min. The aqueous solution was acidified with hydrochloric acid and extracted continuously with ether for 35 hr. The residue obtained by evaporation of the ether extract was heated to 190°, cooled, and mixed with powdered urea (60 mg.). On heating at 200°, this mixture first melted and then became solid. This solid was extracted with ethanol, filtered, and evaporated to small volume (1 ml.) when hydrastimide (66 mg.), m.p. 290–291°, separated.

(d) **4,5-Methylenedioxyanthranilic Acid.**—Hydrastimide (60 mg.) was dissolved in 10% sodium hydroxide solution (2 ml.) by warming to 45°. The solution was cooled to 0° and 0.76 *N* sodium hypochlorite solution (1 ml.) added. The mixture was stirred for 1 hr. at 0° and then warmed to 80° during one hr. After cooling the solution was almost neutralized with 4 *N* sulfuric acid and then brought to a pH of 5 with acetic acid. A buff colored precipitate separated (30 mg.) which was sublimed (200°, 0.001 mm.) to yield a pale yellow sublimate (11 mg.), m.p. 217–218° (dec.). Recrystallization from aqueous ethanol yielded colorless plates of 4,5-methylenedioxyanthranilic acid, m.p. 220–221° (reported,[20] 203°). The infrared spectrum in a KBr pellet had absorptions due to NH_2 at 3440 and 3340 cm.$^{-1}$, and a carbonyl absorption at 1658 cm.$^{-1}$.

Anal. Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 53.43; H, 4.11; N, 7.91.

The activities recorded in Table I are calculated for non-diluted material.

(20) P. Friedlander and W. Schreiber, *Ber.*, **28**, 1382 (1905).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL CO., DIVISION OF CIBA CORPORATION, SUMMIT, N. J.]

Rauwolfia Alkaloids. XLIII.[1] A Facile Ring Closure of Deoxyajmalal-A to Deoxyajmaline

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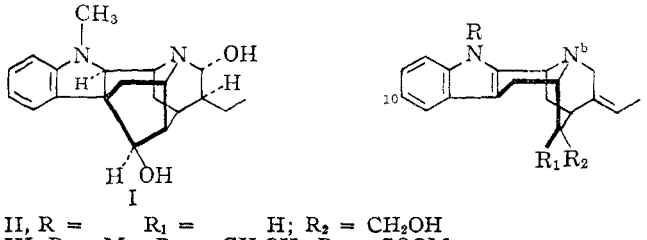
RECEIVED OCTOBER 18, 1962

Deoxyajmalal-A (IX) in strongly acidic solution is shown to exist in the ring closed form, the indoleninium salt X. Reduction of IX in such an acidic medium gives deoxyajmaline (VIII) along with 2-epideoxyajmaline (XIII).

Ajmaline (I) has been degraded in a stepwise stereospecific manner which can be regarded as the reversal of its formal biogenesis.[3] The occurrence and established relationships[2,10] of indole alkaloids as sarpagine (II, $C_{10}OH$),[2,4] macusine-B (II, N_b-methiodide),[5] voachalotine (III),[6] akuammidine (IV),[7] polyneuridine (V)[8] and normacusine-A,[9] on the one hand, and the dihydroindoles, ajmaline[2,3] and its congeners, vincamajine (VII)[10] and its O-acetate, vincamedine, on the other, are in support of this belief. Since deoxyajmalal-A (IX)[2] was readily available from deoxyajmaline (VIII),[11] it was felt that this would be a suitable compound for testing the feasibility of this biogenetically possible ring closure reaction, IX → X → VIII. The



II, R = R_1 = H; R_2 = CH_2OH
III, R = Me; R_1 = CH_2OH; R_2 = COOMe
IV, R = H; R_1 = COOMe; R_2 = CH_2OH
V, R = H; R_1 = CH_2OH; R_2 = COOMe
VI, R = Me; R_1 = CHO; R_2 = COOMe

feeling was that experimental conditions could be found to take advantage of the vicinal location of the nucleophilic β-position of the indole nucleus[12] and the electrophilic aldehyde group.

(1) Most recent paper, Part XLV, M. M. Robison, W. Pierson, R. A. Lucas, I. Hsu and R. Dziemian, *J. Org. Chem.*, in press.

