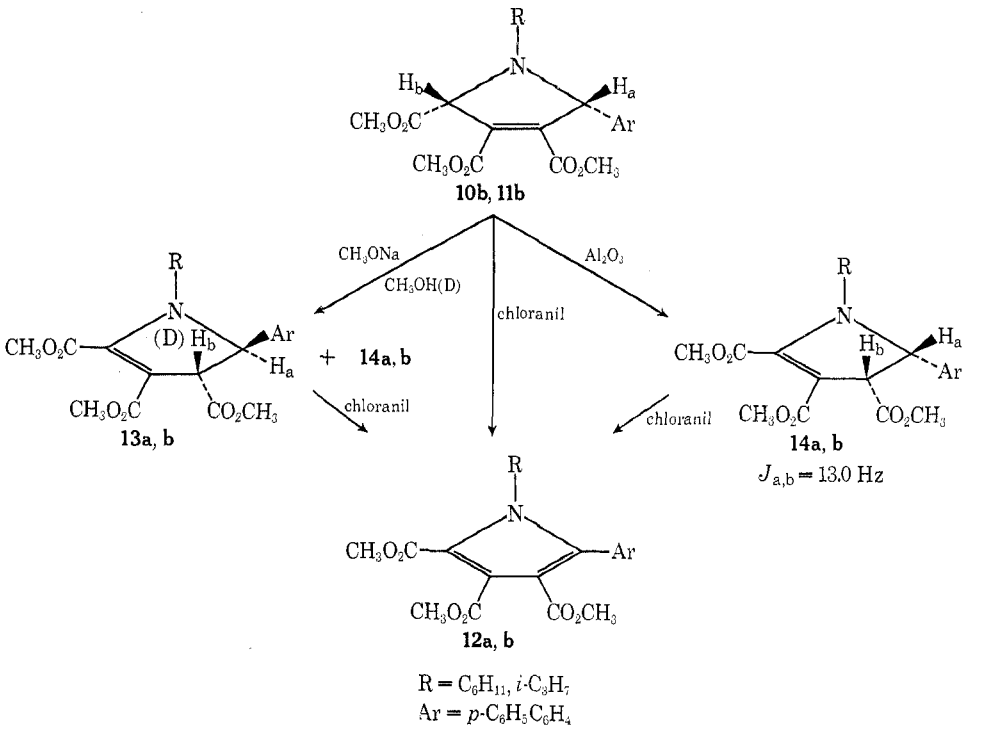
The reaction conditions had a pronounced effect on the proportions of **10a** (or **11a**) and **10b** (or **11b**) produced in the reaction of aziridines **1a,b** (or **2a,b**) with 2 molar equiv of dimethyl acetylenedicarboxylate

SCHEME I



(16) Long-range couplings of similar magnitude have been observed in Δ^3-pyrrolines by Huisgen and Deyrup (ref 9).

SCHEME II



R = C_6H_{11}, i-C_3H_7
Ar = p-$C_6H_5C_6H_4$

in refluxing benzene. Thus, after a 24-hr period of reflux, aziridine **2b** and dimethyl acetylenedicarboxylate afforded a mixture of **11a** (50–60%) and **11b** (40–50%) at which time *ca.* 75% of the aziridine had been consumed. The corresponding *cis*-aziridine **2a** under identical reaction conditions also produced a mixture of the H_2,H_3-*trans* Δ^3-pyrroline **11a** (30–35%) and the H_2,H_3-*cis* Δ^3-pyrroline **11b** (65–70%) with greater than 90% of the aziridine having reacted.

Shorter periods of reflux (10–12 hr) resulted in an increase in the amount of **11a**, while only **11b** could be detected by pmr spectroscopy when the period of reflux was increased to 48 hr. Column chromatography (silica gel or Florisil) of a mixture of **11a** (80%) and **11b** (20%) resulted in isolation of only **11b** (80%). It was noted that, if chloroform or methanol solutions of the crude reaction mixtures containing both **11a** and **11b** were allowed to stand for 10–24 hr at room temperature, the sole detectable isomer was **11b**. In methanol-d_1, the same mixture of **11a** and **11b** afforded the H_2,H_5-*cis* Δ^3-pyrroline **11b** as a mixture of the deuterium-labeled and -unlabeled products. A pure sample of **11b** was recovered unchanged and without deuterium exchange after standing for 24 hr at room temperature in methanol-d_1. These results seem to suggest that the H_2,H_5-*trans*-Δ^3-pyrrolines **10a** and **11a** are readily epimerized to the corresponding H_2,H_5-*cis* isomers **10b** and **11b**, respectively, and that the epimerization occurs more rapidly in polar solvents. As a result, we have been unable to obtain pure samples of **10a** or **11a** and thus to establish whether or not the presence of unreacted aziridine or dimethyl acetylenedicarboxylate catalyzes the isomerization.

The thermal equilibration of aziridines **1a** and **1b** at 80° in benzene-d_6 was followed by pmr spectroscopy, and at equilibrium the mixture consisted of 38% *trans* and 62% *cis* isomer. These same aziridines were not epimerized by strong base. Solutions of **1a** and **1b** in an ether–methanol-d_1 mixture containing a catalytic amount of sodium methoxide were refluxed for 3 days. The respective isomers were recovered unchanged and without deuterium exchange at C_3.

Discussion

All of the aforementioned reactions of aziridines **1a,b** and **2a,b** with activated alkenes and dimethyl acetylenedicarboxylate conform to the concept of 1,3-dipolar cycloaddition reactions as proposed by Huisgen.[17] The thermal process of ring cleavage of aziridines involves stereospecific, conrotatory ring opening.[8b] Thus aziridines **1a** and **1b** would be expected to yield the azomethine ylides **15a** and **15b**, respectively (Scheme III). The ylides can either equilibrate and ring close back to the aziridines (path A)[8b,9] or, in the presence of an unsaturated substrate, undergo stereospecific reaction to form five-membered-ring heterocycles (path B).[17a] Most such reactions are known to be stereospecific and hence concerted.[17b] The results obtained from reaction of aziridines **1a** and **1b** with the fumarate and maleate esters alone confirm that these reactions also proceed stereospecifically.

The cycloaddition to dipolarophiles competes with the equilibration process. In the present investigation not even dimethyl acetylenedicarboxylate was reactive enough to supress the equilibration of the *cis* and *trans* aziridines. The fumarate and maleate esters were found to be of lowest reactivity, while fumaronitrile, maleimide, and N-phenylmaleimide were of about the same reactivity as the acetylene ester.

Orientation phenomena in 1,3-dipolar cycloaddition reactions have been discussed as an interplay of steric and electronic factors.[17b,c] In most instances, the 1,3 dipole reacted with unsymmetrically bonded dipolaro-

(17) (a) R. Huisgen, *Angew. Chem., Intern. Ed. Engl.*, **2**, 565 (1963); (b) *ibid.*, **2**, 633 (1963); (c) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

TABLE III

ISOMER DISTRIBUTION IN CYCLOADDITION REACTIONS

Aziridine R	Aziridine Configuration	Dipolarophile	Adduct[a] (%)
C_6H_{11}	*cis*	Dimethyl fumarate[b]	**3a** (70), **3b** (30)
C_6H_{11}	*trans*	Dimethyl fumarate[b]	**3a** (50), **3b** (50)
C_6H_{11}	*cis*	Dimethyl maleate[b]	**4a** (75), **4b** (25)
C_6H_{11}	*trans*	Dimethyl maleate[c]	**4a** (77), **4b** (23)
C_6H_{11}	*cis*	N-Phenyl maleimide[b]	**6a** (33), **6b** (67)
C_6H_{11}	*trans*	N-Phenyl maleimide[c]	**6a** (35), **6b** (10), **6c** (40), **6d** (15)
i-C_3H_7	*cis*	N-Phenyl maleimide[b]	**7a** (35), **7b** (65)
C_6H_{11}	*cis*	Fumaronitrile[c]	**5a** (50), **5b** (50)
C_6H_{11}	*trans*	Fumaronitrile[c]	**5a** (20), **5b** (20), **5c** (30), **5d** (30)
C_6H_{11}	*cis*	Maleimide[c]	**8a** (50), **8b** (50)
C_6H_{11}	*cis*	Maleic anhydride[c]	**9a** (70), **9b** (30)

[a] Per cent of isomer formed in reaction. [b] Based on total product isolated. [c] By electronic integration of appropriate resonance signals in the pmr spectrum of the crude reaction mixture.

