spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 mHz with a Varian Model A-60 or T-60-A NMR spectrometer, and the ^{13}C NMR spectra were determined at 25 mHz with a JEOL Model PFT-100 Fourier transform spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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Base-Catalyzed Isomerization of *cis*- and *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylates. Nature of the Base-Stable Cis Intermediate

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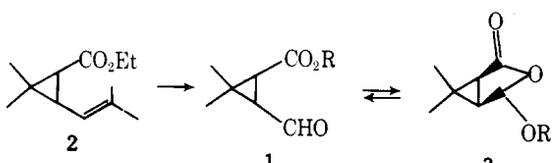
A mixture of isomers of ethyl 2,2-dimethyl-3-formylcyclopropanecarboxylate (**1b**), obtained by ozonolysis of commercial ethyl chrysanthemate, undergoes rapid transesterification and isomerization to the *trans* methyl ester in 15 min at 25 °C in sodium methoxide–methanol. Reaction at this temperature for 24 h rather than 15 min, or refluxing for 3 h, results in the accumulation of a relatively base-stable cis intermediate which is hydrolyzed under acid conditions to hydroxy lactone **3c**. The intermediate has been isolated and identified as the dimethyl acetal of *cis*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (**9**) instead of the previously postulated methoxy lactone **3a**, although methoxy lactone **3a** is implicated as a precursor of the accumulated dimethyl acetal. Anhydrous sodium ethoxide–ethanol can also be used for conversion of a mixture of isomers of **1b** to the pure trans isomer, but it cannot be used for the preparation of the cis isomer, since reaction of **1b** in this medium for 24 h at 25 °C results exclusively in the formation of the *hydrolysis* product *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid. A reaction scheme which rationalizes these observations is suggested. The isomerically pure *cis*- and *trans*-2,2-dimethyl-3-vinylcyclopropanecarboxylic acids and amides have been prepared from the corresponding formyl precursors **3c** and **1a**.

Methodology for stereospecific preparation of 2,2-dimethyl-3-formylcyclopropanecarboxylates (1), particularly



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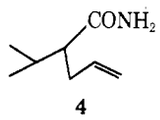
a, R = Me
b, R = Et
c, R = H



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the thermodynamically less stable cis isomers, is of considerable current interest because of the pivotal role these structures play in elaboration of vinyl-modified chrysanthemic acid analogues, essential components of the highly promising pyrethroid insecticides.[1,2] Among methods reported in recent years for the synthesis of isomerically pure *cis*- and *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylates,[3] that disclosed by J. Martel of Roussel UCLAF is particularly ingenious.[4] It involves ozonolysis of *trans*-methyl chrysanthemate (**2a**) to give trans ester aldehyde **1a**, which is converted in refluxing sodium methoxide–methanol to a latent form of the cis isomer, essentially uncharacterized but assigned structure **3a** in the patent.[4] This unisolated precursor is directly hydrolyzed under acidic conditions to hydroxy lactone **3c**, the preferred tautomeric form of the desired *cis*-**1c**.

Our interest in this process stems from our desire, in connection with a study of the destruction of cytochrome P450 by 2-isopropyl-4-pentenamide (**4**),[5,6] to synthesize the conformationally restricted analogues, *cis*- (**5**) and *trans*-2,2-dimethyl-3-vinylcyclopropanecarboxamide (**6**). The procedure outlined by Martel was particularly attractive because of the ready commercial availability of a mixture of *cis*- and *trans*-ethyl chrysanthemates. To our surpirse, only poor and erratic yields of **3c** were obtained when a mixture of isomers of ethyl chrysanthemate was subjected to the literature procedure reported for the pure *trans*-methyl ester.[4] Subsequent detailed studies, the results of which are presented here, demonstrate that the isomerization process is a complex one

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5, X = $CONH_2$; W = $CH{=}CH_2$; Y = Z = H
6, X = $CONH_2$; Z = $CH{=}CH_2$; Y = W = H
7, X = CO_2Et; Y = H; W, Z = H, $CH(OEt)_2$
8a, X = W = CH_2OH; Y = Z = H
8b, X = W = CH_2OAc; Y = Z = H
9, X = CO_2H; W = $CH(OMe)_2$; Y = Z = H
10, X = CO_2H; Z = $CH{=}CH_2$; Y = W = H
11, X = CO_2H; W = $CH{=}CH_2$; Y = Z = H

whose outcome depends on the interplay of several finely balanced competing reactions. Of particular interest is the discovery that **3** (R = alkyl) is *not* the stable form which allows accumulation of the latent cis isomer in the face of basic reaction conditions, the sine qua non of the isomerization process. These results simplify extension of the isomerization sequence to other ring systems.