(2) M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi and E. Wenkert, *J. Am. Chem. Soc.*, **84**, 322 (1962).

(3) R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956).

(4) D. Stauffacher, A. Hofmann and E. Seebeck, *Helv. Chim. Acta*, **40**, 508 (1957); S. K. Talapatra and A. Chatterjee, *Sci. and Culture*, **22**, 692 (1957).

(5) A. R. Battersby and D. A. Yeowell, *Proc. Chem. Soc.*, 17 (1961).

(6) N. Defay, M. Kaisin, J. Pecher and R. H. Martin, *Bull. soc. chim. Belges*, **70**, 475 (1961).

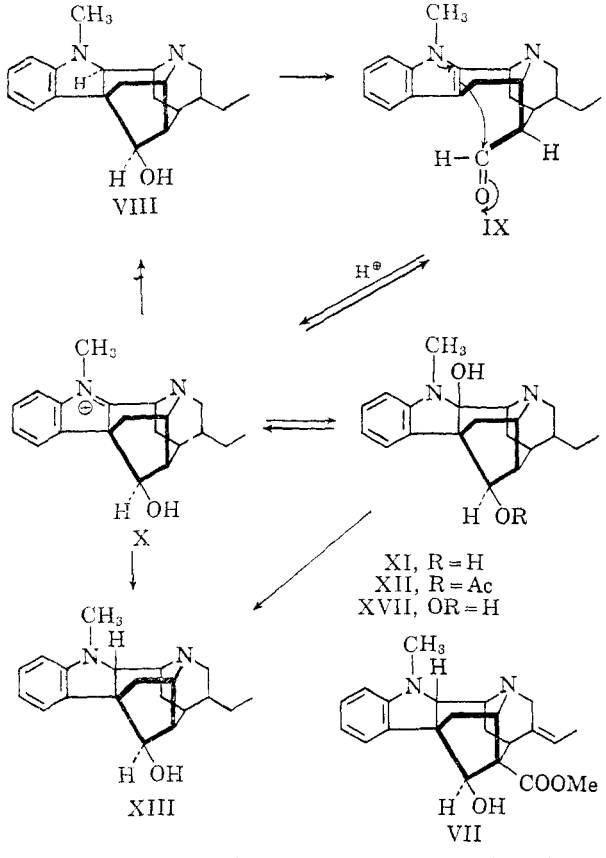
(7) J. Levy, J. Le Men and M.-M. Janot, *Compt. rend.*, **253**, 131 (1961).

(8) L. D. Antonaccio, N. A. Pereira, B. Gilbert, H. Vorbrueggen, H. Budzikiewicz, J. M. Wilson, L. J. Durham and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2161 (1962). The relationship of polyneuridine and macusine-C is discussed in footnote 40, ref. 8.

(9) A. T. McPhail, J. Monteath Robertson, G. A. Sim, A. R. Battersby, H. F. Hodson and D. A. Yeowell, *Proc. Chem. Soc.*, 223 (1961).

(10) M.-M. Janot, J. Le Men, J. Gosset and J. Levy, *Bull. soc. chim. France*, 1079 (1962).

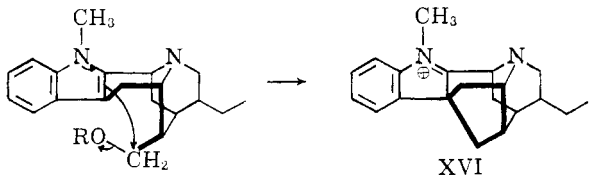
(11) Woodward and Schenker (ref. 3), who first showed that the action of lead tetraacetate on deoxyajmaline gave an indole aldehyde, obtained only the diastereoisomer, deoxyajmalal-B.



As a model reaction deoxyajmalol-A (XIV)[2] was tosylated, thus setting up favorable conditions for an intramolecular substitution reaction, *viz.*, XV → XVI, which could result in 2-hydroxydideoxyajmaline (XVII). Indeed, the desired product was obtained, the cyclization occurring even at room temperature. Reduction of the hydroxy compound with lithium aluminum hydride gave 2-epidideoxyajmaline (XIII, OH = H) in good yield. When the reduction was carried out with zinc in hydrochloric acid, both of the epimeric dideoxyajmalines were produced as determined by paper and thin-layer chromatography.

