

CH=CHSn(CH<sub>3</sub>)<sub>3</sub>,<sup>30</sup> and a similar example is provided by the n.m.r. spectrum of *trans*-propenylbenzene.<sup>31</sup>

The well-established rule<sup>32</sup> that simple *trans* olefins show ultraviolet absorption at longer wave lengths and with higher extinction coefficients than the corresponding *cis* isomers, as well as the often-applied generalization that a strong band in the infrared spectrum between 990 and 965 cm.<sup>-1</sup> is indicative of the *trans* structure,<sup>33</sup> were applied in the structural assignments above.

(30) D. Seyferth, L. G. Vaughan, and R. Suzuki, *J. Organometal. Chem.*, **1**, 437 (1964).

(31) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw Hill Book Co., Inc., New York, N. Y., 1959, p. 238.

(32) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Arnold, London, 1958, pp. 267-274.

(33) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen, London, 1958, pp. 45-48.

(c) *Attempted Wittig Reaction with Cyclohexanone.* To 5 mmoles of triphenylphosphine-*t*-butylmethylene in ca. 100 ml. of ether was added 5 mmoles of cyclohexanone. The color of the solution was discharged immediately with concurrent separation of a thick, white precipitate. The reaction mixture was heated at reflux for 15 hr. Volatiles then were removed by a trap-to-trap distillation *in vacuo*. G.l.c. analysis of the distillate did not show the expected *t*-butylmethylene-cyclohexane. The solid residue was extracted with chloroform and filtered directly into 200 ml. of ethyl acetate. The white, crystalline solid which separated (1.90 g., 82.6%) was identified as neopentyltriphenylphosphonium iodide by mixture melting point and by means of its n.m.r. spectrum.

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## Synthesis and Reactivity in the Benzocalicene Series<sup>1</sup>

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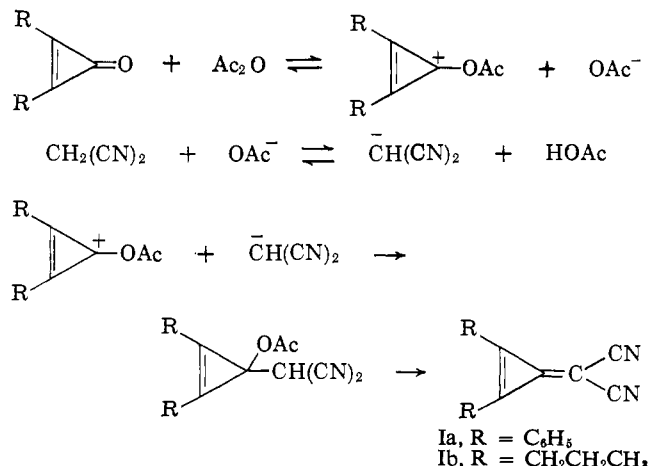
Contribution from the Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

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*Indene-1-carboxylic acid esters and amide react with di-*n*-propylcyclopropanone in acetic anhydride at 120° to give 13-22% yields of the crystalline benzocalicene esters (IVb,c) and nitrile (IVe), respectively. The spectra, dipole moment, and other physical properties of these substances signify a stable and strongly polarized conjugated π-electron system. Reaction of the methyl ester IVb with *N*-bromosuccinimide or bromine has given the monosubstitution product V (R = CO<sub>2</sub>CH<sub>3</sub>). Under Vilsmeier-Haack conditions the methyl ester IVb is converted to a C<sub>23</sub>H<sub>27</sub>O<sub>2</sub>N enamine assigned the structure VII on the basis of spectroscopic evidence. With dimethyl acetylenedicarboxylate the ester IVb undergoes apparent cycloaddition and rearrangement to give a mixture of trimethyl 1,2-dipropylphenanthrene-3,4,9-tricarboxylate (XI) and its isomer XII.*

**Synthesis.** The recent observation<sup>2,3</sup> that malononitrile condenses with disubstituted cyclopropanones in acetic anhydride to give dicyanomethylenecyclopropanes (Ia and Ib) suggested the possibility of employing a parallel method to achieve synthesis of that theoretically interesting<sup>4</sup> but elusive<sup>5</sup> class of compounds based

on the calicene (II) nucleus. If our views of the mechanism of the malononitrile condensation were correct as depicted, the synthesis of calicenes would require the use of a cyclopentadiene derivative having an acidity comparable to that of malononitrile (pK<sub>a</sub> = 11.2).<sup>6</sup> Simple acyl- or carbalkoxy-substituted cyclopentadienes would probably satisfy this requirement, but such



compounds normally exist as dimers rather than as monomers in solution.<sup>7</sup> Our initial attempts toward calicene synthesis therefore utilized the more stable and

calicenes by a hydride-transfer method have recently been reported: W. M. Jones and R. S. Pyron, *J. Am. Chem. Soc.*, **87**, 1608 (1965); H. Prinzbach, *Angew. Chem.*, **77**, 258 (1965).

(6) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

(7) K. Alder, F. H. Flock, A. Hausweiler, and R. Reeber, *Chem. Ber.*, **87**, 1752 (1954).

(1) Calicenes. II. For the preceding paper of this series see A. S. Kende and P. T. Izzo, *J. Am. Chem. Soc.*, **87**, 1609 (1965). A preliminary account of part of this work has been given before the Organic Division, 149th Annual Meeting of the American Chemical Society, Detroit, Mich., April 1965.

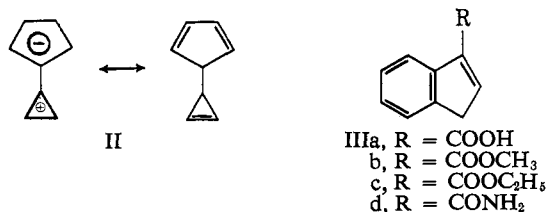
(2) E. D. Bergmann and I. Agranat, *J. Am. Chem. Soc.*, **86**, 3587 (1964).