Ethyl chrysanthemate obtained commercially was found by NMR analysis to be a 7:3 mixture of trans/cis isomers, even though the isomers were not resolved by gas chromatographic analysis on a 6-ft OV-225 column. The physical similarity between the isomers, exemplified by the identity of their retention times on OV-225, makes their separation by physical methods unattractive, although the free acids have been separated by tedious crystallizations.[7] Ozonolysis of the isomer mixture in ethanol at −78 °C, followed by reduction of the ozonide with dimethyl sulfide, gave, presumably, a mixture of the cis and trans isomers of diethyl acetal **7**.[4] These were hydrolyzed in aqueous acetic acid without isolation, as described by Martel for the trans isomer,[4] giving **1b** (34:66 cis/trans) in 82% overall yield. Pure *trans*-**1a** was obtained from the mixture of isomers of ethyl ester **1b** by stirring in 1.25 M sodium methoxide–methanol for 15 min at 25 °C. The transesterification and isomerization reactions are extremely facile, both being half-complete (by GLC analysis) within 1 min of mixing the reagent with the sample. The yield of pure **1a** obtained in this reaction is about 60%, although the yield decreases slightly as the proportion of cis isomer in the original mixture increases. For example, the yield of **1a** obtained from a sample of **1b** containing 72% of the cis isomer was only 39%. The implication that the cis isomer is not only isomerized to the trans isomer but is also subject to a cis-selective (vide infra) competing reaction is consistent with the observation that the yield of *trans*-**1a** is decreased by reaction times longer than 15 min.

Isomerization of *trans*-**1a** to an intermediate which is not isolated but is assigned structure **3a** is reported to occur in refluxing 1.25 M sodium methoxide–methanol in 3 h.[4] Hydrolysis of the intermediate to hydroxy lactone **3c** is then achieved by refluxing in aqueous dioxane.[4] Analogous treatment of the mixture of isomers of **1b** obtained on ozonolysis of **2b**, however, did not give significant amounts of the hydroxy lactone despite rapid in situ formation of *trans*-**1a** by transesterification and isomerization. Instead of hydroxy lactone **3c**, the reaction sequence provided ethoxy lactone **3b** in 39% isolated yield. Isolation of this compound despite the hydrolysis step was subsequently shown to be a consequence of its resistance to mild (aqueous acetic acid) hydrolysis conditions, although it can be hydrolyzed to hydroxy lactone **3c** by stirring for 24 h at 25 °C in 0.2 M aqueous HCl.

The structure and stereochemistry of the unexpected lactone **3b** were firmly established by both chemical and spectroscopic methods. Hydrolysis of the product with potassium hydroxide in water gave *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (*trans*-**1c**), a substance shown subsequently to also be present in the crude mixture from the original isomerization reaction. Reduction with $LiAlH_4$ of the compound assigned structure **3b** yielded **8a**, which in turn gave diacetate **8b**, spectroscopically identical with that reported in the literature.[7]

The spectral data, particularly the proton and ^{13}C NMR results, confirm the structural assignment of **3b** and establish that the ethoxy group is exo to the ring system. This is evident from the small (0.8 Hz) coupling between the cyclopropyl proton (H_a) and the vicinal dioxymethine proton (H_b), a phenomenon consistent[8] with their nearly perpendicular orientation in the *exo*-ethoxide isomer as predicted by molecular models and simple computerized conformational analysis (Figure 1).[10] On the other hand, normal coupling is predicted for these protons in the *endo*-ethoxide isomer. The ethoxymethylene group in **3b** appears in the proton NMR spectrum as a highly complex multiplet due to the diastereotopic nature of H_c and H_d.[9]

