# Nuclear Magnetic Resonance Study of Oxiranes from Ephedrine Salts[1a]

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Reaction of N,N-dimethylpseudoephedrine iodide with potassium *t*-butoxide produced 90% of *cis*-2-methyl-3-phenyloxirane (**3**). Similar treatment of the same derivative of ephedrine gave 74% of the *trans* epoxide (**4**). Nmr analysis of the epoxides supports the utility of assignment of configuration on the basis of the coupling constants of the protons of the oxirane rings, $J_{cis}$ being more than twice as large as $J_{trans}$.

The thermal decomposition of quaternary ammonium hydroxides having a hydroxyl group in the molecule has been reported to lead to cyclic ethers as products rather than alkenes.[2] A number of examples have been cited for the production of epoxides or larger cyclic ethers, but in some cases the reaction occurred in relatively poor yield and gave a mixture of products. The preparation in high yield of the optically active *cis*- and *trans*-oxiranes of β-methyl styrene and the examination of some of their physical properties are the subject of this paper.

The reaction with silver oxide of the quaternary salts of the *threo* and *erythro* isomers of 2-methylamino-1-phenyl-1-propanol [pseudoephedrine (**1**) and ephedrine (**2**), respectively] has been reported to give *cis*- (**3**) and *trans*-2-methyl-3-phenyloxirane (**4**) in 25–30% yield.[3] These amino alcohols have two relatively acidic protons either of which may be removed by base in the initial step of the reaction. Removal of the proton of the hydroxyl group would lead to the epoxide while abstraction of the benzylic hydrogen should produce the enol of propiophenone. The earlier investigators[3] postulated the production of both compounds although only the epoxide was characterized. The low yield of the epoxide was probably the result of the complex work-up of the reaction medium, and it seemed that simplification of the procedure should be possible. Furthermore, a base having a larger steric requirement than hydroxide ion should be hindered from approaching the benzylic proton and the alkoxide anion would be able to undergo an intramolecular nucleophilic displacement to eliminate trimethylamine and produce the epoxide before the enol could form. (See Scheme I.)

Potassium *t*-butoxide was found to satisfy the above requirements and produced 74% of *trans*-2-methyl-3-phenyl oxirane (**4**) from the quaternary salt of ephedrine (**2**) and 90% of the *cis* epoxide **3** from the quaternary salt of pseudoephedrine (**1**). The epoxides gave physical properties which were consistent with those reported (see the Experimental Section), but both gave two peaks in gas chromatographic analysis. None of the peaks could be assigned to propiophenone which had been assumed to be produced in previous studies[3] of the Hofmann degradation of **1** and **2**. The impurity was identified as phenylacetone by addition of a sample of this ketone to the epoxides and observing the corresponding increase in the second peak of the chromatogram. In view of the lack of carbonyl absorption in the infrared spectra of the samples before introduction into the gas chromatograph and the purity of the epoxides on the basis of their physical properties, it seemed that thermal decomposition of the epoxides had occurred in the injection chamber of the gas chromatograph with isomerization to the ketone. Thermal rearrangements of oxiranes have received considerable study.[4] It is interesting to note that the rotation of **4** was concentration dependent while that of **3** was relatively constant over a similar range of concentrations. The ultraviolet absorption spectra were quite similar in the two compounds, but the *trans* isomer **4** showed an additional shoulder at long wavelength and all of its phenyl B bands appeared at slightly longer wavelengths than those of the *cis* epoxide **3**.

Nuclear magnetic resonance has been used to examine the magnetic environments of the protons of oxirane systems.[5–15] Karplus has shown that the mutual spin–spin interaction experienced by the protons of an HCCH system is a function of the dihedral angle defined by that system.[16a] A tabulation of the available experimental data from the literature (Table I) shows that the coupling constants are smaller than would be predicted on the basis of such a correlation, but it is noteworthy that $J_{cis}$ is always significantly greater than $J_{trans}$ for a given isomeric pair of epoxides. Since, however, the range of values of $J_{cis}$ overlaps with the values of $J_{trans}$, the *absolute* values of $J$ cannot be used to assign the ring stereochemistry. This arises from the fact that the coupling constant is not a function of the dihedral angle alone, and other variables such as bond length and electronegativity, as well as hybridization, must be taken into account if reliable quantitative predictions are to be made. When comparisons of data for structurally similar compounds are made, however, the effect of these other variables is minimized. Thus, Karplus has cautioned against the indiscriminate use of these equations without the proper cognizance of structural discrepancies.[16b]

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[1] (a) Abstracted from a thesis presented to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree; (b) Public Health Service Predoctoral Fellow, 1963–1965.