(3) A. S. Kende and P. T. Izzo, *ibid.*, **86**, 3587 (1964).

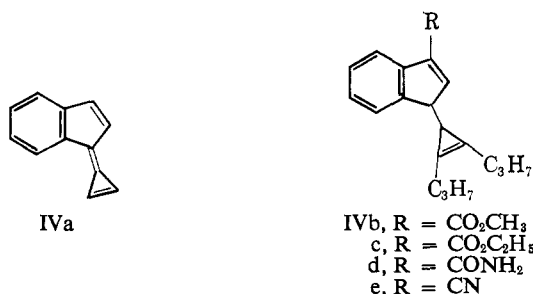
(4) J. D. Roberts, A. Streitwieser, Jr., and C. M. Regan, *ibid.*, **74**, 4579 (1952).

(5) A. Krebs, *Angew. Chem.*, **77**, 10 (1965). Two syntheses of benzo-

accessible derivatives of indene-1-carboxylic acid<sup>8</sup> (IIIa) as the potential nucleophilic reactants.



When indene-1-carboxylic acid itself was warmed with di-*n*-propylcyclopropenone in acetic anhydride as solvent, a strong, new chromophore at 365 m $\mu$  could be observed which did not arise when either of the two reactants was warmed alone in the same solvent. However, all attempts to isolate a discrete, crystalline product from the deeply colored reaction mixture proved unsuccessful. When on the other hand an indene-1-carboxylic ester (IIIb and IIIc) was substituted for the free acid, there was directly obtained from the cooled reaction mixture a cream-colored crystalline condensation product in 10–15% yield. This product gave the correct analytical and molecular weight data for the desired benzocalicene ester (IVb and IVc), a structure which was supported by the 5.91- $\mu$  ester carbonyl band in the infrared and by other maxima at 5.36, 6.49, and 6.68  $\mu$  now known to signal the presence of a methylenecyclopropene grouping.<sup>9</sup> The ultraviolet spectrum of the methyl ester IVb (Figure 1) indicated the presence of an extended conjugated system and was reminiscent of the electronic spectra of some benzofulvenes.<sup>10</sup> Finally, the n.m.r. spectrum of the methyl ester (Figure 2) confirmed the proposed structure, notably by the nearly overlapping signals for the two intact propyl groups, the singlet olefinic hydrogen at  $\tau$  2.43, and the four-proton aromatic multiplet in which the proton *ortho* to the in-plane carbomethoxy group is deshielded some 0.7 p.p.m. from the other three.<sup>11</sup>



Attempts to condense indene itself with di-*n*-propylcyclopropenone in acetic or propionic anhydride were unsuccessful, probably because of the low acidity of the hydrocarbon.<sup>12</sup> Interestingly, indene-1-carboxamide (IIIId) reacted rapidly under the usual reaction conditions to give a single crystalline product which proved not to be the expected benzocalicene carboxamide (IVd) but the corresponding nitrile IVe. The ultraviolet,

(8) A. Melera, M. Claesen, and H. Vanderhaeghe, *J. Org. Chem.*, **29**, 3705 (1964).

(9) E.g., M. Battiste, *J. Am. Chem. Soc.*, **86**, 942 (1964).

(10) E. D. Bergmann, *Progr. Org. Chem.*, **3**, 103 (1965).

(11) This feature of the n.m.r. spectra of indene-1-carboxylic acid derivatives has been frequently observed in these laboratories and is also reported by Melera.<sup>9</sup>

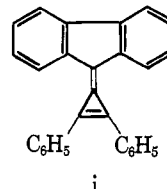
(12) The experimental pK for proton loss from indene has been given as 21 by W. K. McEwen, *J. Am. Chem. Soc.*, **58**, 1124 (1936).

infrared, and n.m.r. spectra of this nitrile were appropriately parallel to those of the esters IVb and IVc; prominent in the infrared of IVe was a strong conjugated C $\equiv$ N stretching maximum at 4.55  $\mu$ .

Simple Hückel molecular orbital calculations on benzocalicene (IVa) indicate appreciable dipolar character to this hydrocarbon<sup>13</sup> and predict a weakly bonding HOMO (highest occupied molecular orbital) at 0.374 $\beta$ . Our data suggest that these properties are to some extent present as well in the derivative IVb. Thus the ester IVb in benzene has a dipole moment of 6.63, as compared with 2.04 D. for the model IIIb. Moreover, IVb reacts reversibly with tetracyanoethylene in methylene chloride to give an unstable indigo complex which shows its longest wave length charge-transfer band at 740  $\pm$  10 m $\mu$ . Since the energy associated with this transition is proportional to the ionization potential of an electron in the HOMO,<sup>14</sup> the observed wave length, which is roughly comparable to the 720-m $\mu$  value reported for pyrene,<sup>15</sup> indicates a weakly bonding HOMO in the benzocalicene IVb at about 0.45 $\beta$ .

*Reactions with Electrophiles.* The predicted and observed polarization of the  $\pi$ -system in benzocalicene derivatives implies an enhanced reactivity of the five-membered ring toward electrophilic reagents.<sup>16</sup> Experimentally we find that the esters IVb and IVc react "instantaneously" with bromine in cold chloroform to give a crystalline monosubstitution product in low yield. With *N*-bromosuccinimide the same product is formed with comparable speed but in much improved yield. This bromo derivative showed neither "positive" nor "ionic" bromine and possessed ultraviolet and infrared spectra differing only slightly from those of its precursor; on this basis it was assigned structure V (R = CO<sub>2</sub>CH<sub>3</sub>). Although too insoluble for direct n.m.r. study, the compound was reversibly soluble in trifluoroacetic acid to give an n.m.r. spectrum showing apparently equivalent propyl groups and a new, one-proton singlet at  $\tau$  4.8, indicating protonation on carbon.<sup>17</sup> The ultraviolet spectrum of this solution showed very weak maxima at 361 and 287 m $\mu$  (log  $\epsilon$   $\sim$  3.6) which did not permit an unambiguous choice

(13) W. Jones and R. Pyron, *ibid.*, **87**, 1608 (1965), have concluded, on the basis of strong solvent effects upon the longest wave length  $\pi \rightarrow \pi^*$  electronic absorption maximum, that the dibenzocalicene i has significant dipolar character in the ground state.