Attention now focused on a study of deoxyajmalal-A (IX) itself. In dilute acid the indoleninium form X could not be detected spectroscopically nor could the

(12) T. S. Stevens in "Chemistry of Carbon Compounds," E. H. Rodd, Editor, Vol. IVa, Elsevier Publishing Co., New York, N. Y., 1957, p. 78.



XIV, R = OH
XV, R = tosyl

XVI

carbinolamine XI be prepared by mild hydrolysis of its 17-O-acetate XII. Upon dissolving deoxyajmalal-A in 5 *N* hydrochloric acid, however, the conjugate acid of the aldehyde was sufficiently nucleophilic[13] to cyclize giving the indoleninium salt X having the same ultraviolet absorption spectrum as 2-hydroxydideoxyajmaline (XVII) and 2-hydroxydeoxyajmaline-17-O-acetate (XII) measured under the identical conditions. The indoleninium salt could be trapped as XII by dissolving deoxyajmalal-A in acetic acid–acetic anhydride saturated at 0° with hydrogen chloride. It was also trapped as 2-epideoxyajmaline (XIII)[2] by reduction with zinc dust or catalytic hydrogenation in the strongly acidic solution. Reduction of 2-hydroxydeoxyajmaline-17-O-acetate (XII) with sodium borohydride also afforded the 2-epi isomer XIII. Finally, deoxyajmaline (VIII) was prepared in 3% yield under certain reductive conditions (see Experimental). By this isolation of deoxyajmaline we have established the feasibility of such ring closures in a synthesis of ajmaline in which the correct stereochemistry[2] at both C_{17} and C_2 has been generated.

Condensations similar to the above have recently been realized in other laboratories. An attempt to prepare the mesyl ester of voachalotine (III) furnished the corresponding 2-hydroxyindoline[14] and the catalytic reduction of aldehyde VI in glacial acetic acid has regenerated vincamajine.[15] This latter reaction taken in conjunction with our earlier work[2] and the present study establishes the C_2 epi configuration for vincamajine. Interestingly, this last reaction proceeded under very mild conditions, a fact which may prove useful in the design of a total synthesis of ajmaline using the cyclization step investigated in the present work.

Experimental

The melting points were taken in evacuated capillaries and are uncorrected. Analytical samples were routinely dried at 80° for 12–24 hours *in vacuo*, and the ultraviolet absorption spectra are expressed in mμ (ε). Sodium sulfate was normally used for drying the organic solvents in the extractions.

2-Hydroxydideoxyajmaline (XVII).[2] (a).—A sample of deoxyajmalol-A O-tosylate[2] (160 mg.) was heated at 80° *in vacuo* for 8 hours. The residue was extracted with methylene chloride from dilute ammonium hydroxide, yielding amorphous 2-hydroxydideoxyajmaline.

(b).—Deoxyajmalol-A (1.00 g.) was dissolved in pyridine (10 ml.) containing *p*-toluenesulfonyl chloride (1.19 g.) and was allowed to stand at room temperature for 3 days under nitrogen. Additional *p*-toluenesulfonyl chloride (1.0 g.) was added, continuing the reaction for 3 more days. The pyridine was partially removed *in vacuo* followed by extraction of the residue with dilute ammonium hydroxide and methylene chloride yielding amorphous 2-hydroxydideoxyajmaline characterized as the diperchlorate,[16] m.p. 287° dec.[17]

Anal. Calcd. for $C_{20}H_{26}N_2O \cdot 2\ HClO_4$: C, 46.97; H, 5.52; N, 5.48. Found: C, 47.20; H, 5.43; N, 5.90.

(13) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 249.

(14) J. Pecher, "International Symposium on Organic Chemistry," Brussels, June 14, 1962.

(15) J. Le Men, personal communication.

(16) In one case 1 to 2 mg. of the diperchlorate sealed in a capillary tube *in vacuo* exploded at its decomposition point with such violence that oil was splashed from the apparatus causing severe facial burns to the experimentalist.

(17) Previously reported at 340° (ref. 2).