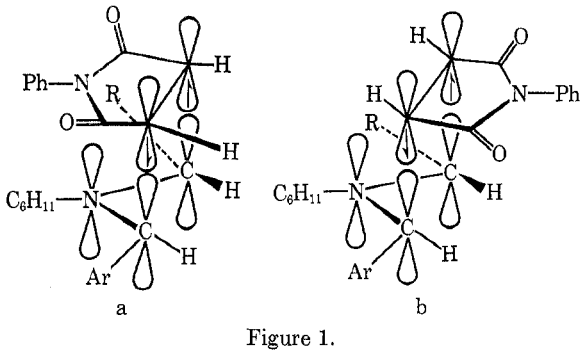
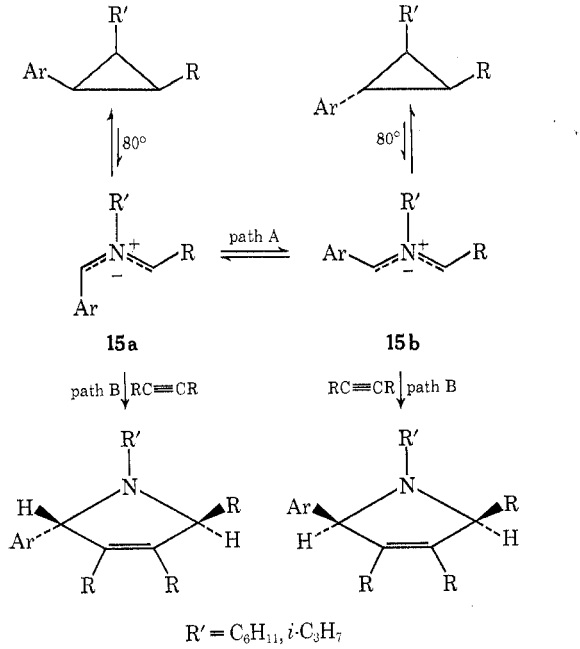


Figure 1.

philes which contained heteroatoms or which were of the alkene or alkyne series. Moreover, kinetic studies[17b] have amply demonstrated the influence of steric factors on the rates of these cycloaddition reactions. In the present investigation, each of the azomethine ylides would be expected to produce two adducts corresponding to two orientations of the 1,3 dipole and the dipolarophile in the activated complex

SCHEME III



leading to the transition state. It is interesting to note that, with the exception of N-phenylmaleimide, aziridine **1a** and the remaining dipolarophiles employed produced mainly that isomer in which the C_4 and C_5 substituents are *cis*. The reverse was observed with **1a** and N-phenylmaleimide (Table III). On the other hand, the corresponding *trans*-aziridine **1b** reacted with N-phenylmaleimide to afford the all-*cis* cycloadduct **6c** in major amount. Conrotatory ring opening of the *trans*-aziridines would be expected to proceed in such a manner as to minimize any steric compression of the ring substituents during the rotation process. Thus one might expect exclusive formation of ylide **15b** from either **1a** or **2a**. Figure 1 indicates the orientation of the 1,3 dipole and the dipolarophile (N-phenylmaleimide) required for formation of **6c** and **6d**, respectively. Approach of the two components as shown in Figure 1a would be expected to be severely hindered as a result of eclipsing of the aryl and the methoxycarbonyl groups of the 1,3 dipole with the carbonyl groups of the dipolarophile. Further nonbonded interactions exist between the N-aryl and N-alkyl groups in the two components, implying that formation of **6d** would be favored. However, the orientation depicted in Figure 1a is more like that proposed for the Diels–Alder reaction, in which there is maximum overlap of the π orbitals in the two components.[18]

The situation with the *cis*-aziridine is further complicated by the fact that ring opening may proceed by either clockwise or counterclockwise rotation of the substituents. Morevoer, until it can be demonstrated that the product distribution in these reactions is kinetically controlled, any attempt to explain these results in accordance with established concepts[17b,c] is premature.

The isolation of Δ^3-pyrrolines from reaction of aziridines **1a,b** and **2a,b** with dimethyl acetylenedicarboxylate is in accordance with the results of other workers[6,8b,9,10a] but is in contrast to the results reported by Padwa and Hamilton,[7b] in which *cis*- and *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine reacted with dimethyl acetylenedicarboxylate in refluxing benzene and were reported to produce dimethyl 1-cyclohexyl-2-phenyl-5-benzoyl-Δ^2-pyrroline-3,4-dicarboxylate and dimethyl 1-cyclohexyl-2-phenyl-5-benzoyl-pyrrole-3,4-dicarboxylate. The same dipolarophile, when heated

(18) R. Woodward and T. Katz, *Tetrahedron*, **5**, 70 (1959).

to 78–100° with the respective *cis* and *trans* forms of some 1-aryl-2-carbonyl-substituted aziridines[8b,9] afforded H_2,H_5-*trans* and H_2,H_5-*cis* Δ^3-pyrrolines, respectively. The N-aryl-Δ^3-pyrrolines were found to be stable under the reaction conditions.

These results lend support to our proposal that the N-alkyl-Δ^3-pyrrolines **10a** and **11a** are considerably less stable than the N-phenyl-Δ^3-pyrrolines in that the former compounds readily undergo epimerization to the corresponding H_2,H_5-*cis* isomers **10b** and **11b**, respectively. The epimerization of the H_2,H_5-*trans* isomer **10a** in refluxing benzene does not appear to proceed by reversal of **10a** to the aziridine and the dipolarophile with subsequent recombination, for, when a benzene solution of **10a**, **10b**, and methyl *cis*-1-cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1c**) was refluxed for 24 hr, pmr spectroscopy revealed that the sole adduct **10b** contained no deuterium at C_5. Presumably an important factor in the epimerization is the basicity of the Δ^3-pyrroline nitrogen atom. However, until suitable evidence is available, speculation concerning the mechanistic question of whether the epimerization proceeds by an intermolecular or by an intramolecular process must be postponed.

While the H_2,H_5-*trans* Δ^3-pyrrolines **10a** and **11a** are the kinetically favored products, molecular models indicate that the corresponding H_2,H_3-*cis* isomers **10b** and **11b** could possibly derive their apparent thermodynamic stability from relief of nonbonded interactions between the N-alkyl group and the substituents at C_2 and C_5. A similar explanation can be invoked to explain, at least in part, the greater stability of the *cis* forms of some 1-alkyl-2,3-dibenzoylaziridines,[19] 1-alkyl-2-aryl-3-aroylaziridines,[12,19] and methyl 1-alkyl-2-aryl-3-aziridinecarboxylates[20] relative to the corresponding *trans* isomers and is the subject of a forthcoming publication.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The infrared spectra were determined on Perkin-Elmer Model 237 and Perkin-Elmer Model 21 instruments as solutions (carbon tetrachloride, chloroform), potassium bromide disks, or neat. Ultraviolet spectra were obtained with a Cary Model 11 or a Cary Model 14 instrument employing methanol solutions. The 60-MHz nmr spectra were determined on a Varian A-60 spectrometer and the chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (δ 0.0). Mass spectral analyses were determined on a Hitachi Perkin-Elmer RMU-6D spectrometer operating at 80 eV.

Synthesis of *cis*- and *trans*-Methyl 1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates. A. Preparation of Methyl α-Bromo-*p*-phenylcinnamate. ***trans*-*p*-Phenylcinnamic Acid.**—Condensation of *p*-phenylbenzaldehyde (mp 57–58°, Kent Chemicals Ltd., Vancouver, Canada) with malonic acid according to the method of Koo, *et al.*,[21] afforded *p*-phenylcinnamic acid, mp 223–224° (lit.[22] mp 224–225°), in 97% yield.

***trans*-Methyl *p*-Phenylcinnamate.**—Esterification of *p*-phenylcinnamic acid in a refluxing benzene–methanol mixture containing a catalytic amount of concentrated H_2SO_4 gave the crystalline product (90%): mp 150–151°; pmr ($CDCl_3$) δ 3.81 (s, 3 H, methoxy), 6.48 (d, 1 H, J = 16.6 Hz, α-vinyl), 7.2–7.7 (m, 9 H, aromatic), and 7.77 (d, 1 H, J = 16.6 Hz, β-vinyl); ir (CCl_4) $\nu_{C=O}$ 1725 cm^{-1}; uv (CH_3OH) λ_{max} 308 mμ (ϵ 29,000).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.54; H, 5.80.