(14) R. E. Merrifield and W. D. Phillips, *ibid.*, **80**, 2778 (1958).

(15) M. J. S. Dewar and H. Rogers, *ibid.*, **84**, 395 (1962).

(16) Localization energy for electrophilic attack on the unsubstituted position of the five-membered ring of IVb, using the simple Hückel treatment and disregarding the ester function, is  $-2.202\beta$ . This would predict reactivity comparable to, say, pyrene ( $L^+ = -2.190\beta$ ) but much less than in electrophilic attack on calicene itself ( $L^+ = -1.998\beta$ ); cf. O. Chalvet, R. Daudel, and J. J. Kaufman, *J. Phys. Chem.*, **68**, 490 (1964).

(17) The apparent equivalence of the propyl groups in acid, while possibly a solvent effect, could also arise from a low barrier to rotation about the intericyclic bond in VIa. Similar phenomena in the n.m.r. spectra of unsymmetrical calicenes have been observed in these laboratories even in the absence of protonation on carbon in the conjugate acids (to be published).

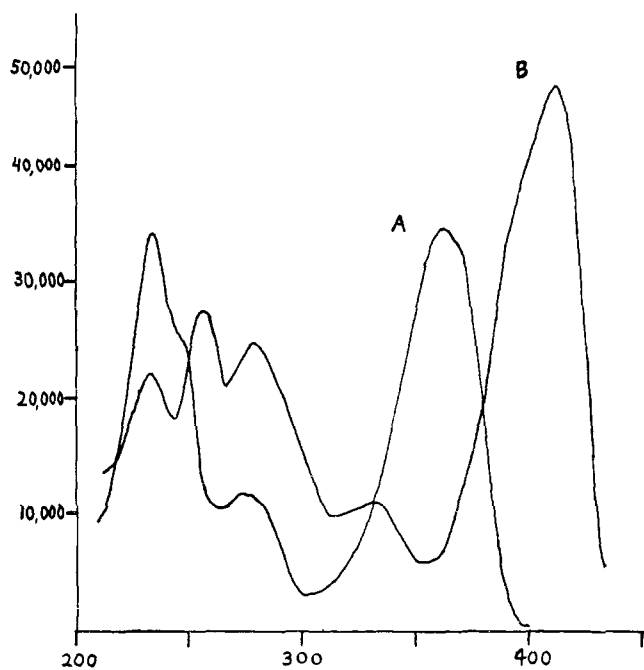
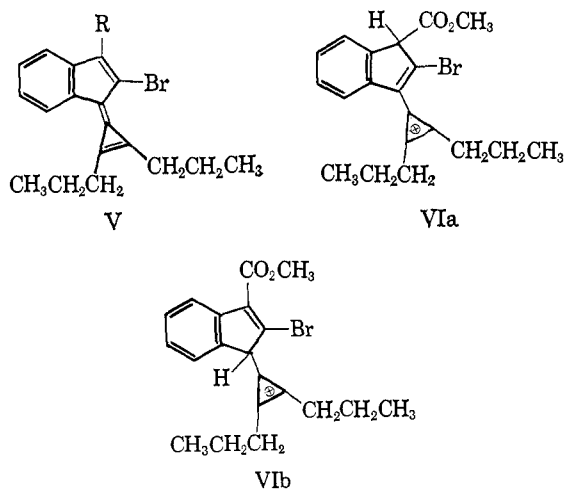


Figure 1. Ultraviolet spectra (in methanol) of (A) methyl 1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate (IVb) and (B) methyl 1-((2-dimethylamino-1-ethylvinyl)propylcyclopropenylidene)-3-indenecarboxylate (VII).

between the possible conjugate acids VIa or VIb, but the very narrow, four-proton aromatic resonance ( $\tau$  2.34  $\pm$  0.10) seemed to lack the deshielded *ortho* proton expected of the olefinic ester system in VIb. Direct evidence for the position of the bromine was obtained from n.m.r. examination in deuteriochloroform solution of the more soluble brominated ethyl ester (V, R = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>), the spectrum of which clearly lacked the  $\tau$  2.43 olefinic singlet of the precursor IVc and was otherwise consistent with the proposed structure.



The facile substitution of the five-membered ring in IVb and IVc observed on bromination could not be extended to reaction with other electrophiles. Treatment of ester IVb with nitronium fluoroborate<sup>18</sup> or with *p*-nitrobenzenediazonium fluoroborate at low temperatures in acetonitrile led to rapid and substantially complete destruction of the benzocalicene chromophore with the formation of orange gums which resisted

(18) S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.*, **83**, 4564 (1961).