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[4] A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 230–250.

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[6] (a) H. S. Gutowsky, M Karplus, and D. M Grant, *J. Chem. Phys.*, **31**, 1278 (1959); (b) J. I. Musher and R. G. Gordon, *ibid.*, **36**, 3097 (1962).

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[16] (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) *J. Am. Chem. Soc.*, **85**, 2870 (1963).

SCHEME I

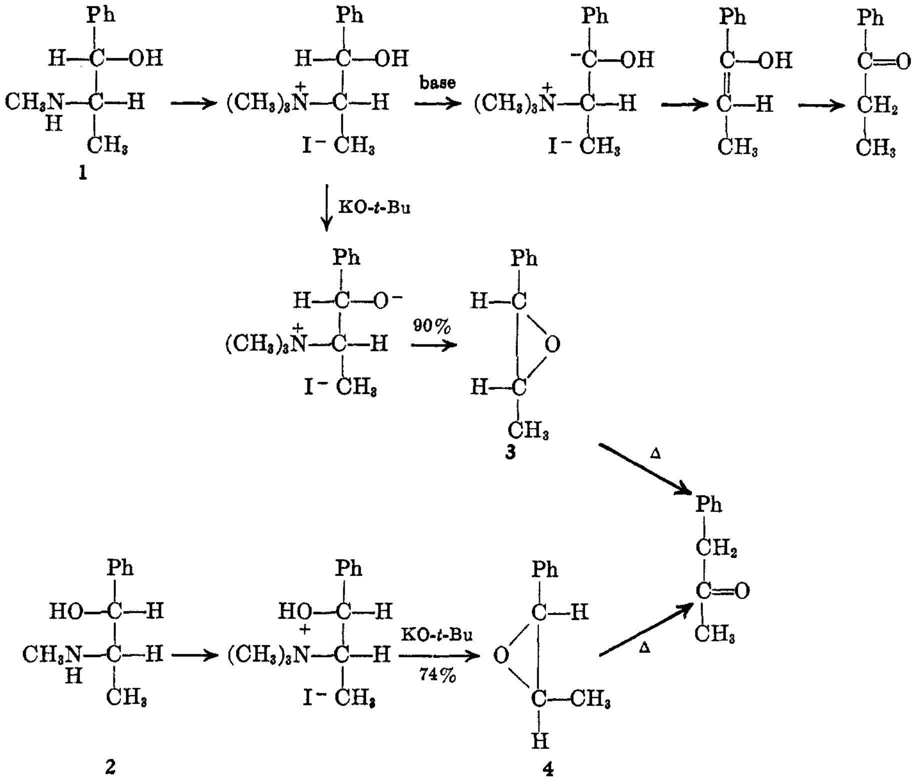
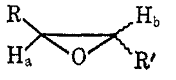


TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PROTONS OF 2,3-SUBSTITUTED OXIRANES[a]



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| Compd | R | R′ | δ, ppm cis | δ, ppm trans | J, cps cis | J, cps trans | Ref |
|---|---|---|---|---|---|---|---|
| 7a | CH=CH$_2$ | CH=CH$_2$ | 3.15 | 2.85 | | | 14 |
| 7b | Ph | Ph | 4.17 | 3.67 | | | 14 |
| 7c | CH$_3$ | CH$_3$ | 2.70 | 2.57 | | | 14 |
| 7d | Ph | CN | | | 4.06 | 2.52 | 9 |
| 7e | Ph | —OAc | | | 2.5 | 0.5 | 9 |
| 7f[b] | CH$_3$ | n-C$_3$H$_7$ | | | 4.6 | 2.2 | 13 |
| 7g | CH$_3$ | i-Pr and t-butyl | | | ≈4.4 | ≈2.3 | 15 |
| 3, 4 | Ph | CH$_3$ | 3.89 (H$_a$)<br>3.12 (H$_b$) | 3.38 (H$_a$)<br>2.80 (H$_b$) | 4.3 | 2.0 | This study[c] |