Reductions of 2-Hydroxydideoxyajmaline. (a).—2-Hydroxydideoxyajmaline (316 mg.) and lithium aluminum hydride (570 mg.) were added to ether (50 ml.) and refluxed for 2 days. After addition of excess water the solvent was filtered through filter cell, washing with ether and water. The ether layer yielded a colorless oil (224 mg.) crystallizing on standing to furnish **2-epidideoxyajmaline (XIII, OH = H)**, m.p. 66–68°. A sample was converted to the maleate salt, crystallizing from methanol–ether; m.p. 177–178°, $[\alpha]_D$ +17.3° (methanol), identical with an authentic sample.[18]

Anal. Calcd. for $C_{20}H_{26}N_2 \cdot C_2H_4O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.23; H, 7.65; N, 6.99.

(b).—2-Hydroxydideoxyajmaline (1.0 g.) was dissolved in 2 *N* hydrochloric acid and treated with zinc dust (1.0 g.). After stirring under reflux for 5 hours, the solution was filtered, made basic with ammonium hydroxide and extracted with methylene chloride yielding a light brown oil (950 mg.) that was chromatographed on alumina (28 × 100 mm.). The first 200 ml. of benzene eluent contained mainly **dideoxyajmaline**[2] as detected by paper chromatography, with subsequent benzene fractions primarily **2-epidideoxyajmaline.** Attempts to isolate pure material from the chromatogram fractions were unsuccessful, although thin-layer chromatography showed that both isomers were present.[19]

2-Hydroxydeoxyajmaline-17-O-acetate (XII) from Deoxyajmalal-A.—Deoxyajmalal-A (317 mg.) was left overnight at room temperature in a closed flask with glacial acetic acid (25 ml.) and acetic anhydride (2 ml.), saturated at 0° with hydrogen chloride. The solution was partially evaporated, diluted with water, made basic (NH_4OH) and extracted with methylene chloride, yielding amorphous 2-hydroxydeoxyajmaline-17-O-acetate (368 mg.).

Reduction of 2-Hydroxydeoxyajmaline-17-O-acetate.—Sodium borohydride (1.0 g.) was added to 2-hydroxydeoxyajmaline-17-O-acetate in methanol (25 ml.) and stirred for 3 days. The solution was extracted with methylene chloride and water yielding a residue (286 mg.) crystallizing from ether (200 mg.); m.p. 215–219°, increasing to 243–245° on recrystallization from methanol–ethyl acetate. There was no depression of the melting point on admixing with authentic **2-epideoxyajmaline (XIII).**[2]

Ultraviolet Absorption Spectra.—(a) **Deoxyajmalal-A (IX):** $\lambda_{max}^{2\ N\ HCl}$ 224 (20,700), 281 (7,400); $\lambda_{shld.}$ 244 (3,700), 272 (6,700), 292 (6,300). λ_{min} 238 (3,100); $\lambda_{max}^{5\ N\ HCl}$ 239 (5,500), 244 (5,400), 292–296 (6,600). λ_{min} 232 (5,100), 242 (5,300), 258 (2,300). (b) **2-Hydroxydideoxyajmaline (XVII):** $\lambda_{max}^{5\ N\ HCl}$ 238 (5,800), 244 (5,900), 294–296 (7,500); λ_{min} 241 (5,100), 251 (1,100). (c) **2-Hydroxydeoxyajmaline-17-O-acetate (XII):** $\lambda_{max}^{5\ N\ HCl}$ 226 (7,100), 237 (5,800), 243 (5,700), 293 (6,700); λ_{min} 235 (5,600), 241 (5,200), 251 (1,900). (d) **1-Demethyl-Δ^1-dideoxyajmaline:** $\lambda_{max}^{5\ N\ HCl}$ 243 (4,800), 297 (7,300); $\lambda_{shld.}$ 237 (4,200); λ_{min} 239 (4,300), 249 (1,800).

Reductions of Deoxyajmalal-A. (a).—Deoxyajmalal-A (1.0 g.) was rapidly stirred in 5 *N* hydrochloric acid (50 ml.) and treated with zinc dust (2.0 g.). After 4 hours the ultraviolet absorption spectrum was indolic. An additional 1 g. of zinc dust was added after the fourth and fifth hours of stirring which was continued overnight. After making the solution basic with ammonium hydroxide and extraction with methylene chloride, a residue (1.03 g.) crystallizing from benzene was obtained, yielding **2-epideoxyajmaline (XIII)** (300 mg.), m.p. 228–230°, increasing to 243–244° on recrystallization from methanol. The total yield of pure material was increased to 360 mg. by chromatographing the mother liquors on alumina.