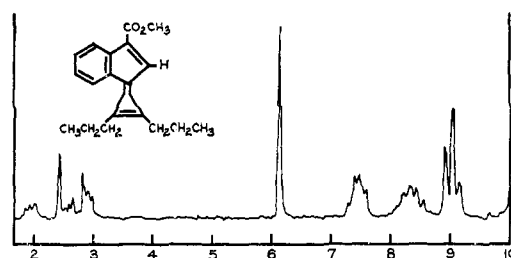


Figure 2. Nuclear magnetic resonance spectrum, taken at 60 Mc. in CDCl<sub>3</sub> solution, of methyl 1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate (IVb). The calibrations are in  $\tau$  units relative to internal tetramethylsilane.

crystallization. A remarkable reaction was observed however when the ester IVb or IVc was treated with the phosphorus oxychloride–dimethylformamide complex at  $-7^\circ$  in an attempted Vilsmeier–Haack formylation.<sup>19</sup> With the methyl ester IVb, neutral aqueous work-up produced, in 70% yield, a bright yellow crystalline product, m.p. 160–161°, which gave analytical and molecular weight data indicating a C<sub>23</sub>H<sub>27</sub>O<sub>2</sub>N structure, *i.e.*, IVb + NC<sub>3</sub>H<sub>5</sub>. This compound retained the infrared maxima at 5.43, 5.93, and 6.8  $\mu$  indicative of a calicene ester grouping and exhibited in addition a strong new peak at 6.20  $\mu$ . The ultraviolet spectrum (Figure 1) was similar in shape to that of the precursor IVb but was bathochromically displaced some 30–50 m $\mu$ ; moreover, unlike IVb, the C<sub>23</sub>H<sub>27</sub>O<sub>2</sub>N product was sufficiently basic to dissolve readily in strong hydrochloric acid with a reversible shift in ultraviolet spectrum to 362 and 292 m $\mu$ . The n.m.r. spectrum in DMSO-*d*<sub>6</sub> showed a presumptive N(CH<sub>3</sub>)<sub>2</sub> six-proton singlet at  $\tau$  6.73, a probable OCH<sub>3</sub> singlet at 6.22, two appreciably dissimilar C-methyl triplets near 9, an ill-defined methylene region, and seemingly a six-proton aromatic region. In trifluoroacetic acid the spectrum was grossly similar except for the appearance of a somewhat broad one-proton signal at  $\tau$  4.98 presumably representing formation of a new C–H bond in the conjugate acid.

The spectroscopic features suggest that the C<sub>23</sub>H<sub>27</sub>O<sub>2</sub>N compound retains the essentials of the benzocalicene structure, modified by the presence of extended conjugation. The position of the –N(CH<sub>3</sub>)<sub>2</sub> resonance and the new band at 6.20  $\mu$  in the infrared both point to the grouping (CH<sub>3</sub>)<sub>2</sub>NC=C. A structure which fits all of the spectroscopic data and moreover rationalizes the enhanced basicity of the yellow compound is provided by formula VII, which represents one of four possible geometric isomers which can formally be written for such a molecule.<sup>20</sup> Its genesis by way of a second methylenecyclopropene tautomer of a benzocalicene–Lewis acid complex, as shown below, is suggested as a possible reaction mechanism.<sup>21</sup> Analogous formation of stable enamines during Vilsmeier–Haack reactions of

(19) For a general review of the Vilsmeier–Haack reaction, the reader is directed to the work of M.-R. de Maheas, *Bull. soc. chim. France*, 1989 (1962). The formylation of fulvenes by this technique is described by K. Hafner, *Angew. Chem.*, **75**, 35 (1963).

(20) We have no information regarding the stereochemistry of the crystalline product actually obtained, nor whether it is the product of kinetic or thermodynamic control.

(21) Compare the similar exocyclic acylation of alkyltropylium salts by Vilsmeier complexes, as reported by C. Jutz, *Chem. Ber.*, **97**, 2050 (1964). We are indebted to a referee for drawing our attention to this reference.

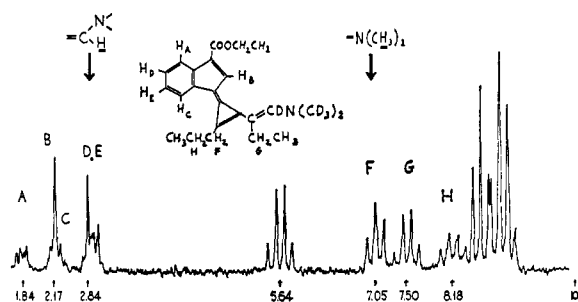


Figure 3. Nuclear magnetic resonance spectrum, measured at 60 Mc. in  $\text{CDCl}_3$  solution, of the partially deuterated enamine VIII. Arrows mark the positions of additional signals observed in the spectrum of the undeuterated counterpart of VIII.

active methylene compounds has occasionally been observed.<sup>22</sup>

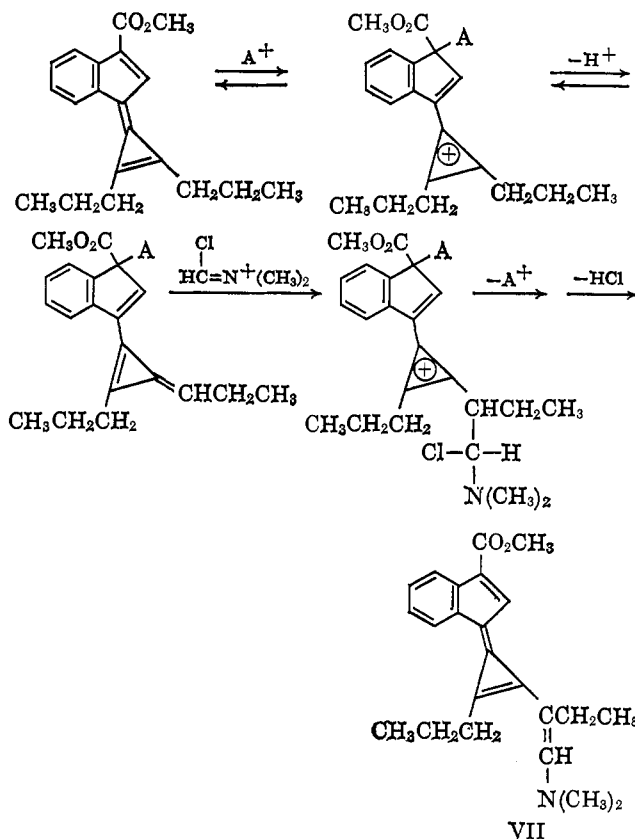
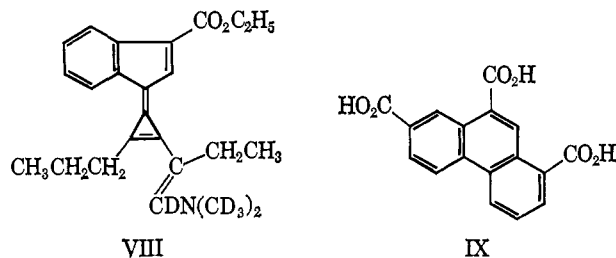