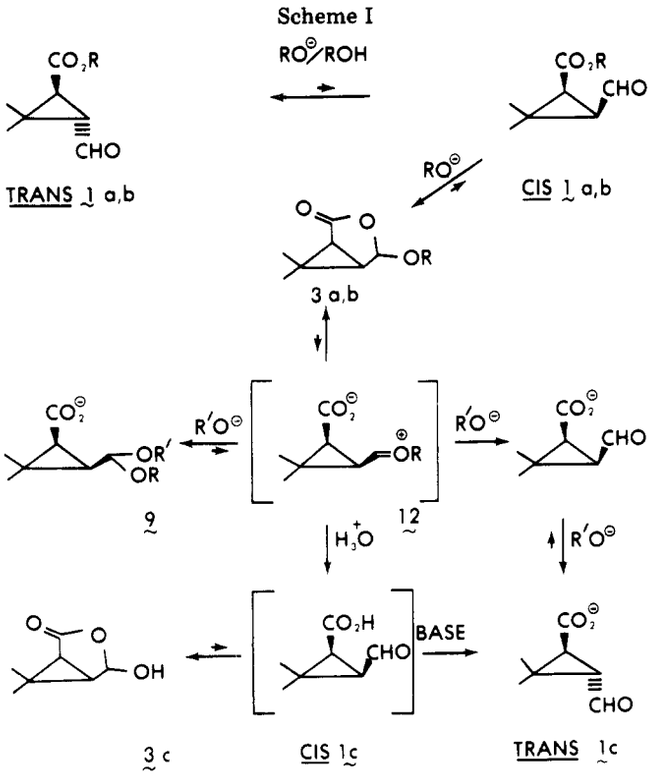
Ethoxy lactone **3b** was an unexpected product because the only ethanol present in the sodium methoxide–methanol promoted isomerization of **1b** was that released by transesterification of the ethyl ester. This very minor ethanol component does not compete successfully with methanol in the lactonization reaction as shown by the presence of only traces of **3b** (GLC analysis) in the reaction mixture prior to workup. Ethoxy lactone **3b** is therefore formed by secondary reaction during workup of a precursor present in the isomerization reaction mixture. One viable explanation for the formation of **3b** during workup is that the higher concentration of ethanol incidentally achieved during solvent removal results in reaction of the ethanol with a labile precursor present in the reaction mixture. The formation of **3b**, possibly through an exchange reaction, was the first indication that methoxy lactone **3a** might not be the base-stable cis intermediate (see Discussion).

Isolation of ethoxy lactone **3b** suggested that conversion of the mixture of isomers of **1b** to **3b** by refluxing in sodium ethoxide–ethanol might represent a more efficient synthesis of **3c**. This reaction, however, only gave intractable products despite the fact that pure *trans*-**1b** could be isolated in 67% yield after 5 min of reaction at room temperature. Extension of the room temperature reaction to 21 h, on the other hand, led to the formation in high yield of *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (*trans*-**1c**).

In order to suppress the formation of **3b** during workup, the product mixture obtained on isomerization of a mixture of *cis*- and *trans*-**1b** in sodium methoxide–methanol was directly quenched by pouring into a pH 4.1 citrate buffer solution without concentration on a rotary evaporator.[16] The aqueous solution was extracted with ether and the crude product obtained on removal of the ether was subjected to NMR analysis. The crude product mixture depended on the pH of the workup, but usually consisted of approximately 40–60% dimethyl acetal **9** (vide infra), 10% aldehydes **1a** and **1c**, and 5–30% of methoxy lactone **3a**. The remaining material represented various unidentified side products. Crystallization of the crude product from ether–pentane yielded approximately 20% of pure dimethyl acetal **9**. This structure is firmly established by complete analytical and spectroscopic characterization. The complete conversion of **9** to **3b** when the reaction mixture was worked up at pH 2 rather than at pH 4.1 and the observation that **9** slowly loses methanol even in the crystalline state provide a ready explanation for the original identification of **3b** as the essential reaction intermediate.[4]

Wittig condensation of methyltriphenylphosphonium bromide with *trans*-**1a**, using sodium hydride as the base and dimethyl sulfoxide as the solvent,[11] gave ethyl 2,2-dimethyl-3-vinylcyclopropanecarboxylate which was directly hydrolyzed to acid **10** by stirring 2 h in 2 M aqueous ethanolic potassium hydroxide (58% overall yield). Isolation of the ester

Scheme I



was possible, but resulted in lower yields due to its volatility. The acid was spectroscopically identical with that previously described,[11] not only confirming the structure and stereochemistry of **1a** but also providing the precursor for the desired amide **6**. The amide was prepared in good yield by treatment of the acid with thionyl chloride followed by ammonium hydroxide. Condensation of triphenylphosphonium methylide with hydroxy lactone **3c** was also carried out in dimethyl sulfoxide, except that 2 equiv of ylide had to be used due to the acidic proton on **3c**. Attempts to pregenerate the free aldehyde by removal of the hydroxyl proton resulted in rapid isomerization to *trans*-**1c**, and consequently in the formation of **10**. The formation of **11** from **3c** by Wittig reaction[11] confirmed the structure of **3c** and provided the starting material for the synthesis of amide **5**.