Methyl 2,3-dibromo-3-(*p*-biphenyl)propionate, mp 148–149°, was obtained in 94% yield by bromination of methyl-*p* phenylcinnamate in carbon tetrachloride: pmr ($CDCl_3$) δ 3.90 (s, 3 H, methoxy), 4.90 and 5.46 (two d, 1 H each, J = 12.4 Hz, C_2H and C_3H, respectively), and 7.1–7.8 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1757 cm^{-1}; uv (CH_3OH) λ_{max} 269 mμ (ϵ 21,000).

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.45; Br, 40.14. Found: C, 48.53; H, 3.52; Br, 40.30.

Methyl α-Bromo-*p*-phenylcinnamate (*cis* and *trans*).—Dehydrohalogenation of the dibromo ester with N-methylpiperidine in refluxing benzene for 24 hr gave the desired α-bromo-α,β-unsaturated ester as a mixture of the *cis* and *trans* isomers.

The *trans* isomer gave the following data: mp 128–129°; pmr ($CDCl_3$) δ 3.83 (s, 3 H, methoxy), 7.1–8.0 (m, 9 H, aromatic), and 8.25 (s, 1 H, vinyl); ir (CCl_4) $\nu_{C=O}$, 1721 and 1734 cm^{-1}; ir (Nujol) $\nu_{C=O}$, 1725 cm^{-1}; uv (CH_3OH) λ_{max} 312 mμ (ϵ 29,000).

Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13; Br, 25.19. Found: C, 60.76; H, 4.18; Br, 25.16.

The *cis* isomer gave the following data: mp 65–66°; pmr ($CDCl_3$) δ 3.75 (s, 3 H, methoxy) and 7.2–7.6 (m, 10 H, aromatic and β-vinyl proton); ir (KBr) $\nu_{C=O}$ 1723 cm^{-1}; ir (CCl_4) 1733 cm^{-1}; uv (CH_3OH) λ_{max} 300 mμ (ϵ 24,600).

Anal. Found: C, 60.63; H, 4.23; Br, 25.20.

B. Aziridine Esters. Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* and *trans*) (1a,b).—A solution of *trans*-methyl α-bromo-*p*-phenylcinnamate (10 g, 3.15 mmol) in dry benzene (10 ml) containing cyclohexylamine (4.67 g, 47.2 mmol) was stirred for 48 hr at room temperature. The reaction mixture was diluted with ether, the precipitated amine salt was collected, and the solvent was evaporated under reduced pressure. The excess amine was removed under high vacuum with gentle heating (*ca.* 40°) and the residue was diluted with low-boiling petroleum ether (bp 30–60°). The solid material was extracted twice with hot petroleum ether and the remaining solid was recrystallized from this same solvent to afford 0.5 g of pure methyl *cis*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1a**): mp 122–124°; pmr ($CDCl_3$) δ 1.0–2.0 (m, 11 H, cyclohexyl), 2.49 and 2.88 (two d, 1 H each, J = 7.0 Hz, C_3H and C_2H, respectively), 3.45 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1752 and 1730 cm^{-1}; ir (Nujol) 1747 cm^{-1}; uv (CH_3OH) λ_{max} 257 mμ (ϵ 23,900).

Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18; mol wt, 335.43. Found: C, 78.84; H, 7.63; N, 4.16; mol wt, 335 (mass spectrum).

The combined petroleum ether extracts were evaporated and the remaining oil was diluted with methanol. Cooling produced a crystalline solid which was recrystallized twice from methanol to give 0.31 g of pure methyl *trans*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1b**): mp 94–95°; pmr ($CDCl_3$) δ 1.0–2.0 and 2.2–2.5 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 2.73 (d, 1 H, J = 2.5 Hz, C_3 H), 3.26 (br s, 1 H, C_2 H), 3.71 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1734 cm^{-1}; ir (Nujol) 1727 cm^{-1}; uv (CH_3OH) λ_{max} 257 mμ (ϵ 26,600).

Anal. Found: C, 78.60; H, 7.60; N, 4.21; mol wt, 335 (mass spectrum).

Methyl 1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* and *trans*) (2a,b).—A solution of the *trans*-α-bromo-α,β-unsaturated ester (2.0 g, 6.3 mmol) dissolved in benzene (20 ml) was treated with a 15-fold excess (5.57 g, 94.5 mmol) of isopropylamine. After being stirred for 48 hr at room temperature, the reaction mixture was diluted with ether, the amine salt was removed, and the solution was evaporated to dryness. The residue was recrystallized from methanol and two successive crops of pure methyl *trans*-1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**2b**), mp 122–124°, were obtained totaling 0.80 g: pmr ($CDCl_3$) δ 1.03 and 1.12 (two d, 6 H, J = 9.4 Hz, isopropyl methyls), 2.73 (d, J = 2.5 Hz), 3.25 (br s), and 2.7–3.4 (m) (3 H, C_3 H, C_2 H, and isopropyl methine, respectively), 3.71 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1732 cm^{-1}; ir (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.49; H, 7.26; N, 4.76.

(19) (a) R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968); (b) A. B. Turner, J. Irving, and J. B. Bush, Jr., *J. Amer. Chem. Soc.*, **87**, 1050 (1965); (c) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967), footnote 6.

(20) P. B. Woller and N. H. Cromwell, unpublished results.

(21) J. Koo, *et al.*, in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 327.

(22) V. Skvarchenko, D. Tsybikova, and R. Levina, *Zh. Obshch. Khim.*, **31**, 1819 (1961).

Evaporation of the methanol filtrate yielded an oil which was diluted with petroleum ether. Cooling produced 0.48 g of pure methyl *cis*-1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**2a**): mp 88–90°; pmr ($CDCl_3$) δ 1.20 (d, J = 5.4 Hz) and 1.66 (m, 7 H, isopropyl methyls and methine, respectively), 2.44 and 2.86 (two d, 1 H each, J = 7.0 Hz, C_2 H and C_3 H, respectively), 3.40 (s, 3 H, methoxy), and 7.1–7.6 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1727 and 1753 cm^{-1}; ir (KBr) 1750 cm^{-1}.

Anal. Found: C, 77.22; H, 7.19; N, 4.78.

C. Deuterium-Labeled Aziridine Esters. Preparation of Methyl α-Bromo-β-d_1-*p*-phenylcinnamate.—*p*-Phenylbenzaldehyde-d_1, mp 57–58°, was prepared in a manner analogous to that described for benzaldehyde-d_1.[23] Subsequent condensation with malonic acid, esterification, bromination, and dehydrohalogenation as previously described afforded *trans*-methyl α-bromo-β-d_1-*p*-phenylcinnamate, mp 129–130°.

Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-2-d_1-3-aziridinecarboxylate (*cis* and *trans*) (1c,d).—These compounds were prepared by reaction of *trans*-methyl α-bromo-β-d_1-*p*-phenylcinnamate with a 15-fold excess of cyclohexylamine in benzene. The products were isolated as described for the synthesis of **1a** and **1b**. The ring-proton spectra of the deuterium-labeled aziridines **1c** and **1d** consisted of singlets at δ 2.88 and 2.73 for the *cis* (**1c**) and *trans* (**1d**) forms, respectively, and confirmed the previous chemical-shift assignments of the ring protons in **1a** and **1b**.

Methyl 1-Cyclohexyl-2,3-d_2-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* and *trans*) (1e,f).—Reaction of cyclohexylamine-N-d_2[24] with the deuterium-labeled α-bromo-α,β-unsaturated ester as described for the synthesis of **1a** and **1b** produced the deuterium-labeled aziridine esters **1e** and **1f**. The ring-proton spectra of these compounds indicated >90% deuterium labeling at C_2 and C_3.