Figure 4. Nuclear magnetic resonance spectrum, taken at 56.4 Mc. in  $\text{CDCl}_3$  solution, of the phenanthrene triester, m.p. 122–123°.

tographic "homogeneity," a single compound, m.p. 122–123°, could be isolated in about 20% over-all yield by careful fractional crystallization. This component gave an excellent analysis for a 1:1 adduct and its n.m.r. spectrum (Figure 4) was consistent with that



interpretation. The ultraviolet spectrum of this adduct, with maxima at 318  $m\mu$  ( $\log \epsilon$  4.04) and 269  $m\mu$  ( $\log \epsilon$  4.59), differed profoundly from that of the benzocyclobutene precursor as did its infrared spectrum which lacked the 5.4- $\mu$  band diagnostic of methylenecyclopropenes but did suggest the presence of conjugated (5.81  $\mu$ ) and unconjugated (5.76  $\mu$ ) ester carbonyl groups. The initial experimental clue to the structure came from the ultraviolet spectrum of its lithium aluminum hydride reduction product (see Experimental), a spectrum which was characteristic of a polyalkylphenanthrene.<sup>23</sup> This observation suggested that the 123° adduct itself may be a substituted phenanthrenetricarboxylic ester, and indeed its spectrum was seen to be much like that of a rough surrogate, IX.<sup>24</sup>

The formation of a phenanthrene in this reaction can be rationalized by a mechanism initiated by cycloaddition of the acetylene to the intericyclic double bond of the benzocyclobutene to give the cyclobutene X,<sup>25</sup> followed by ring expansion and phenyl or vinyl migration<sup>26</sup> to form in each case a Dewar benzene, and ultimate aromatization.

An alternative mechanism, in which the 1,4-adduct XIII is initially formed, can be written along similar

Support for structure VII, a vinylogous aminocyclopropene, is found in the well-resolved n.m.r. spectrum (Figure 3) of the yellow enamine VIII obtained by treatment of the ethyl ester IVc under Vilsmeier-Haack conditions using dimethylformamide- $d_7$ . The absence of interfering signals from the  $=\text{CHN}(\text{CH}_3)_2$  group allows the individual signal assignments for each type of proton in VIII to be specified as in Figure 3.

**Cycloaddition of Dimethyl Acetylenedicarboxylate.** Although the ester IVb was relatively inert to the usual dienophiles, the action of dimethyl acetylenedicarboxylate at 140° led to the isolation of a crystalline material, m.p. 113–121°, in about 55% yield. From this material, obviously a mixture despite its chroma-

(22) J. Zemlicka and Z. Arnold, *Collection Czech. Chem. Commun.*, **26**, 2852 (1961).

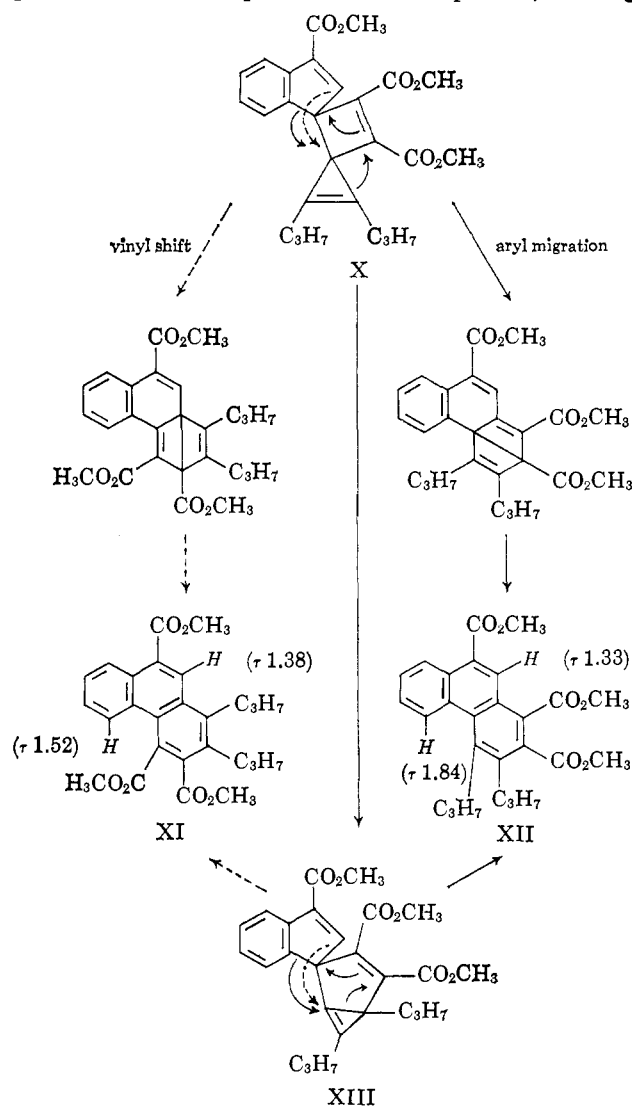
(23) E.g., 4-ethyl-5,8-dimethylphenanthrene-1-acetic acid,  $\lambda_{\text{max}}$  358  $m\mu$  ( $\log \epsilon$  2.78), 343 (2.80), 316 (4.22), 303 (4.18), 292 (4.01), and 261 (4.8), recorded by R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(24) A. D. Kuzovkov, *Zh. Obshch. Khim.*, **28**, 558 (1958); **30**, 1727 (1960).