Discussion

Transesterification and cis–trans isomerization of 2,2-dimethyl-3-formylcyclopropanecarboxylic acid esters are very facile, providing a simple route for preparation of pure trans isomers starting with isomeric mixtures. Stirring in sodium methoxide–methanol for a few minutes, for example, cleanly converts a mixture of isomers of **1b** into pure *trans*-**1a**. On the other hand, prolonged stirring at room temperature, or refluxing the solution for 3 h, results in accumulation of an intermediate which we have identified as **9** rather than the originally suspected **3a**.[4] In view of the rapidity with which transesterification occurs in this system, it is retrospectively unreasonable to expect that methoxy lactone **3a** would accumulate in a solution in which it could react with methoxide to regenerate *cis*-**1a**, itself in equilibrium with the thermodynamically favored trans isomer. On the other hand, dimethyl acetal **9** should be relatively stable to methoxide, particularly since the carboxyl would bear a negative charge in basic solution. A reasonable mechanism can be written for the formation of **9** from *cis*-**1a**, although it involves **3a** as a transient intermediate. Methoxy lactone **3a**, formed by addition of methoxide to the aldehyde followed by intramolecular lactonization, is likely to be in equilibrium with oxonium zwitterion **12** as well as with *cis*-**1a**. Addition of methoxide at the oxonium carbon then easily accounts for the formation of **9**. Formation of the oxonium ion by internal oxygen elimination, a reaction with ample precedent,[12] is particularly favored in the present case due to the potential for delocalization of the cationic charge into the cyclopropyl ring.[13] Reversion of **9** to the oxonium ion under basic conditions is also possible, but less favored because the leaving group would be an alkoxide rather than a carboxylate anion.

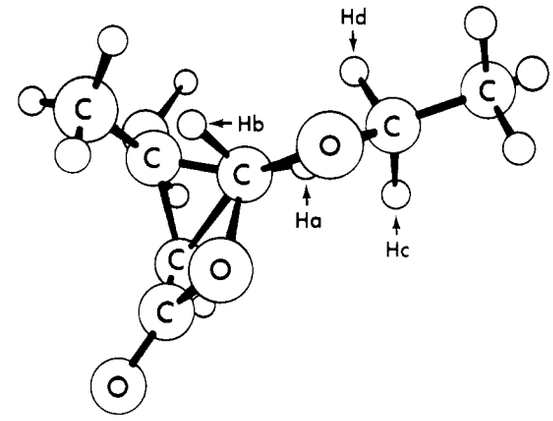


Figure 1. Three-dimensional projection of the calculated conformation of *exo*-ethoxy lactone **3b**. All unlabeled atoms are hydrogens. The carbon atom bearing Hb conceals the ring carbon bearing Ha, as in a Newman projection.

In view of the ease of formation of **9** with sodium methoxide–methanol, it is significant that the corresponding diethyl acetal is not obtained in sodium ethoxide–ethanol. Under these conditions the only isolable product was trans aldehyde acid **1c**. The change in reaction course was not due to an effect on cis–trans isomerization, or to an inability to form **3b**, since both were shown to occur with ease. The change in reaction product is most reasonably[15] explained by a competition between the two general pathways known for reaction of oxonium salts with nucleophiles, addition to the oxonium carbon atom or displacement of the substituent on oxygen (Scheme I).[12,14] Thus, reaction of **12** with an alkoxide by displacement of the oxygen from group R would yield *cis*-**1c**, which in basic solution rapidly isomerizes to the isolated trans isomer. It is of interest in this context to note that trace amounts of *trans*-**1c** were also observed by NMR and GLC analysis of isomerization reactions run in methanol–sodium methoxide. A summary of the postulated reaction network is given in Scheme I.