1,3-Dipolar Cycloaddition Reactions with Activated Olefins. General Procedure.—Equimolar quantities of the aziridine and the dipolarophile were refluxed in dry benzene for 24–48 hr, after which time the solution was filtered. In all cases, evaporation of the solvent under reduced pressure afforded a pale yellow to yellow oil which was chromatographed on silica gel, alumina, or Florisil.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Dimethyl Fumarate.—A sample (335 mg, 1.0 mmol) of the aziridine ester **1a** and diethyl fumarate (144 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr, cooled to room temperature, and filtered. The pale yellow oil obtained after removal of the solvent was diluted with methanol and cooled to afford 310 mg (63%) of H_2,H_3-*cis*-H_3,H_4-*trans*-H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**3a**) as a crystalline solid: mp 146–148°; pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11 (s, 3 H, methoxy of C_4 substituent), 3.66 and 3.67 (two s, 3 H each, two methoxy groups), 3.99–4.35 (m, 2 H, C_3 H and C_4 H), 4.50 (d of d, 1 H, J = 6.9, −0.6 Hz, C_3 H), 4.89 (br d, 1 H, J = 9.5 Hz, C_5 H), and 7.1–7.9 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1730 and 1744 cm^{-1}.

Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.12; H, 6.94; N, 2.92; mol wt, 479.55. Found: C, 70.06; H, 6.93; N, 3.04; mol wt, 479 (mass spectrum).

The methanol filtrate was evaporated to dryness and the residual oil was chromatographed on a column of Florisil (13 g). Elution with benzene (500 ml) and then with 3% ether–benzene (300 ml) gave small amounts of unreacted aziridine ester **1a** and dimethyl fumarate in the benzene fractions. The ether–benzene eluents contained 125 mg (26%) of a colorless oil which resisted all attempts to induce crystallization. This material was recognized as being isomeric with the crystalline pyrrolidine **3a** and assigned the structure H_2,H_3-*trans*-H_3,H_4-*trans*-H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**3b**) on the basis of spectral data: pmr ($CDCl_3$) δ 0.6–2.3 and 2.4–3.0 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.55–3.70 (m, 2 H, C_3 H and C_4 H), 3.77 and 4.00 (two s, 9 H, three methoxy groups), 4.57 (d, 1 H, J = 1.0 Hz, C_2 H), 4.91 (br d, 1 H, J = 5.7 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1743 cm^{-1}; mol wt, 479 (mass spectrum).

Methyl *cis*-1-Cyclohexyl-2,3-d_2-2-(*p*-biphenyl)-3-aziridinecarboxylate (1c) and Dimethyl Fumarate.—Trimethyl 1-cyclohexyl-2,5-d_2-5-(*p*-biphenyl)-pyrrolidine-2,3,4-tricarboxylate (**3a'**), mp 147–148°, was produced by reaction of the deuterium-labeled aziridine ester **1c** and dimethyl fumarate in refluxing benzene: pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11, 3.66, and 3.67 (three s, 3 H each, three methoxy groups), 3.95 and 4.13 (two d, 1 H each, J = 11.5 Hz, C_3 H and C_4 H), and 7.1–7.9 (m, 9 H, aromatic).

Methyl *cis*-1-Cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (1e) and Dimethyl Fumarate.—Reaction of equimolar quantities of **1e** and dimethyl fumarate in refluxing benzene afforded trimethyl 1-cyclohexyl-5-d_1-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate: mp 147–148°; pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11, 3.66, and 3.67 (three s, 3 H each, three methoxy groups), 3.99–4.35 (m, 2 H, C_3 H and C_4 H), 4.50 (d, 1 H, J = 6.9 Hz, C_2 H), and 7.1–7.9 (m, 9 H, aromatic).

Computer simulation of the pmr spectrum of this adduct and spin-decoupling experiments permitted assignment of chemical shifts of δ 3.95 and 4.13 for C_3 H and C_4 H, respectively.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Fumarate.—The *trans*-aziridine ester **1b** and dimethyl fumarate in refluxing benzene (48 hr) reacted to give 44% crystalline pyrrolidine **3a** and 45% isomeric adduct **3b**.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Dimethyl Maleate.—Refluxing a benzene (10 ml) solution of the *cis* aziridine ester **1a** (335 mg, 1.0 mmol) and dimethyl maleate (144 mg, 1.0 mmol) for 24 hr gave, after removal of the solvent, a pale yellow oil. Column chromatography (Florisil, 50 g) of the crude material afforded 320 mg (67%) of a colorless oil from early 3% ether–benzene fractions after initial elution of small amounts of unreacted aziridine and dimethyl maleate with benzene (1 l.). The oil was diluted with a small amount of methanol and cooled to yield white granules of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**4a**): mp 92–93°; pmr ($CDCl_3$) δ 0.7–2.2 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.15 (s, 3 H, methoxy of C_4 substituent), 3.39 (d of d, 1 H, J = 9.0, 3.5 Hz, C_3 H), 3.67 and 3.76 (two s, 3 H each, two methoxy groups), 3.88 (d of d, 1 H, J = 9.0, 8.3 Hz, C_4 H), 4.63 (d, 1 H, J = 3.5 Hz, C_2 H), 5.00 (d, 1 H, J = 8.3 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1725, 1730, and 1735 cm^{-1}.

Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.12; H, 6.94; N, 2.92; mol wt, 479.55. Found: C, 70.10; H, 6.90; N, 2.90; mol wt, 479 (mass spectrum).

Further elution with ether gave 105 mg (22%) of a crystalline solid which was recrystallized from methanol and identified as H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**4b**): mp 122–124°; pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.7 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.16 (d of d, 1 H, J = 3.9, 10.0 Hz, C_4 H), 3.53 (d of d, 1 H, J = 10.0, 6.3 Hz, C_3 H), 3.67, 3.73, and 3.75 (three s, 3 H each, three methoxy groups), 4.28 (d, 1 H, J = 6.3 Hz, C_2 H), 5.07 (d, 1 H, J = 3.9 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1742 cm^{-1}.

Anal. Found: C, 70.18; H, 6.93; N, 3.02; mol wt, 479 (mass spectrum).

The reaction was repeated in refluxing toluene and the percentages of **4a** and **4b** were determined to be 83:17, respectively, by pmr spectroscopy.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Maleate.—Reaction of the *trans*-aziridine ester **1b** and dimethyl maleate in refluxing benzene (48 hr) produced 70 and 21% **4a** and **4b**, respectively.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Fumaronitrile.—A sample (335 mg, 1.0 mmol) of the *cis*-aziridine was dissolved in benzene (10 ml) containing fumaronitrile (78 mg, 1.0 mmol) and the resulting solution was refluxed for 24 hr. The oil remaining after evaporation of the solvent was chromatographed on a column of Florisil (50 g) and initially eluted with benzene (500 ml) to afford small amounts of the two reactants. Subsequent elution with 2% ether–benzene afforded 360 mg of a colorless oil. Crystalline material was obtained by diluting the oil with ether and addition of pentane until turbid. The crystalline solid analyzed correctly for the gross structure methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate. The pmr spectrum of this material indicated a mixture of two isomers in a ratio of *ca.* 1:1.

(23) D. Seebach, R. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(24) D. B. Denney and M. A. Greenbaum, *J. Amer. Chem. Soc.*, **79**, 3701 (1957).

Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.33; H, 6.56; N, 10.29.

A pure sample of H_2,H_3-*cis*-H_3,H_4-*trans*-H_4,H_5-*cis* methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate (**5a**), mp 138–141°, was obtained by column chromatography of the mixture on alumina and elution with benzene: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.50 (d of d, 1 H, J = 6.5, 11.0 Hz, C_3 H), 3.85 (s, 3 H, methoxy), 4.25 (d of d, 1 H, J = 9.4, 11.0 Hz, 4.43 (d, 1 H, J = 6.5 Hz, C_2 H), 4.89 (d, 1 H, J = 9.4 Hz, C_5 H), and 7.3–7.7 (m, 9 H, aromatic); ir (KBr) $\nu_{C\equiv N}$ 2252 cm^{-1}; $\nu_{C=O}$ 1735 cm^{-1}.

The second product was assigned the structure H_2,H_3-*trans*-H_3,H_4-*trans*-H_4,H_5-*trans* methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate (**5b**) on the basis of pmr spectral data. This product could not be isolated without contamination of **5a** and apparently decomposed during chromatography of the crude material on alumina: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.24 (d of d, 1 H, J = 6.6, 3.0 Hz, C_3 H), 3.46 (d of d, 1 H, J = 3.0, 0.8 Hz, C_3 H), 3.78 (s, 3 H, methoxy), 4.44 (d, 1 H, J = 0.8 Hz, C_2 H), 4.81 (d, 1 H, J = 6.6 Hz, C_5 H), and 7.3–7.7 (m, 9 H, aromatic).