[a] The nmr spectra of 12 compounds having R′ = H have been reported assuming in every case $J_{cis} > J_{trans}$ when R′ = H. The range of coupling constants is as follows: 2.2–5.2 for the *cis* protons and 1.4–2.6 for the *trans* protons.[4-12] [b] The assignment of configuration to this pair of oxiranes is apparently in question.[15] The configurations shown in this table are those initially made.[13] Although the nmr clearly supports this assignment, the fact that the lower boiling isomer was assigned the *cis* configuration is inconsistent with the remaining members of the homologous series. Furthermore, the method of synthesis by the California workers[15] is stereoselective, but unfortunately they failed to report any nmr data. [c] Determined as the neat material relative to the internal TMS standard on a Varian A-60 instrument.

Relatively few pairs of symmetrically substituted epoxides **7** have been reported in the literature after nmr analysis, and in three cases (**7a–c**) the chemical shifts were given[14] while with **7d–g** the coupling constants alone were reported[9,13,15] (Table I). The protons of the *cis*-oxirane appeared at somewhat lower field than the corresponding protons of the *trans* epoxide ($\Delta\delta$ = from 0.13 to 0.7 ppm). Of even more potential, however, the coupling constants of the protons of the *cis* isomers were significantly larger than those of the isomeric *trans* epoxides. Of the group of oxiranes previously studied, the substituents have not included any case in which an alkyl group is opposed by an aromatic group. It has been shown that the electronegativity of the substituents may cause significant differences in coupling constants of the oxirane protons,[12] and comparison of the epoxides **3** and **4** was a necessary accompaniment to the list to provide a model of established stereochemistry.[3]

The epoxides **3** and **4** showed the same pattern of coupling constant as the examples in Table I, $J_{cis}$ being more than twice as large as $J_{trans}$. The chemical shifts of the ring protons of the *cis* isomers are also farther downfield than those of the *trans*-oxiranes as has been noted previously,[11,14] but the use of the coupling constants for stereochemical assignments appears to be

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA FOR OXIRANES FROM EPHEDRA BASES[a]

| Oxirane | $CH_3$ doublet | C-3 H octet | C-2 H doublet | Phenyl resonance |
|---|---|---|---|---|
| *cis*-3-Methyl-2-phenyloxirane (**3**) | 0.92 ($J$ = 5.5 cps) | 3.12 | 3.89 ($J$ = 4.3 cps) | 7.22 |
| *trans*-3-Methyl-2-phenyloxirane (**4**) | 1.22 ($J$ = 5.2 cps) | 2.79 | 3.39 ($J$ = 2.1 cps) | 7.18 |

[a] Chemical shifts are reported in parts per million downfield from the internal TMS reference.

TABLE III

NUCLEAR MAGNETIC RESONANCE DATA FOR THE EPHEDRA BASES[a]

| Compd | Phenyl resonance | CHO doublet | CHN multiplet | $NCH_3$ singlet | $CCH_3$ doublet |
|---|---|---|---|---|---|
| Pseudoephedrine (**1**) | | | | | |
| In chloroform-*d* | 7.32 | 4.19 ($J$ = 8.3 cps) | 2.6 | 2.34 | 0.83 ($J$ = 6.3 cps) |
| In formic acid | 7.48 | 4.83 ($J$ = 9.4 cps) | | 2.96 | 1.21 ($J$ = 6.9 cps) |
| Ephedrine (**2**) | | | | | |
| In chloroform-*d* | 7.32 | 4.76 ($J$ = 4.0 cps) | 2.7 | 2.41 | 0.86 ($J$ = 6.7 cps) |
| In formic acid | 7.25 | 5.12 ($J$ = 3.4 cps) | | 2.78 | 1.00 ($J$ = 7.0 cps) |

[a] Chemical shifts are reported in parts per million from the internal TMS reference.

more predictable than the values for the chemical shifts which may be more subject to electronegativity considerations of substituents.