(b).—Deoxyajmalal-A (290 mg.) was reduced with hydrogen in constant boiling aqueous hydrochloric acid (45 ml.) containing prereduced platinum catalyst (170 mg.). The uptake of hydrogen was steady at 9 ml. per 20 minutes with no break at 1 equivalent. When 1 mole of hydrogen was absorbed, the reaction was stopped, the solution filtered, made basic with ammonium hydroxide and extracted with methylene chloride to yield **2-epideoxyajmaline** (120 mg.), m.p. 246–247°.

(c).—Deoxyajmalal-A (476 mg.) was stirred in 6 *N* perchloric acid at 80°. Zinc dust (2.0 g.) was added and stirring at this temperature was continued for 40 minutes. Reduction to a dihydroindole was complete; the solution was filtered, diluted with water, made basic with ammonium hydroxide and extracted with methylene chloride, giving a residue (490 mg.) yielding **deoxyajmaline** (15 mg.), m.p. 325° on crystallization from methanol–ether.

(d).—Deoxyajmalal-A (310 mg.) was stirred in concentrated hydrochloric acid (30 ml.) at room temperature. Upon addition of zinc dust (2.0 g.) the temperature increased to 50° and stirring was continued without external heating. After 2.5 hours, additional zinc dust (1.0 g.) was added, and the stirring was continued for 1 hour. The solution was made basic with ammonium hydroxide and extracted with methylene chloride, giving a resi-

(18) Unpublished work from this Laboratory.

(19) The paper and thin-layer chromatography were carried out by B. Korzun and S. Brody.

due from which **deoxyajmaline** (7 mg.), m.p. 310°, crystallized from methanol.

(e).—Procedure d was repeated, using glacial acetic acid (15 ml.) and concentrated hydrochloric acid (15 ml.) as the solvent. The yield of **deoxyajmaline** was 5 mg., m.p. 323–324°.

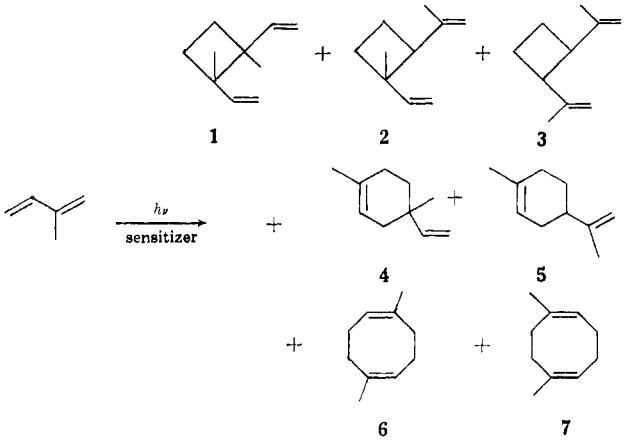
Acknowledgments.—We are grateful to Dr. E. Schlittler for his constant interest and encouragement. We wish to express our thanks to Mr. L. Dorfman and his staff for the analytical and spectral data.

COMMUNICATIONS TO THE EDITOR

STEREOISOMERIC TRIPLET STATES OF CONJUGATED DIENES[1]

Sir:

At an earlier time[2] we reported that irradiation of butadiene containing various carbonyl compounds as sensitizers leads to formation of butadiene dimers. At that time it was pointed out that the composition of the product mixtures varied as the sensitizer was changed and that this fact was not predicted by the simple theory[3] of sensitization by transfer of excitation from the lowest triplet states of the sensitizers to the diene. We now find that the same kind of variation, with the nature of the sensitizer, is observed in sensitized dimerization of isoprene, 2,3-dimethylbutadiene and the 1,3-pentadienes (piperylenes). The case of isoprene has been studied in detail. Irradiation of solutions of various sensitizers in neat isoprene leads to formation of seven dimers.