The reaction was repeated and monitored by pmr spectroscopy. A solution of the *cis*-aziridine ester **1a** (167 mg, 0.5 mmol) and the dipolarophile (39 mg, 0.5 mmol) in benzene-d_6 (0.3 ml) was transferred to an nmr tube, and the tube was sealed and placed in an oil bath maintained at 80 ± 1°. At 8-hr intervals the reaction mixture was examined by pmr spectroscopy. After 32 hr, all aziridine had been consumed and **5a** and **5b** were present in equal amounts. The methyl ester resonance signals for **5a** and **5b** were located at δ 3.53 and 3.56, respectively.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Fumaronitrile.—The reaction of the *trans*-aziridine ester **1b** with fumaronitrile in benzene at 81° was monitored as described for reaction of **1a** with fumaronitrile. After 48 hr, the reaction mixture was examined by pmr spectroscopy. Four distinct methyl ester resonance signals were observed at δ 3.53 (**5a**, 20%), 3.56 (**5b**, 20%), 3.58 (**5c**, 30%), and 3.61 (**5d**, 30%).

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and N-Phenylmaleimide.—A sample (335 mg, 1.0 mmol) of the *cis*-aziridine ester **1a** and N-phenylmaleimide (173 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr and the crude reaction mixture was chromatographed on a column of Florisil (50 g). Initial elution with benzene (500 ml) gave small amounts of unreacted aziridine and dipolarophile while a colorless solid was obtained upon further elution with benzene (500 ml) and 3% ether–benzene (250 ml). This material was recrystallized from methanol to give 300 mg (59%) of pure H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6b**): mp 191–192°; pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.9 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.32 (d of d, 1 H, J = 10.0, 5.4 Hz, C_4 H), 3.66 (s, 3 H, methoxy), 3.70 (d of d, 1 H, J = 8.7, 10.0 Hz, C_3 H), 4.53 (d, 1 H, J = 8.7 Hz, C_2 H), 4.92 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.1–7.7 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1790 and 1725 cm^{-1}.

Anal. Calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.55; H, 6.35; N, 5.65.

Further elution with 3% ether–benzene afforded a colorless oil which was crystallized by the addition of pentane. Recrystallization from an ether–pentane mixture gave 150 mg (30%) of a solid material, mp 150–151°, which was assigned the structure of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6a**): pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.29 (d, 1 H, J = 8.0 Hz, C_3 H), 3.73 (s, 3 H, methoxy), 3.80 (d of d, 1 H, J = 9.5, 8.0 Hz, C_4 H), 4.63 (s, 1 H, C_2 H), 5.11 (d, 1 H, J = 9.5 Hz, C_5 H), and 7.0–7.7 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1770 and 1750 cm^{-1}.

Anal. Found: C, 75.76; H, 6.46; N, 5.23.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and N-Phenylmaleimide.—A benzene (10 ml) solution of the *trans*-aziridine ester **1b** (670 mg, 2.0 mmol) and N-phenylmaleimide (346 mg, 2.0 mmol) was refluxed for 48 hr. Evaporation of the solvent afforded a pale yellow oil which was chromatographed on Florisil (70 g). Elution with benzene (1.5 l.) gave small amounts (<10%) of unreacted starting materials in early fractions and 300 mg (29%) of **6a** in later fractions. Further elution with a 3% ether–benzene mixture (1.5 l.) gave a mixture of two isomeric adducts. Recrystallization from a minimal amount of ether gave 300 mg (29%) of crystalline material, mp 205–207°, which was assigned the structure of H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6c**): pmr ($CDCl_3$) δ 0.7–2.1 and 2.2–3.0 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.5–3.7 (m, 2 H, C_3 H and C_4 H), 3.83 (s, 3 H, methoxy), 4.11 and 4.56 (two m, 1 H each, C_2 H and C_3 H, respectively) (these assignments and couplings of 7.6 and 8.8 Hz, respectively, were verified by spin-decoupling experiments) and 6.8–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1715 and 1760 cm^{-1}.

Anal. Found: C, 75.43; H, 6.28; N, 5.60.

The ether filtrate was reduced in volume and diluted with pentane. Cooling afforded 90 mg (9%) of **6b**. The column was washed with ethyl acetate (250 ml) to give only trace amounts of material.

When the experiment was repeated and monitored by pmr spectroscopy as described for the reaction of **1a** with fumaronitrile, a fourth methyl ester resonance signal was observed which did not correspond to the signals for **6a–6c** and was ascribed to the presence of **6d**. The percentages of the four isomeric adducts **6a–6d** were estimated to be 25:10:40:15, respectively.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Maleimide.—A solution of aziridine **1a** (167 mg, 0.5 mmol) and maleimide (49 mg, 0.5 mmol) in benzene (5 ml) was refluxed for 24 hr and the solvent was evaporated. The residue was recrystallized from methanol–chloroform (1:1, v/v) to afford 86 mg (40%) of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-2-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboximide (**8a**), mp 211–212°. The analytical sample, recrystallized from methanol, was found to contain water of crystallization: pmr ($CDCl_3$) δ 0.7–2.0 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.10 (d, 1 H, J = 8.0 Hz, C_3 H), 3.58 (d of d, 1 H, J = 9.8, 8.0 Hz, C_4 H), 3.73 (s, 3 H, methoxy), 4.45 (s, 1 H, C_2 H), 4.98 (d, 1 H, J = 9.8 Hz, C_5 H), and 7.1–7.7 (m, 10 H, aromatic and NH); ir (KBr) ν_{NH} 3400 cm^{-1}; $\nu_{C=O}$ 1720 and 1780 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}N_2O_4 \cdot H_2O$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.41; H, 6.63; N, 6.11.

Evaporation of the filtrate afforded a colorless oil which was chromatographed on a column of silica gel (5 g). Initial elution with benzene (200 ml) gave small amounts of unreacted starting materials. H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboximide (**8b**) was obtained as a crystalline solid (75 mg, 35%), mp 220–221°, from 1% ethyl acetate–benzene fractions: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.7 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.26 (d of d, 1 H, J = 10.0, 5.4 Hz, C_4 H), 3.70 (d of d, J = 8.8, 10.0 Hz) and 3.71 (s, 4 H, C_3 H and methoxy), 4.49 (d, 1 H, J = 8.8 Hz, C_2 H), 4.86 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 10 H, aromatic and NH); ir (KBr) ν_{NH} 3450 cm^{-1}; $\nu_{C=O}$ 1701, 1742, and 1779 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.61; H, 6.63; N, 6.37.

The adducts **8a** and **8b** were found to be present in equal amounts as determined from the pmr spectrum of the crude reaction mixture.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Maleic Anhydride.—Refluxing a benzene (5 ml) solution of the *cis* aziridine **1a** (167 mg, 0.5 mmol) and maleic anhydride (48 mg, 0.5 mmol) for 24 hr and evaporation of the solvent afforded a pale yellow oil. Crystalline material, mp 159–180°, was obtained by dilution with ether and addition of pentane until turbid. Repeated recrystallization did not improve the melting point. The infrared spectrum (KBr) exhibited prominent carbonyl absorptions at 1722, 1785, and 1865 cm^{-1}. Elemental analysis of the solid was consonant with the molecular formula $C_{26}H_{27}NO_5$. Pmr spectral data indicated the presence of two isomeric compounds, the structures of which were assigned as H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* and H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboxylic anhydride (**9a** and **9b**, respectively).

Anal. Calcd for $C_{26}H_{27}NO_5$: C, 72.02; H, 6.28; N, 3.23. Found: C, 72.01; H, 6.31; N, 3.23.

Compound **9a** gave the following data: pmr ($CDCl_3$) δ 0.7–2.1 and 2.2–2.8 (two m, cyclohexyl methylenes and methine, respectively), 3.48 (d, J = 8.7 Hz, C_3 H), 3.76 (s, methoxy),

3.88 (d of d, J = 9.8, 8.7 Hz, C_4 H), 4.59 (s, C_2 H), 5.13 (d, J = 9.6 Hz, C_5 H), and 7.2–7.8 (m, aromatic).

Compound **9b** gave the following data: pmr ($CDCl_3$) δ 3.73 (s, methoxy), 4.44 (d, J = 8.3 Hz, C_2H), and 4.80 (d, J = 5.0 Hz, C_5H).