(25) Compare the cycloaddition of tetracyanoethylene to the exocyclic double bond of a methylenecyclopropene ester observed by M. Battiste.<sup>9</sup>

(26) A similar ring expansion of a cyclopropene appears to be involved in the rearrangement of a cyclopropenylcarbinol described by R. Breslow and M. Battiste, *J. Am. Chem. Soc.*, **82**, 3626 (1960).

lines. In each case the formation of both the phenanthrene XI and the isomer XII, resulting from vinyl and phenyl migration, respectively, is possible. Our evidence indicates that the crude crystalline adduct, m.p. 113–121°, is indeed a mixture of these isomers, present in roughly equal amounts. Those fractions of the adduct from which most of the 123° component has been removed give substantially the same ultraviolet spectrum and analysis as the 123° compound, and n.m.r. spectra likewise indicate a second alkylphenanthrene triester as the other component. Proton decoupling studies on the 123° compound permit signal assignments as depicted in Figure 4. In the spectrum of the impure second component, the sig-



nals corresponding to protons B and C are shifted, respectively, 0.05 p.p.m. downfield and 0.32 p.p.m. upfield relative to their position in Figure 4. These data are well accommodated if the 123° compound is assigned structure XI in which the proton C is deshielded by the *peri*-carbomethoxy group, while structure XII probably corresponds to the component not yet obtained pure.

The retention of the benzocalicene framework during bromination and the "abnormal Vilsmeier-Haack" reaction signifies a measure of thermodynamic stability for this delocalized  $\pi$ -electron system. The extent to which this stability is influenced by the fused benzene

ring can be assayed by a study of simpler calicenes lacking that feature. The synthesis of such compounds will be described in the next paper of this series.

## Experimental

### 1-Dicyanomethylene-2,3-di-*n*-propylcyclopropene.

A mixture of 2.5 g. (0.018 mole) of 2,3-dipropylcyclopropenone, 1.25 g. (0.020 mole) of malononitrile, and 30 ml. of freshly distilled acetic anhydride was heated at 140–145° for 2 hr. The acetic anhydride was removed by distillation at reduced pressure. Last traces were removed by distilling with benzene to give a reddish brown liquid residue. This material was separated into various fractions by a slow, evaporative distillation. The more volatile fractions (b.p. 62–78° at 0.15 mm.) showed the following significant bands in the infrared: 5.50, 5.75, 5.89, and 6.07  $\mu$ ; the CN band was absent. The desired product distilled at about 100° (0.1 mm.) as a straw-colored oil. The infrared spectrum showed strong bands at 4.51 (CN), 5.32, and 6.61  $\mu$ . The yield was 0.77 g. It was estimated by infrared that this material contained 80% of the desired compound. Thus the yield was 18%. An analytical sample was obtained by subjecting this material to partition chromatography using heptane-methanol on diatomaceous earth. The moving phase (heptane) eluted small amounts of impurities. The desired compound was left on the column and was recovered in the methanol wash. Evaporation of the solvent gave a yellow liquid which was further purified by an evaporative distillation at 92° (0.01 mm.).

*Anal.* Calcd. for  $C_{12}H_{14}N_2$ : C, 77.38; H, 7.58; N, 15.04. Found: C, 76.77; H, 7.42; N, 15.01.

Spectroscopic data on this compound have been given in the preliminary communication.<sup>3</sup>

*Methyl 1-(2,3-Dipropylcyclopropenylidene)-3-indene-carboxylate.* A solution of 8.65 g. of methyl 1-indene-carboxylate (b.p. 86–88° at 1 mm.) and 7.60 g. of di-*n*-propylcyclopropenone in 40 ml. of reagent acetic anhydride was stirred at  $123 \pm 3^\circ$  under a nitrogen atmosphere for a period of 3 hr. After the reaction mixture was allowed to stand at room temperature overnight, the precipitated crystalline product was removed by suction filtration and thoroughly washed with petroleum ether (b.p. 30–60°). In this manner was obtained 2.27 g. (15% yield) of cream-colored needles, m.p. 156–158°, of essentially pure condensation product. The analytical sample was obtained by one recrystallization from ethyl acetate as colorless needles, m.p. 157–158°, dried at 60° (0.1 mm.) for 2 hr. prior to analysis.

*Anal.* Calcd. for  $C_{20}H_{22}O_2$ : C, 81.60; H, 7.53; mol. wt., 294.38. Found: C, 81.71; H, 7.88; mol. wt., 293 (vapor pressure thermistor).

*Ethyl 1-(2,3-Dipropylcyclopropenylidene)-3-indene-carboxylate.* A mixture of 0.941 g. (0.005 mole) of ethyl 1-indenecarboxylate, 1.38 g. (0.01 mole) of dipropylcyclopropenone, and 10 ml. of acetic anhydride was stirred under a nitrogen atmosphere at 120° (oil bath temperature) for 4 hr. Cooling of the reaction mixture in ice caused the precipitation of a yellow, crystalline crop, which was collected on a filter and washed with hexane. The yield was 0.20 g. (13%), m.p. 132–134°. A recrystallization from alcohol gave 192 mg. of yellow needles, m.p. 135–136°.

*Anal.* Calcd. for  $C_{21}H_{24}O_2$ : C, 81.78; H, 7.84. Found: C, 81.73; H, 8.06.

The spectroscopic data on this compound were closely parallel to those of the corresponding methyl ester.