The chemical shift of the methyl group attached to the oxirane ring is also of interest. It has been reported that where *t*-butyl opposed methyl (**7g**) the methyl resonance of the *cis*-oxirane occurs farther downfield than that of the *trans* isomer.[15] In contrast, the methyl signal of **7g** (R′ = *i*-Pr) is the same in both isomers while in **7c** it is upfield in the *cis* isomer. In the *cis* epoxide **3**, the methyl resonance occurs upfield (Table II) compared with that of **4**, almost at the same position as in the simplest of the dialkyl oxiranes **7c**. It is possible that the large alkyl groups may cause some distortion of the bond between the ring carbon and methyl group thus bending the methyl group farther from the shielding effect of the oxygen of the ring. The phenyl group, however, may produce both steric and electronic effects resulting in the upfield chemical shift of the methyl group in the *cis* isomer **3** as compared with the *trans* isomer **4**.

The stereochemistry of the starting amino alcohol could be deduced from the structure of the epoxide because the pathway for the conversion of the amino alcohol to the oxirane proceeds with known stereospecificity.[17] Assignment of the configuration to the amino alcohols may also be possible from analysis of the nmr data. The nmr spectra of the amino alcohols **1** and **2** showed small differences in the chemical shifts of the substituent groups, but of primary interest were the coupling constants of the benzylic protons (Table III). In the case of ephedrine (**2**), the benzylic proton and hydrogen on C-2 were coupled with a value of 4.0 cps in neutral medium (3.4 cps in formic acid), while the same hydrogens on the *threo* compound **1** gave a coupling constant of 8.3 cps (9.4 cps in formic acid). A suggestion has been made[18] that this is a consistent and predictable pattern for such compounds. The chemical shifts of the other protons were consistent with the structures of the ephedrine isomers (Table III). Thus the stereochemistry of the amino alcohols and their derived epoxides can be determined by nmr spectroscopy.

## Experimental Section[19]

**(+)-Pseudoephedrine** (**1**).—Pseudoephedrine hydrochloride (Koch-Light Laboratories, Inc.) was converted to the base **1** which was recrystallized from ether: mp 117–119° (lit.[20] mp 117.5°); $\lambda_{max}$ 242 sh m$\mu$ (log $\epsilon$ 2.00), 247 sh (2.15), 252 (2.25), 258 (2.34), and 264 (2.22). In deuteriochloroform the benzylic proton appeared as a doublet ($J$ = 8.3 cps) at 4.19 ppm while the CHN proton to which it was coupled appeared as a multiplet at 2.6 ppm. The remainder of the data are given in Table III.

N-Methylpseudoephedrine methiodide was prepared from the free base by the procedure used for the preparation of the diastereomeric salt as described by Witkop and Foltz,[3] mp 212–215° (lit.[21] mp 211–212°).

**(−)-Ephedrine** (**2**).—Ephedrine monohydrate was prepared from commercial ephedrine sulfate (Mallinckrodt Chemical Works) and recrystallized from ether: mp 33–41° (lit.[20] mp 39–40°); $\lambda_{max}$ 248 sh m$\mu$ (log $\epsilon$ 2.23), 253 (2.36), 258 (2.41), and 262 sh (2.28). The nmr spectrum showed a doublet for for the benzylic proton with $J$ = 4.0 cps in deuteriochloroform. The remaining data are summarized in Table III.

N-Methylephedrine methiodide was prepared from ephedrine monohydrate by the method of Witkop and Foltz[3] in 57% yield, mp 210–212° (lit.[3] mp 207–214°).

***cis*-3-Methyl-(2*S*)-phenyloxirane** (**3**).—To a warm solution of 3.0 g of potasium *t*-butoxide in 10 ml of *t*-butyl alcohol 3.4 g of N-methylpseudoephedrine methiodide was added. The resulting suspension was heated under reflux for 5 hr, and the odor of trimethylamine was clearly evident. The reaction mixture was twice subjected to filtration and the filter cake was washed with ether. The volatile solvents were removed from the filtrate by distillation at atmospheric pressure and the oil was distilled yielding **3**: 1.2 g (92 %); bp 68° (4 mm) [lit.[3] bp 80.0–80.5° (17 mm)]; $n^{24}$D 1.517; $[\alpha]^{24}$D +39.6° (*c* 0.42) [lit.[21] $n^{24}$D 1.5203, $[\alpha]^{20}$D +41.5° (*c* 3.47)]; $\lambda_{max}$ 244 sh m$\mu$ (log $\epsilon$ 1.89), 249 sh (2.08), 254 (2.21), 259 (2.31), and 266 (2.17). The nmr data are given in Table II.