Experimental Section

Solvents and Reagents. Anhydrous methanol and ethanol were prepared by distillation of absolute grade alcohols from sodium, dry dimethyl sulfoxide (Me_2SO) was obtained by distillation in vacuo from calcium hydride, while hexane, pentane, and pyridine were dried by allowing reagent grade solvents to stand at least 18 h over 3A molecular sieves. Anhydrous ether, obtained from freshly opened cans, was used without further treatment. Reagents were of the highest quality commercially available and were used as received except where otherwise indicated. Sodium methoxide solutions were prepared by appropriate methanol dilution of the commercially available 25% methanol solution. Ethyl chrysanthemate was obtained from Aldrich Chemical Co.

General Procedures. Infrared spectra were determined on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A (proton) or on a Varian XL-100 Fourier transform instrument (proton and ^{13}C). All spectra are 60 MHz unless otherwise indicated, with peak positions reported as parts per million shifts from an internal tetramethylsilane standard. Chemical ionization mass spectra were determined on a modified AEI MS-902 spectrometer. Gas chromatography was performed on a Varian 2100 flame ionization instrument, using a 6-ft all-glass column packed with 3% OV-225. Ozone was generated in a Welsbach Model T408 apparatus at an oxygen inlet

pressure of 7 psi and a flow rate of 2.5 L/min (110 VAC). The drying agent used throughout was anhydrous $MgSO_4$. Elemental analyses were performed by the Microchemical Laboratory, University of California, Berkeley.

Computer modeling and conformational calculations were carried out on the PROPHET system, a specialized computer resource developed by the Chemical/Biological Information Handling Program of the National Institutes of Health.[10] Conformational analysis in this system is achieved by minimization of steric interactions using standardized bond lengths and atomic radii, without specific allowance for electronic effects.

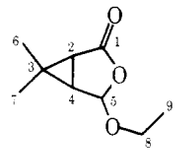
Ethyl 2,2-Dimethyl-3-formylcyclopropanecarboxylate (1b, Cis–Trans Mixture). The procedure of Martel was modified as follows.[4] Ethyl chrysanthemate (100 g, 0.51 mol) was dissolved in 750 mL of absolute ethanol and was cooled with exclusion of moisture ($CaSO_4$ drying tube) in a dry ice–acetone bath. A mixture of ozone in oxygen was bubbled through the cold solution with stirring until a faint blue color persisted in the solution (approximately 5 h). The solution was purged with dry N_2 for 15 min at −78 °C before addition of 100 mL (85 g, 1.4 mol) of dimethyl sulfide. The mixture was stirred overnight at 25 °C, after which time a small aliquot added to aqueous sodium iodide liberated no iodine. The reaction mixture was concentrated on the rotary evaporator and was diluted with 200 mL of ether. The ether solution was washed with water (3 × 100 mL) and brine (100 mL), dried, and filtered. The crude product obtained on solvent removal at a rotary evaporator, presumably diethyl acetal **7** (98 g), was suspended in 700 mL of 30% acetic acid under nitrogen. The mixture was stirred at 75–85 °C until it became homogeneous (approximately 15 min) and was then cooled to 25 °C, diluted with 400 mL of water, and neutralized with solid sodium bicarbonate. The resulting solution was extracted with three 250-mL portions of ether. The combined extracts, washed with water (250 mL) and brine (250 mL), were dried and filtered. Removal of the ether on a rotary evaporator yielded 79 g of crude product which was distilled in vacuo to give 71.6 g (82%) of a 34:66 mixture (by GLC) of *cis*-/*trans*-**1b:** bp 49–53 °C (0.15 torr); IR (film) 2717 (CHO), 1704 and 1722 cm^{-1} (carbonyls); NMR ($CDCl_3$) 1.30 (3 H, t, J = 7 Hz, $OCH_2\mathbf{CH_3}$), 1.33 and 1.37 (6 H, 2 s, ring CH_3), signals at 1.58 (s), 1.7–2.4 (m), and 2.48 (d, J = 2 Hz) due to two ring protons in cis and trans isomers, 4.22 (2 H, q, J = 7 Hz, $O\mathbf{CH_2}CH_3$), 9.67 (m, CHO, trans isomer), and 9.83 ppm (d, J = 6.5 Hz, CHO, cis isomer).