*3-Cyano-1-(2,3-dipropylcyclopropenylidene)indene.* A mixture of 320 mg. (0.002 mole) of 1-indenecarboxamide, 600 mg. (0.0043 mole) of dipropylcyclopropenone, and 4 ml. of acetic anhydride was stirred and heated at 120–125° (oil bath temperature) for 2 hr. under a nitrogen atmosphere. The mixture was cooled in ice for several hours and the crystalline crop which separated was collected, washed with petroleum ether, and dried. This material which was essentially pure product weighed 116 mg. (22%), m.p. 149–151°. Two recrystallizations from alcohol (charcoal) gave nearly white needles: m.p. 151–152°; infrared  $\lambda_{\text{max}}^{\text{KBr}}$  4.55, 5.36, 6.22, 6.50, and 6.69  $\mu$ ; ultraviolet  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  355 m $\mu$  (log  $\epsilon$  4.56), 274 (4.15), and 288 (4.62); n.m.r. (in  $\text{CDCl}_3$ ) one-proton singlet at  $\tau$  2.6 amidst a four-aromatic proton multiplet and two nonequivalent propyls.

*Anal.* Calcd. for  $C_{19}H_{19}N$ : C, 87.31; H, 7.33; N, 5.36. Found: C, 87.07; H, 7.67; N, 5.59.

*Methyl 2-Bromo-1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate.* A. *By Reaction with NBS.* To a solution of the benzocyclopropene methyl ester IVb (58 mg., 0.2 mmole) in 5 ml. of chloroform was added 41 mg. (0.23 mmole) of N-bromosuccinimide in portions, with occasional stirring. After 10–15 min. at room temperature, the yellow solution was diluted with 40 ml. of chloroform, washed once with dilute acidified potassium iodide solution (no coloration) and twice with water (to remove succinimide), then dried for a few minutes over magnesium sulfate. Removal of solvent gave a solid which was recrystallized from hot ethyl acetate to give 41 mg. (56%) of the cream-colored bromo derivative, m.p. 189–190°.

*Anal.* Calcd. for  $C_{20}H_{21}BrO_2$ : Br, 21.43. Found: Br, 21.18.

The substitution product exhibited infrared maxima (KBr) at 5.38, 5.90, 6.56, 6.83, 7.03, 8.60, 8.69, and 9.02  $\mu$ , with ultraviolet absorption in methanol at  $\lambda_{\text{max}}$  365 m $\mu$  (log  $\epsilon$  4.51), 281 (4.06), and 234 (4.57). The crystalline product did not oxidize acidified iodide, nor did it react with ethanolic silver nitrate.

B. *By Reaction with Bromine.* To a solution of 29 mg. of ester IVb in a mixture of chloroform (1.0 ml.) and ether (0.5 ml.) was added dropwise at 10° approximately 0.13 ml. of a 0.75 M solution of bromine in carbon tetrachloride. The bromination product crystallized during this addition. After dilution with 1 ml. of ether and filtration, there was obtained 22 mg. of crude product, m.p. 172–174° dec. One recrystallization from chloroform-ether gave 12 mg. of lemon yellow crystals, m.p. 186–187°, having an infrared spectrum superimposable with that of the product obtained in A, above, using N-bromosuccinimide. A mixture melting point of the two samples was undepressed.

*Methyl 1-([2-Dimethylamino-1-ethylvinyl]propylcyclopropenylidene)-3-indenecarboxylate.* To dry, amine-free dimethylformamide (3.0 ml.), stirred at –5° under a nitrogen atmosphere, was slowly added 0.30 ml. of phosphorus oxychloride and the mixture was stirred at –5° for 30 min. To this cold reagent

was added the solid methyl ester IVb (60 mg.), and the suspension was stirred at –7° until all of the ester had dissolved. After an additional 5 min. the entire reaction mixture was poured into ice water containing 100 mg. of sodium acetate. The yellow precipitate which formed was isolated by suction filtration, washed with ice water, and dried at oil pump vacuum. The resulting gummy solid was taken up in chloroform, filtered, evaporated to dryness, and recrystallized from methanol to give 43 mg. of the enamine VII, m.p. 159–160° dec.

A sample for analysis was prepared by further recrystallization from methanol, m.p. 160–161°. It was dried at 85° for 2 hr. at 100 mm. prior to analysis.

*Anal.* Calcd. for  $C_{23}H_{27}NO_2$ : C, 79.05; H, 7.79; N, 4.01; mol. wt., 349.4. Found: C, 79.73; H, 8.04; N, 4.05; mol. wt., 348.

*Ethyl 1-([2-Dimethylamino-1-ethylvinyl]propylcyclopropenylidene)-3-indenecarboxylate.* The Vilsmeier-Haack reagent was prepared by stirring a mixture of 3 ml. of dry, amine-free dimethylformamide and 0.30 ml. of phosphorus oxychloride at –5° for 30 min. To this was added in portions 60 mg. (0.2 mmole) of ethyl 1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate, and the mixture was stirred at –5° until it changed to a clear yellow solution (ca. 25 min.). A bright yellow, crystalline product precipitated when this solution was poured into about 40 g. of ice and water containing 100 mg. of sodium acetate. The crystalline crop was collected, air-dried briefly, and dissolved in 25 ml. of chloroform. The resulting solution was dried ( $\text{MgSO}_4$ ) and evaporated to give a solid which when recrystallized from ethyl acetate gave 45 mg. (62%) of yellow needles, m.p. 167–169°.

*Anal.* Calcd. for  $C_{24}H_{29}NO_2$ : C, 79.30; H, 8.04; N, 3.85. Found: C, 79.49; H, 8.01; N, 3.86.

*Ethyl 2-Bromo-1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate.* To a solution of 61 mg. (0.2 mmole) of ethyl 1-(2,3-dipropylcyclopropenylidene)-3-indenecarboxylate in 5 ml. of chloroform was added in portions 41 mg. (0.23 mmole) of N-bromosuccinimide. The solution was stirred magnetically at room temperature for 20 min., diluted with 40 ml. of chloroform, and washed once with dilute potassium iodide solution and twice with water. Removal of the solvent gave a cream-colored solid which on recrystallization from alcohol gave 30 mg. (40%) of crystalline product, m.p. 164–165°. Another recrystallization from ethyl acetate did not alter this melting point; infrared  $\lambda_{\text{max}}^{\text{KBr}}$  5.39, 5.93 and 6.54  $\mu$ ; ultraviolet  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  365 m $\mu$  (log  $\epsilon$  4.49), 280 (4.05), and 236 (4.55); n.m.r. one-proton multiplet at  $\tau$  1.92 and three-proton multiplet at 2.75, comprising the four aromatic protons, plus apparently equivalent propyl groups and an ethoxyl group.