Electronic integration of the appropiate resonance signals in the pmr spectrum of the crude material indicated 70% **9a** and 30% **9b**.

Methyl *cis*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2a) and N-Phenylmaleimide.—A solution of the *cis* aziridine **2a** (295 mg, 1.0 mmol) and N-phenylmaleimide (173 mg, 1.0 mmol) was refluxed in 10 ml of benzene for 24 hr. Evaporation of the solvent gave a pale yellow oil which was chromatographed on Florisil (40 g) and eluted as previously described for reaction of **1a** with N-phenylmaleimide. The first eluted product (260 mg, 55%) was recrystallized from methanol and assigned the structure H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-isopropyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**7b**): mp 185–187°; pmr ($CDCl_3$) δ 0.81 and 1.11 (two d, 6 H, J = 7.0 Hz, two methyls), 2.95 (m, 1 H, isopropyl methine), 3.36 (d of d, 1 H, J = 5.4, 10.3 Hz, C_3 H), 3.65 (s, 3 H, methoxy), 3.75 (d of d, 1 H, J = 8.7, 10.3 Hz, C_4 H), 4.53 (d, 1 H, J = 8.7 Hz, C_2 H), 4.85 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1705, 1725, and 1775 cm^{-1}.

Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.18; H, 6.13; N, 5.92.

H_2,H_3-*trans*-$H_3$$H_4$-*cis*-$H_4$,$H_5$-*cis* methyl 1-isopropyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**7a**) was obtained from 3% ether–benzene fractions. Recrystallization from methanol afforded 140 mg (30%) of pure **7a**: mp 171–172°; pmr ($CDCl_3$) δ 0.81 and 1.16 (two d, 3 H, J = 7.0 Hz, isopropyl methyls), 3.02 (m, 1 H, isopropyl methine), 3.33 (d, 1 H, J = 8.4 Hz, C_3 H), 3.75 (s, 3 H, methoxy), 3.83 (two d, 1 H, J = 9.8, 8.4 Hz, C_4 H), 4.63 (s, 1 H, C_2 H), 5.03 (d, 1 H, J = 9.8 Hz, C_5 H), and 7.1–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1710, 1725, 1770 cm^{-1}.

Anal. Found: C, 74.14; H, 6.22; N, 5.94.

Electronic integration of the pmr spectrum of the crude material indicated the percentages of **7a** and **7b** to be 35:65, respectively.

Dipolar Cycloaddition Reactions with Dimethyl Acetylenedicarboxylate. General Procedure.—Benzene solutions of 1 molar equiv of the aziridine ester and 2 molar equiv of dimethyl acetylenedicarboxylate were refluxed for varying periods of time, the solvents were removed under reduced pressure, and the residue was examined by pmr spectroscopy. The products were isolated by column chromatography on silica gel or Florisil.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) with Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (335 mg, 1.0 mmol) and the dipolarophile 284 mg, 2.0 mmol) was refluxed in benzene (10 ml) for 24 hr. The solvent was removed and the residue was chromatographed on silica gel (40 g). The column was eluted successively with 50% petroleum ether–benzene (250 ml), benzene (500 ml), and 1% ethyl acetate–benzene (500 ml). The benzene and ethyl acetate–benzene fractions contained the excess dimethyl acetylenedicarboxylate. Further elution with ethyl acetate–benzene mixtures (1:49, 500 ml; 3:97, 500 ml; 2:48, 500 ml) afforded 380 mg (80%) of a pale yellow oil. This material could not be obtained in a crystalline form and was assigned the structure H_2,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10b**) on the basis of spectral and chemical evidence cited below: pmr ($CDCl_3$) δ 0.8–2.8 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.55, 3.68, and 3.80 (three s, 3 H each, three methoxy groups), 4.81 and 5.31 (two d, 1 H each, J = 4.6 Hz, C_2 H and C_5 H, respectively), and 7.2–7.7 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1726 and 1742 cm^{-1}, $\nu_{C=C}$, 1670 cm^{-1}.

When this material was chromatographed on alumina (Woelm, neutral, activity grade I) and eluted with ethyl acetate, a bright yellow oil was obtained. This material resisted all attempts to induce crystallization. The pmr spectrum indicated the structure of H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**14a**): pmr ($CDCl_3$) δ 0.8–2.0 and 2.8–3.2 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.09 (s, 3 H, methoxy of C_4 substituent), 3.81 and 4.00 (two s, 3 H each, two methoxy groups), 4.43 and 5.26 (two d, 1 H each, J = 13.0 Hz, C_4 H and C_5 H, respectively), and 7.3–7.9 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1745 cm^{-1}, $\nu_{C=C}$ 1680 and 1580 cm^{-1}.

Oxidation of H_2,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10b).—A solution of **10b** (238 mg, 0.5 mmol) and chloranil (246 mg, 1.0 mmol) in xylene (15 ml) was refluxed for 6 hr. The cooled solution was diluted with ether (50 ml), and washed successively with three 20-ml portions of 4% aqueous sodium hydroxide solution containing 1% sodium bisulfite and then with water. The organic layer was dried (anhydrous $MgSO_4$) and the solvent was evaporated. The residue was recrystallized from methanol to afford 75 mg (31%) of trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrole-2,3,4-tricarboxylate (**12a**): mp 176–178°; pmr ($CDCl_3$) δ 0.8–2.5 (m, 10 H, cyclohexyl methylene), 3.66, 3.83, and 3.91 (three s, 3 H, each, three methoxy groups), 3.8–4.6 (m, 1 H, cyclohexyl methine), and 7.3–7.8 (9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1705, 1730, and 1745 cm^{-1}.

Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.75; H, 5.99; N, 2.92.

Oxidation of H_4,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (14a).—A sample (119 mg, 0.25 mmol) of **14a** was oxidized with chloranil as described for the oxidation of **10b** to afford 24 mg (20%) of **12a**.

Base-Catalyzed Isomerization of H_2,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10b).—A sample (238 mg, 0.5 mmol) of **10b** in methanol (10 ml) was treated with sodium methoxide (5 mg). A deep yellow color developed immediately and the solution was allowed to stand for 24 hr at room temperature, after which time the solvent was evaporated under reduced pressure. The residue was diluted with ether, washed with water, and dried (anhydrous $MgSO_4$). The bright yellow oil which remained after evaporation of the solvent was chromatographed on a column of silica gel (15 g). A small amount (10 mg) of a bright yellow material was eluted with 1% ethyl acetate–benzene (500 ml), and a colorless oil was obtained upon elution with 2% ethyl acetate–benzene. Crystallization was induced by dilution with ether and then addition of pentane until turbid. Cooling produced colorless crystals (175 mg, 74%) of H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13a**): mp 130–131°; pmr ($CDCl_3$) δ 0.8–2.2 and 2.8–3.3 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.63 (s, 3 H, methoxy), 3.73 (d, 1 H, J = 5.4 Hz, C_4 H), 3.76 and 3.96 (two s, 3 H each, two methoxy groups), 5.00 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1730 and 1745 cm^{-1}, $\nu_{C=C}$ 1685 and 1600 cm^{-1}.

Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.63; H, 6.62; N, 2.88.

The experiment was repeated in methanol-d_1 as solvent and the ether extracts were washed with D_2O during work-up. The pmr spectrum of the crystalline solid, mp 130–131°, obtained upon column chromatography of the crude material was identical with that of **13a**, with the exception that the high-field doublet ascribed to C_4 H was absent and the resonance signal for C_5 H appeared as a slightly broadened singlet at δ 5.00.

Oxidation of H_4,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (13a).—A solution of **13a** (238 mg, 0.5 mmol) was oxidized with chloranil (246 mg, 1.0 mmol) in refluxing xylene. After 10 hr, the product was isolated as described for oxidation of **10b** to **12a** to afford 50 mg (21%) of **12a**.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Acetylenedicarboxylate.—A sample (335 mg, 1.0 mmol) of the *trans*-aziridine ester **1b** and the dipolarophile (284 mg, 2.0 mmol) in benzene (10 ml) was heated to reflux, during which time the solution developed a deep red color. The reaction mixture was refluxed for 30 hr and worked up according to the procedure described for the reaction of the *cis* aziridine **1a** and dimethyl acetylenedicarboxylate to afford 360 mg (75%) of a pale yellow oil. The pmr spectrum of this material was identical with that of H_2,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10b**).