Methyl *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylate (*trans*-1a). A mixture of isomers of **1b** (35.8 g, 0.21 mol) was dissolved in 300 mL of anhydrous methanol under N_2 and 120 mL of a 25% sodium methoxide–methanol solution (0.53 mol) was added. The mixture was stirred 15 min at 25 °C before being diluted with 525 mL of ice-cold 1 M HCl and extracted with four 250-mL portions of ether. The combined extracts were washed with 250 mL of brine, dried, and filtered. Removal of the ether gave a residue which was distilled in vacuo to yield 19.5 g (60%) of *trans*-**1a** as a clear colorless oil: bp 47–49 °C (0.75 torr) [lit.[4] 96 °C (14 torr)]; IR (film) 2728 (CHO), 1732 (ester C=O), 1700 cm^{-1} (aldehyde C=O); NMR ($CDCl_3$) 1.32 and 1.36 (6 H, 2 s, ring CH_3), 2.49 (2 H, m, ring protons), 3.74 (3 H, s, OCH_3), and 9.67 ppm (1 H, m, CHO).

Ethyl *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylate (*trans*-1b). A mixture of isomers of **1b** (340 mg, 2.0 mmol) was added in 1 mL of anhydrous ethanol to the solution resulting from dissolving sodium metal (0.12 g, 5.2 mmol) in 3 mL of anhydrous ethanol. The mixture was stirred 5 min under N_2 at 25 °C before being diluted with 25 mL of 0.2 M HCl. Extraction with ether (3 × 25 mL), drying of the combined extracts, solvent removal, and bulb-to-bulb distillation (oven temperature 80–85 °C, 1 torr) gave 227 mg (67%) of pure *trans*-**1b,** a colorless oil: IR (film) 2776 (CHO), 1721 (ester C=O), and 1705 cm^{-1} (aldehyde C=O); NMR ($CDCl_3$) 1.28 (3 H, t, J = 7 Hz, ethoxy CH_3), 1.33 and 1.37 (6 H, 2 s, ring CH_3), 1.65 (2 H, d, J = 2 Hz, ring protons), 4.22 (2 H, q, J = 7 Hz, ethoxy CH_2), and 9.68 ppm (H, m, CHO).

Repetition of the above reaction, except with a reaction time of 21 h instead of 5 min, yielded 271 mg (95%) of virtually pure *trans*-**1c** as the only isolable product.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Lactone–Monoethyl Acetal (3b).** In analogy to Martel's procedure for the isomerization of pure *trans*-**1a,**[4] a mixture of cis–trans isomers of **1b** (25.0 g, 147 mmol) was dissolved in 180 mL of absolute methanol (N_2 atmosphere), 68 mL (0.3 mol) of 25% sodium methoxide in methanol was added, and the mixture was stirred and refluxed for 3 h. The mixture was then concentrated on a rotary evaporator and the residue was taken up in 100 mL of ice cold 3 M HCl. The aqueous solution was extracted with three 50-mL ether portions which were combined, washed with brine (50 mL), dried, and filtered. Removal of the ether on a rotary evaporator gave 21.5 g of viscous yellow oil which was dissolved in 60 mL of tetrahydrofuran. Water (120 mL) and acetic acid (5 mL) were added and the mixture was refluxed with stirring under N_2 for 3 h. The cooled solution was concentrated on a rotary evaporator and the residue was taken up in 150 mL of ether. The ether solution was washed with 1 M $NaHCO_3$ (3 × 50 mL). The combined aqueous fractions were in turn backwashed with ether (6 × 50 mL). The combined ether fractions were dried and filtered. Removal of the ether gave 12.9 g of viscous yellow oil which was distilled under vacuum, yielding 9.67 g (39%) of **3b** as a clear, colorless oil: bp 58.5–60 °C (0.2 torr). A trace of *trans*-**1a** was present in this sample. Analytically pure material was obtained by partitioning the sample between ether and water and bulb-to-bulb distillation of the organic fraction: IR (film) 1757 (lactone carbonyl), 1166 and 1116 cm^{-1} (C–O); NMR ($CDCl_3$, 100 MHz) 1.191 and 1.170 (6 H, 2 s, ring CH_3), 1.250 (3 H, t, J = 7.0 Hz, ethoxy CH_3), 2.046 (H, s, ring proton by C=O), 2.027 (H, d, J = 0.8 Hz, ring proton distal to C=O), 3.985–3.537 (2 H, m, ethoxy CH_2), and 5.156 ppm (H, d, J = 0.8 Hz, OCHO); NMR (^{13}C, $CDCl_3$, 25 MHz) 15.0 (2 C, 2 q, J_{CH} = 130 Hz, C-7 and C-9), 24.4 (1 C, s, C-3), 25.4 (1 C, q, J_{CH} = 130 Hz, C-6), 30.1 (1 C, d, J_{CH} = 180 Hz, C-4), 35.5 (1 C, d, J_{CH} = 180 Hz, C-2), 64.8 (1 C, t, J_{CH} = 140 Hz, C-8), 101.4 (1 C, d, J_{CH} = 175 Hz, C-5), and 173.3 ppm (1 C, s, C-1); CIMS *m/e* 171 (MH^+), 153 ($MH - H_2O$), 127, 125, and 57. Anal. Calcd for $C_9H_{14}O_3$; C, 63.51; H, 8.29. Found: C, 63.50; H, 8.21.