*Anal.* Calcd. for  $C_{21}H_{23}BrO_2$ : C, 65.12; H, 5.98; Br, 20.63. Found: C, 65.36; H, 6.14, Br, 20.54.

*Adduct Formation with Dimethyl Acetylenedicarboxylate.* A mixture of 200 mg. of benzocyclopropene methyl ester IVb, 0.60 ml. of dimethyl acetylenedicarboxylate, and 4.0 ml. of dry xylene was stirred under nitrogen at 135–137° for 16 hr. After addition of 20 ml. of xylene and concentration of the solution to a sirup under vacuum, the reaction mixture was dissolved in 1:1 hexane-benzene and chromatographed

over 150 g. of neutral alumina. After initial elution with benzene and benzene-3% ethyl acetate, the use of benzene-6% ethyl acetate removed the bulk of the reaction products. From these latter cuts was obtained a cream-colored crystalline mass which was readily recrystallizable from methanol to give 177 mg. of crude adduct, m.p. 113-120°, representing a total yield of 60% based on starting benzocalicene ester.

Four recrystallizations of this crude adduct from ether-petroleum ether gave 66 mg. of *trimethyl 1,2-dipropylphenanthrene-3,4,9-tricarboxylate*, m.p. 122-123°, exhibiting principal infrared maxima (KBr) at 5.74, 5.80, 6.96, 7.83, 7.96, and 8.33  $\mu$ . The triester was dried at 70° and oil pump vacuum for 30 min. prior to analysis.

*Anal.* Calcd. for  $C_{26}H_{28}O_6$ : C, 71.54; H, 6.47. Found: C, 72.00; H, 6.66.

Crystallization of the combined mother liquors gave, first, another 15 mg. of the slightly impure triester described above; the subsequent crop gave 82 mg. of the mixture of isomeric esters. This crop had m.p. 113-126°, and an ultraviolet spectrum substantially identical with that of the pure triester, m.p. 122-123°. A combustion analysis of this mixture was slightly low in carbon.

*Anal.* Calcd. for  $C_{26}H_{28}O_6$ : C, 71.54; H, 6.47. Found: C, 70.69; H, 6.46.

*Hydride Reduction of Trimethyl 1,2-Dipropylphenanthrene-3,4,9-tricarboxylate.* A solution of the 123° triester (6 mg.) in freshly distilled, peroxide-free tetrahydrofuran (3.0 ml.) was stirred under nitrogen with 150 mg. of lithium aluminum hydride. The temperature of the suspension was warmed to 55-60° and the reduction was monitored by ultraviolet spectrophotometry. After 1 hr. at this temperature, the spectrum remained constant. Semiquantitative assay of an aliquot in acidified methanol gave the following maxima: 363 m $\mu$  (log  $\epsilon$  2.4), 347 (2.4), 313 (2.8), 302 (2.9), and 263 (4.6). Because of scarcity of sample this product was not further investigated.

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## Biosynthesis of the *Vinca* Alkaloids. I. Feeding Experiments with Tryptophan-2-C<sup>14</sup> and Acetate-1-C<sup>14</sup><sup>1</sup>

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*Radioactive vindoline was isolated from Vinca rosea plants which had been fed DL-tryptophan-2-C<sup>14</sup>. A systematic degradation of this alkaloid established that essentially all the activity was located at C-10, substantiating the hypothesis that tryptophan is a most probable precursor of this type of dihydroindole alkaloid. Administration of sodium acetate-1-C<sup>14</sup> to the same species resulted in the formation of radioactive vindoline, catharanthine, and ajmalicine. Partial degradations were carried out on these alkaloids and the results obtained indicate that acetate is not serving as a direct precursor for the nontryptophan-derived portion of these alkaloids.*

The plant *Vinca rosea* Linn.<sup>5</sup> has been extensively investigated in the last few years because it has been

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(3) On leave of absence from the Pakistan Atomic Energy Commission.

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found to contain potent oncolytic agents. The major alkaloid found in the leaves is vindoline (I). The pentacyclic ring system found in this compound<sup>6</sup> has been previously encountered in the alkaloid aspidospermine,<sup>7</sup> and a large group of alkaloids is now known with this type of skeleton.<sup>8</sup>

Since the  $\beta$ -(2-aminoethyl)indole moiety is present in vindoline, it has generally been accepted that this part of the alkaloid is derived from tryptophan or its decarboxylation product tryptamine.<sup>9</sup> We have now concluded that tryptophan is indeed a most probable direct precursor of this part of the vindoline molecule

(5) Cf. G. H. Svoboda, I. S. Johnson, M. Gorman, and N. Neuss, *J. Pharm. Sci.*, **51**, 707 (1962), for a review on the numerous alkaloids found in this plant, the correct botanical name of which is apparently *Catharanthus roseus* G. Don.

(6) (a) M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, and N. J. Cone, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 256 (1959); (b) M. Gorman, N. Neuss, and K. Biemann, *J. Am. Chem. Soc.*, **84**, 1058 (1962).

(7) J. F. D. Mills and S. C. Nyburg, *Tetrahedron Letters*, No. 11, 1 (1959); H. Conroy, P. R. Brook, and Y. Amiel, *ibid.*, No. 11, 4 (1959).

(8) Cf. "The Alkaloids, Chemistry and Physiology," Vol. VIII, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1965.

(9) It has been suggested by E. Wenkert, *J. Am. Chem. Soc.*, **84**, 98 (1962), that the aspidospermine type alkaloids are formed not from tryptophan, but from its progenitors, namely derivatives of anthranilic acid.