All of the products have been separated by preparative vapor chromatography and characterized by n.m.r. and infrared spectroscopy. Compound **5** is the well known *d,l*-limonene. Compound **4** is identical with one of the thermal dimers of isoprene[4,5] which, however, has only been subjected to a structural study as a part of an unseparated mixture. Likewise, a mixture of **6** and **7** has been characterized as a product of the thermal reaction. Structures have been assigned to compounds **1, 2, 3, 4, 6** and **7** on the basis of spectra and a study, to be reported in detail later, of the thermal rearrangements of **1, 2,** and **3**.

Variation of the composition of the product mixture fits a very striking pattern. Any change which increases the yield of **1** also increases the yields of **2, 3, 6** and **7** and decreases the yields of **4** and **5**, the two derivatives of cyclohexene. The ratios of the yields of compounds within the two groups remain constant within experimental error. Apparently the variation involves two parameters; *i.e.*, there is one precursor which reacts to give predominantly cyclobutanes and cycloöctadienes[6] and another which reacts to give relatively large amounts of cyclohexenes. The pattern of variation is shown in Fig. 1 in which the percentage of the total yield represented by the sum of the yields of **1, 2, 3, 6** and **7** is plotted against the $S_0 \rightarrow T_1$ excitation energies of the various sensitizers.[7] Sensitizers having high triplet energies all give the same results; those having excitation energies of 62 kcal. or less per mole give a variety of results. A very pronounced minimum in the plot shows up near 53 kcal. This behavior is reminiscent of that observed in our studies of sensitized *cis–trans* isomerization of unsaturated compounds.[3,8] In the latter cases the results have been partially accounted for by the assumption that the substrate systems can undergo two or more transitions. It is not immediately obvious that a similar explanation applies to dienes such as butadiene and isoprene. However, reflection shows that there should be two transitions originating from the s-*trans* and s-*cis* forms of the dienes. Furthermore, the lowest excited states of the dienes should have large barriers to rotation about the central bonds. The last conclusion follows from the fact that excitation involves promotion of an electron from an orbital which is antibonding between carbon atoms 2 and 3 to an orbital which is bonding between those centers.[9] The 0–0 components of the $S_0 \rightarrow T_1$ transitions of butadiene and isoprene were reported by Evans[10] to occur at 59.6 kcal. (20,830 cm.$^{-1}$) and 60 kcal. (21,000 cm.$^{-1}$), respectively. These transitions undoubtedly arise from light absorption by molecules in the *trans* configuration. The corresponding transition of 1,3-cyclohexadiene occurs at 53.5 kcal. (18,700 cm.$^{-1}$) and is probably typical of *cis*-1,3-dienes. The data of Fig. 1 are consistent with the assumption that high energy sensitizers produce predominantly *trans*-triplets of isoprene which in turn react with isoprene to give primarily cyclobutanes and cycloöctadienes.[6,11] When the energy of the sensitizer falls below 60 kcal., transfer to produce *trans* triplets begins to become inefficient and relatively large amounts of *cis*

(1) Mechanisms of Photoreactions in Solution XIII. Part XII is G. S. Hammond and J. Saltiel, *J. Am. Chem. Soc.*, **84**, 4983 (1962).

(2) G. S. Hammond, N. J. Turro and A. Fischer, *ibid.*, **83**, 4674 (1961).

(3) G. S. Hammond, N. J. Turro and P. A. Leermakers, *J. Phys. Chem.*, **66**, 1144 (1962).

(4) C. Walling and J. Peisach, *J. Am. Chem. Soc.*, **80**, 5819 (1958).

(5) J. L. Binder, K. C. Eberly and G. E. P. Smith, Jr., *J. Polymer Sci.*, **38**, 229 (1959).

(6) The cycloöctadienes may not be primary photoproducts. Consideration of the reactivity of 1,2-dialkenylcyclobutanes suggests that the cyclooctadienes may have been formed by rearrangement of the *cis* isomers of **1** and **2** during vapor chromatographic analysis. This would not alter the present interpretation of results.

(7) Most values have been redetermined in this Laboratory by W. G. Herkstroeter and J. Saltiel by either phosphorescence spectroscopy or by singlet–triplet absorption measurements in ethyl iodide solution.

(8) Unpublished extensions of earlier studies.

(9) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, New York, N. Y., 1961, p. 30.

(10) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

(11) Transfer of energy from *trans* triplets to *cis* diene molecules could decrease the number of *trans* triplets.