The experiment was repeated with the period of reflux decreased to 20 hr. Examination of the crude material by pmr spectroscopy indicated the presence of **10b** and a second adduct which was recognized as being isomeric with **10b**. The second product was assigned the structure H_2,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10a**). The pyrroline ring proton spectrum of **10a** consisted of two doublets located at δ 5.17 (C_2 H) and 5.60 (C_5 H) with $J_{2,5}$ = 7.0 Hz. Electronic integration indicated the ratio of **10a** to **10b** to be 3:1 (40%); *ca.* 60% of the aziridine had been con-

sumed. After an additional 28-hr period of reflux, the ratio of **10a** to **10b** was 1:3 and 80% of the aziridine had reacted. None of the isomeric *cis*-aziridine **1a** could be detected at either time. Repetition of this experiment with equimolar quantities of the two reactants produced nearly identical results.

Attempted Isolation of H_2,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10a).—A solution of aziridine **1b** (335 mg, 1.0 mmol) and dimethyl acetylenedicarboxylate (142 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr. The residue which remained after evaporation of the solvent was examined by pmr spectroscopy and found to consist of nearly equal amounts of **10a** and **10b**. Column chromatography of this material on silica gel and elution as described for the reaction of **1a** and dimethyl acetylenedicarboxylate afforded 150 mg (45%) of aziridine **1b** and 200 mg (42%) of **10b**. None of the isomeric Δ^3-pyrroline **10a** could be detected in any of the ethyl acetate–benzene fractions or in the ethyl acetate washings.

Methyl *cis*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2a) and Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (590 mg, 2.0 mmol) and the dipolarophile (568 mg, 4.0 mmol) was refluxed for 24 hr in benzene. Evaporation of the solvent afforded a yellow oil which was chromatographed on silica gel (80 g) as described for the reaction of aziridine **1a** with dimethyl acetylenedicarboxylate to afford 700 mg (80%) of a pale yellow oil. This material could not be obtained in a crystalline form and was assigned the structure H_2,H_5-*cis* trimethyl-1-isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**11b**) on the basis of spectral data: pmr ($CDCl_3$) δ 0.99 and 1.02 (two d, 6 H, J = 6.5 Hz, isopropyl methyls), 3.10 (m, 1 H, isopropyl methine), 3.59, 3.74, and 3.83 (three s, 3 H each, three methoxy groups), 4.81 and 5.31 (two d, 1 H each, J = 4.5 Hz, C_2 H and C_5 H, respectively), and 7.4–7.8 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1724 and 1739 cm^{-1}, $\nu_{C=C}$ 1667 cm^{-1}.

Repetition of the experiment and examination of the crude material by pmr spectroscopy indicated a mixture of **11b** and a second isomeric product which was assigned the structure H_2,H_5-*trans* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**11a**). The ring-proton spectrum of **11a** consisted of two doublets (J = 4.6 Hz) located at δ 5.15 (C_2 H) and 5.58 (C_5 H). The isomeric adducts were formed in a ratio of **11a** to **11b** of 2:3 and in a combined yield of *ca.* 90%. This ratio was not appreciably altered when the experiment was conducted with the rigorous exclusion of light during the period of reflux and evaporation of the solvent. In contrast, shorter periods of reflux (10–12 hr) produced a ratio of **11a** to **11b** of 4:1 while prolonged refluxing (48 hr) afforded only **11b**.

Methyl *trans*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2b) and Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (295 mg, 1.0 mmol) and the dipolarophile (284 mg, 2.0 mmol) in benzene (10 ml) was refluxed for 24 hr and the solvent was removed under reduced pressure. Examination of the residue by pmr spectroscopy indicated a ratio of **11a** to **11b** of 3:2 and *ca.* 25% of aziridine **2b** as yet unreacted.

Epimerization of H_2,H_5-*trans* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-Tricarboxylate (11a) to 11b.—A mixture of **11a** and **11b** was produced by the reaction of the *cis*-aziridine **2a** (590 mg, 2.0 mmol) with dimethyl acetylenedicarboxylate (568 mg, 4.0 mmol) in refluxing benzene (20 ml) for 20 hr. The reaction mixture was divided into three equal portions and treated as described below.

Method A. In Chloroform.—After evaporation of the solvent from two of the samples the residues were each diluted with deuteriochloroform (0.5 ml) and examined by pmr spectroscopy. The isomeric Δ^3-pyrrolines **11a** and **11b** were in a ratio of **11a** to **11b** of 1:1. The pmr spectrum was again determined after an 18-hr time lapse, during which time one sample was placed in the dark and the other was exposed to normal laboratory lighting and diffuse sunlight. Conversion of **11a** into **11b** was nearly quantitative in both instances at room temperature.

Method B. In Methanol-d_1.—The residue remaining after evaporation of the solvent from the third sample was diluted with methanol-d_1 (2.0 ml). After 10 hr at room temperature the solvent was removed under reduced pressure and the residue was examined by pmr spectroscopy ($CDCl_3$). None of the H_2,H_5-*trans* Δ^3-pyrroline **11a** could be detected and the epimeric H_2,H_5-*cis* product **11b** was present as a mixture of deuterium-labeled and -unlabeled compounds. No loss of deuterium from the labeled product was observed after 24 hr in methanol. A pure sample of **11b** in methanol-d_1 did not exchange deuterium during a 24-hr period at room temperature.

Oxidation of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—A sample (546 mg, 1.25 mmol) of **11b** was oxidized with chloranil in boiling xylene as previously described for the oxidation of **10b**. After work-up, the crude material was recrystallized from methanol to afford 200 mg (37%) of trimethyl 1-isopropyl-5-(*p*-biphenyl)pyrrole-2,3,4-tricarboxylate (**14b**): mp 171–173°; pmr ($CDCl_3$) δ 1.45, (d, 6 H, J = 7.3 Hz, isopropyl methyls), 3.59, 3.86, and 3.95 (three s, 3 H each, methoxy groups), 4.70 (m, 1 H, isopropyl methine), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1720 cm^{-1} (broad).

Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 69.11; H, 5.91; N, 3.19.

Base-Catalyzed Isomerization of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—Treatment of a sample of **11b** (300 mg, 0.68 mmol) in methanol (10 ml) with sodium methoxide (5 mg) resulted in the development of a deep yellow color upon addition of the base. After 6 hr at room temperature, the reaction was worked up as previously described for the isomerization of **10b** to **13a**. The crude material was examined by pmr spectroscopy and found to be a mixture of two isomeric products. The isomer present in major amount (90%) was assigned the structure H_4,H_5-*trans* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13b**). The epimeric compound, H_4,H_5-*cis* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**14b**), was present to the extent of 10%.

Compound **13b** gave the following data: pmr ($CDCl_3$) δ 0.93 and 1.24 (two d, 6 H, J = 6.5 Hz, isopropyl methyls), 3.33–3.80 and 3.63 (m and s, 4 H, isopropyl methine and methoxy group), 3.73 (d, 1 H, J = 6.0 Hz, C_4 H), 3.76 and 3.96 (two s, 3 H each, two methoxy), 4.93 (d, 1 H, J = 6.0 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic).

Compound **14b** gave the following data: pmr ($CDCl_3$) δ 1.00 and 1.20 (two d, 6 H, J = 6.5 Hz, two methyls), 3.13 (s, 1 H, methyl of C_4 substituent), 3.33–3.80 (m, 1 H, isopropyl methine), 3.76 and 3.96 (two s, 3 H each, two methoxy groups), 4.39 and 5.19 (two d, 1 H, J = 13.4 Hz, C_4 H and C_5 H, respectively), and 7.3–7.8 (m, 9 H, aromatic).

These products were not characterized further.

Thermal Epimerization of H_2,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10a) to 10b in the Presence of Methyl *cis*-1-Cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (1c).—A benzene (10 ml) solution of aziridine ester **1a** (252 mg, 0.75 mmol) and dimethyl acetylenedicarboxylate (105 mg, 0.75 mmol) was refluxed for 24 hr. The reaction mixture was cooled to room temperature and the deuterium-labeled aziridine **1c** (167 mg, 0.5 mmol) was added. The resulting solution was refluxed for an additional 24 hr, the solvent was evaporated, and the residue was examined by pmr spectroscopy. The crude material was found to be a mixture of **1c** and **10b**. No detectable amount of deuterium was incorporated in **10b**.