A sample (0.2 $\mu$l) of the product from a typical reaction on injection into a gas chromatograph (Aerograph Model 90-P3, using a 5-ft stainless steel column packed with a 20% silicone SF-96 stationary phase on a 60–80 mesh firebrick support with injector temperature 180°, column temperature 137°, and flow rate 120 ml/min) gave two peaks having relative areas of 15:85. On addition of benzyl methyl ketone to a sample of the above reaction product, the gas chromatogram obtained under identical conditions as above still gave only two peaks having relative areas of 8:92.

***trans*-3-Methyl-(2*R*)-phenyloxirane** (**4**).—N-Methylephedrine

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[17] Reference 4, p 173.

[18] J. W. Huffman and R. P. Elliott, *J. Org. Chem.*, **30**, 365 (1965), footnote 9.

[19] Ultraviolet absorption spectra were measured in 95% ethanol on a Perkin-Elmer Model 4000 Spectracord. Optical rotations at the D line were obtained on a Franz Schmidt and Haensch polarimeter with solution in 95% ethanol in 2-dm tubes. Nmr data were recorded at 60 Mc with a Varian A-60 spectrometer, purchased with a grant (G 22718) from the National Science Foundation.

[20] H. Emde, *Helv. Chim. Acta*, **12**, 365 (1929).

[21] F. Fischer, *Chem. Ber.*, **94**, 893 (1961).

methiodide (5.67 g) was added as the powder to a warm solution of 6.8 g of potassium *t*-butoxide (courtesy of the MSA Research Laboratories, Callery, Pa.) in 20 ml of *t*-butyl alcohol, whereupon the odor of trimethylamine was immediately detected. The yellow reaction mixture was heated under reflux for 4 hr, cooled, and diluted with water. The resulting slurry was separated by filtration and the precipitate was washed with ether and discarded. The aqueous phase was drawn off and extracted twice with ether. After removing the volatile solvents from the combined ether extracts by distillation at atmospheric pressure, the product was distilled under reduced pressure yielding 1.75 g (74%) of a colorless liquid with a characteristic odor remotely resembling that of wintergreen: bp 38° (0.3 mm) [lit.[3] bp 87.0–87.5° (15 mm)]; $n^{25}\text{D}$ 1.5183; $[\alpha]^{24}\text{D}$ +58.0° (*c* 0.242), $[\alpha]^{24}\text{D}$ +77.4° (*c* 1.69), $[\alpha]^{24}\text{D}$ +81.8° (*c* 4.22) [lit.[21] $n^{20}\text{D}$ 1.5198, $[\alpha]^{20}\text{D}$ +70.7° (*c* 4.39)]; $\lambda_{\max}$ 217 mμ (log ε 4.06), 245 sh (2.00), 250 sh (2.15), 256 (2.27), 261 (2.35), 267 sh (2.24), and 270 sh (2.05). The nmr data are reported in Table II.

When a sample of the reaction product was subjected to gas chromatographic analysis under the same conditions as those described for the *cis*-oxirane, two peaks were obtained having a ratio of areas of 37:63. On addition of benzyl methyl ketone to the reaction product, only the relative areas of the two peaks was altered changing to 14:86.

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# Aziridines. XIII. Reactions of 1,2,3-Triarylaziridines with Activated Alkenes and Alkynes

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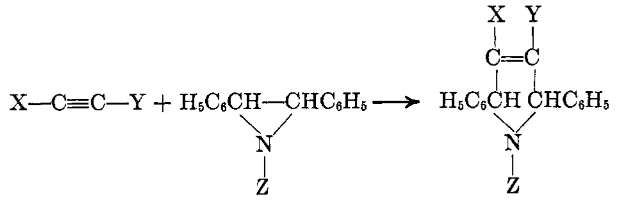
1,2,3-Triphenylaziridine and 1-*p*-bromophenyl-2,3-diphenylaziridine react with ethynes and ethenes in refluxing toluene or xylene to form 3-pyrrolines and pyrrolidines, respectively. A novel decarboxylative elimination of 3,4,5-triphenyl-1,2-dicarbethoxy-1,2,4-triazolidine into benzalazine and aniline is described.