Thermal Stability of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—A sample (437 mg, 1.0 mmol) of **11b** in toluene (20 ml) was refluxed for 12 hr and the solvent was evaporated. Examination of the residue by pmr spectroscopy indicated the presence of **11b** (95%) and **13b** (5%). None of the isomeric H_2,H_5-*cis* Δ^3-pyrroline **11a** could be detected.

Attempted Epimerization of Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylates 1a and 1b. Method A (Refluxing Methanol).—A solution of the *cis*-aziridine ester **1a** (110 mg, 0.33 mmol) in methanol-d_1 (10 ml) containing sodium methoxide (5 mg) was refluxed for 24 hr. The solvent was removed under reduced pressure, diluted with D_2O, and extracted with ether. The ether extracts were dried (anhydrous $MgSO_4$) and concentrated to give an oil which smelled of cyclohexylamine. The pmr spectrum of this oil indicated the absence of either of the aziridine esters **1a** and **1b**. Concentration of the sample, addition of methanol, and cooling produced 25 mg of a crystalline material, mp 57–58°. A mixture melting point experiment with an authentic sample of *p*-phenylbenzaldehyde showed no depression.

Identical results were obtained upon treatment of the *trans*-aziridine ester **1b** as described for **1a**.

Method B (Refluxing Ether).—A sample (110 mg, 0.33 mmol) of the *cis*-aziridine ester **1a** and sodium methoxide (5 mg) in 25 ml of an ether–methanol-d_1 mixture (4:1, v/v) was refluxed for

24 hr. The solvent was then evaporated, and the residue was diluted with D_2O and extracted with ether. The dried (anhydrous $MgSO_4$) ether extracts were evaporated and the residue (95 mg) was examined by pmr spectroscopy. The sole product was the starting aziridine **1a** with no detectable incorporation of deuterium.

The corresponding *trans*-aziridine ester was recovered unchanged and without deuterium exchange when subjected to identical reaction conditions.

Thermal Equilibration of Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylates (1a and 1b).—A solution of the *cis*-aziridine ester (167 mg, 0.5 mmol) in benzene-d_6 (0.3 ml) was transferred to an nmr tube, and the tube was sealed and placed in a constant-temperature bath maintained at 80 ± 0.2°. At 8-hr intervals the pmr spectrum was determined. After 40 hr, the percentages of **1a** and **1b** were determined as 68:32, respectively, by electronic integration. These percentages were not altered after an additional 16 hr at 80°.

Similarly, the corresponding *trans*-aziridine ester **1b** afforded the same equilibrium mixture after being heated to 80° for 72 hr in benzene-d_6.

Registry No.— **1a**, 19474-27-2; **1b**, 23214-20-2; **2a**, 23214-21-3; **2b**, 23214-22-4; **3a**, 23214-23-5; **3a′**, 23214-24-6; **3b**, 23214-25-7; **4a**, 23263-68-5; **4b**, 23214-26-8; **5a**, 23263-69-6; **5b**, 23214-27-9; **6a**, 23263-70-9; **6b**, 23214-28-0; **6c**, 23263-71-0; **7a**, 23214-29-1; **7b**, 23263-72-1; **8a**, 23214-30-4; **8b**, 23263-73-2; **9a**, 23214-31-5; **9b**, 23214-32-6; **10a**, 23214-33-7; **10b**, 23214-34-8; **11a**, 23214-35-9; **11b**, 23214-36-0; **12a**, 23230-36-6; **13a**, 23214-37-1; **13b**, 23214-38-2; **14a**, 23263-74-3; **14b**, 23214-39-3; *trans*-methyl *p*-phenylcinnamate, 22837-75-8; methyl 2,3-dibromo-3-(*p*-biphenyl)propionate, 23230-37-7; *cis*-methyl α-bromo-*p*-phenylcinnamate, 23214-40-6; *trans*-methyl α-bromo-*p*-phenylcinnamate, 23214-41-7; methyl α-bromo-β-d_1-*p*-phenylcinnamate (*trans*), 23214-42-8; trimethyl 1-cyclohexyl-5-d_1-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate, 23230-38-8.

Hydroboration of Dihydropyrans and Dihydrofurans

GEORGE ZWEIFEL AND JOSEPH PLAMONDON

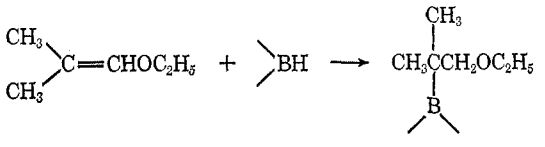
Department of Chemistry, University of California, Davis, California 95616

Received June 23, 1969

The hydroborations of Δ^2-dihydropyran, Δ^3-dihydropyran, 2-ethoxy-3,4-dihydropyran, 2,3-dihydrofuran, 2,5-dihydrofuran, and 2-methyl-4,5-dihydrofuran with diborane and with disiamylborane[bis(3-methyl-2-butyl)-borane] have been investigated. Except in the case of Δ^3-dihydropyran, the hetero oxygens direct the addition of boron nearly exclusively to the β positions. Oxidation of the intermediate β-organoboranes with alkaline hydrogen peroxide affords the corresponding β-hydroxy derivatives in better than 70% yields. Addition of boron trifluoride to the β-organoboranes derived from the heterocyclic olefins results in β elimination to give, after hydrolysis, the corresponding acyclic unsaturated alcohols in 70–90% yields. Hydroboration of dihydropyrans and dihydrofurans with excess diborane followed by oxidation produces mixtures of acyclic diols.

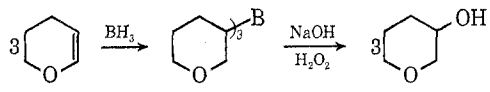
In connection with our pursuit of certain synthetic objectives, we were confronted with the problem of developing simple, high-yield syntheses of 3-hydroxytetrahydropyrans and 3-hydroxytetrahydrofurans. We had previously synthesized 3-hydroxytetrahydropyran; however, it was obtained in only a modest yield and required a four-step synthesis starting with dihydropyran.[1] Thus we were prompted to examine the hydrations of dihydropyrans and dihydrofurans *via* the hydroboration–oxidation reaction.

Various research groups have observed marked directive effects by alkoxy groups in the hydroboration of vinyl ethers. Thus Mikhailov and Shchegoleva reported that the hydroboration of ethyl vinyl ether produces *tris*(2-ethoxyethyl)borane in 67% yield.[2] Likewise, Pasto and Cumbo found that enol ethers undergo hydroboration predominantly at their β positions.[3] β-Ethoxystyrene gives, after hydroboration followed by oxidation of the intermediate organoborane, a 75% yield of 2-ethoxy-1-phenylethanol. Ethoxycyclohexene is converted by the same reaction sequence into *trans*-2-ethoxycyclohexanol. Finally, Brown and Sharp have recently shown that the hydroboration of isobutenyl ethyl ether results in the sterically unfavorable addition of at least 88% of the boron to the hindered tertiary carbon.[4]



Results and Discussion

Hydroboration of Dihydropyrans and Dihydrofurans.—The reaction of Δ^2-dihydropyran with borane (BH_3) in a 3:1 ratio in tetrahydrofuran solution at 0° proceeded rapidly to the trialkylborane stage. To assess the direction of addition of BH to the double bond, the trialkylborane was oxidized with alkaline hydrogen peroxide. Gas–liquid partition chromatography (glpc) revealed the formation of a single alcohol, 3-hydroxytetrahydropyran, in 86% yield. No evidence was obtained for the formation of any 2-hydroxytetrahydropyran. It is possible, however, that a small amount of the boron may have added to the 2 position of the pyran ring, but that the α-boron intermediate is unstable under the reaction conditions.



The hydroboration of 2-ethoxy-3,4-dihydropyran in tetrahydrofuran solvent was quite slow at 0°. However, if the hydroboration was carried out at 25° for 3 hr, analysis for residual hydride indicated that the

(1) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).

(2) B. M. Mikhailov and T. A. Shchegoleva, *Izv. Akad. Nauk SSSR*, 546 (1959).

(3) D. J. Pasto and C. C. Cumbo, *J. Amer. Chem. Soc.*, **86**, 4343 (1964).

(4) H. C. Brown and R. L. Sharp, *ibid.*, **90**, 2915 (1968).