A recent communication described the reaction of 1,2,3-triphenylaziridine with diethylacetylene dicarboxylate and maleic anhydride.[1] Carbon–carbon bond scission of the aziridine ring occurred in these reactions and the products were 1,2,5-triphenyl-3,4-dicarbethoxy-3-pyrroline and 1,2,5-triphenylpyrrolidine-3,4-dicarboxylic anhydride, respectively. Other aziridines were subsequently reported to form adducts with various ethenes and ethynes by carbon–carbon cleavage of the aziridine ring.[2,3]

We now wish to report in detail the reaction of 1,2,3-triphenylaziridine and 1-*p*-bromophenyl-2,3-diphenylaziridine with a number of alkynes and alkenes. In each instance carbon–carbon cleavage of the aziridine ring was observed.

Near-quantitative yields of 3-pyrrolines (1–6) were obtained when toluene or *p*-xylene solutions of



$$X{-}C{\equiv}C{-}Y + \underset{\underset{Z}{|}}{H_5C_6CH{-}CHC_6H_5 \atop \diagdown N \diagup} \longrightarrow \underset{\underset{Z}{|}}{\overset{X\quad Y}{H_5C_6CH\;CHC_6H_5} \atop \diagdown N \diagup}$$

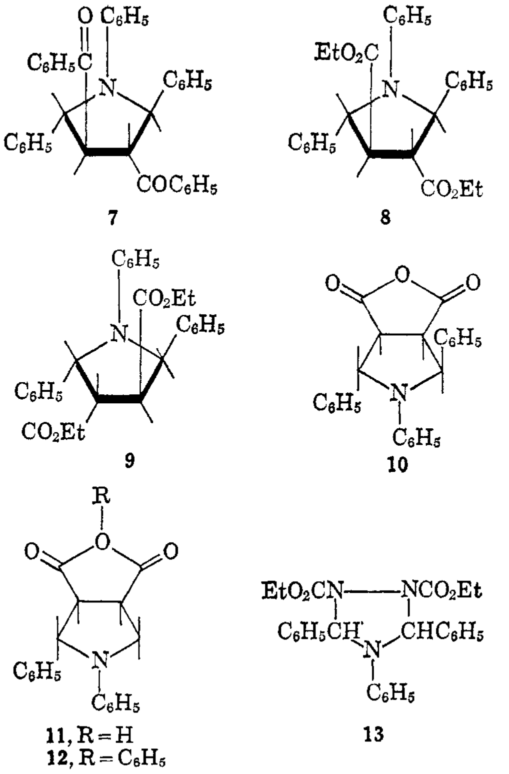
1–6

**1**, X, Y = $CO_2C_2H_5$; Z = $C_6H_5$
**2**, X = $CO_2C_2H_5$; Y = H; Z = $C_6H_5$
**3**, X, Y = $C_6H_5CO$; Z = $C_6H_5$
**4**, X, Y = $CF_3$; Z = $C_6H_5$
**5**, X, Y = $CO_2C_2H_5$; Z = *p*-$BrC_6H_4$
**6**, X, Y = $C_6H_5CO$; Z = *p*-$BrC_6H_4$

1,2,3-triphenylaziridine or 1-*p*-bromophenyl-2,3-diphenylaziridine were heated for several hours with diethylacetylene dicarboxylate, ethyl propiolate, dibenzoylacetylene, and hexafluoro-2-butyne.

Heating toluene solutions of 1,2,3-triphenylaziridine with *trans*-dibenzoylethene, ethyl fumarate, ethyl maleate, maleic anhydride, maleimide, N-phenylmaleimide, and diethyl azodicarboxylate gave the adducts **7–13**, (Chart I), respectively. It is to be noted that the carbethoxy groups of the adduct **9** are *trans* rather than *cis*. The evidence for this fact is given below.

CHART I



The observed chemical shifts and, where appropriate, the coupling constants of the methine protons for adducts **1–13** are listed in Table I. Deuteriochloroform was used as the solvent for the nmr studies.

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(1) H. W. Heine and R. E. Peavy, *Tetrahedron Letters*, 3123 (1965).
(2) A. Padwa and L. Hamilton, *ibid.*, 4363 (1965).
(3) R. Huisgen, W. Scheer, G. Szeimies, and H. Huber, *ibid.*, 397 (1966).