The aqueous $NaHCO_3$ washes from the above procedure were acidified to pH 1.5 with concentrated HCl and then extracted with ether. Solvent removal from the dried ether extracts yielded 3.36 g (16%) of waxy off-white *trans*-**1c** contaminated with a small amount (5%) of **3b:** IR (film) 1695 cm^{-1} (carbonyl); NMR ($CDCl_3$) 1.35 and 1.41 (6 H, 2 s, ring CH_3), 2.51 (2 H, m, ring CH), 9.65 (H, m, CHO), and 11.35 ppm (H, br s, exch. D_2O, CO_2H).

Reduction of 3b with $LiAlH_4$. To 42 mg (1.1 mol) of $LiAlH_4$ in 4 mL of dry ether at 0 °C under N_2 was added 170 mg (1.00 mmol) of **3b** in 1 mL of dry ether. The mixture was stirred 2 h at 25 °C before quenching with 0.12 mL of saturated sodium sulfate solution. After stirring 15 min, filtering, and solvent removal, 133 mg of colorless highly viscous oil was obtained. Bulb-to-bulb distillation of this oil [95 °C (0.05 torr)] gave 114 mg (88%) of pure **8a:** IR (film) 3300 (br, OH stretch) and 1030 cm^{-1} (OH bend); NMR ($CDCl_3$) 1.06 and 1.10 (6 H, 2 s, ring CH_3), 0.8–1.4 (2 H, m, ring CH), and 3.3–4.2 ppm (6 H, m, CH_2OH).

Acetylation of 8a. Acetic anhydride (0.25 mL, 0.27 g, 2.6 mmol) was added to 76 mg (0.58 mmol) of **8a** in 1 mL of dry pyridine under N_2. The mixture, after stirring 24 h at 25 °C, was diluted with 25 mL of ether. Washing the ether solution with 1 M HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL), followed by drying, filtration, and solvent removal, yielded 112 mg (90%) of colorless **8b:** IR (film) 1728 (C=O), 1240 and 1022 cm^{-1} (C–O); NMR spectrum identical with that in the literature.[7]

Hydrolysis of 3b with Aqueous KOH. To 170 mg (1.00 mol) of **3b** in 4 mL of absolute ethanol was added 1 mL of 10 M aqueous KOH. The mixture, after stirring 3 h at 25 °C, was added to 25 mL of 0.5 M aqueous HCl. The pH was brought to a value of 1.5 with concentrated HCl and the resulting solution was extracted with ether (3 × 25 mL). The combined extracts were dried and filtered, and the ether was removed on a rotary evaporator, yielding 165 mg of viscous pale yellow oil whose NMR spectrum identified it as *trans*-**1c.**

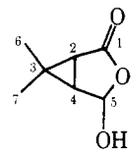
Hydrolysis of 3b with Aqueous HCl. To 170 mg (1.00 mmol) of **3b** in 4 mL of H_2O was added 1 mL of 1 M HCl. The mixture was allowed to stir 24 h at 25 °C before being diluted with 25 mL of brine and extracted with five 15-mL portions of ether. Solvent removal from the combined extracts after drying and filtering yielded 147 mg of white solid, which recrystallized from ether–pentane to give 88 mg (62%) of pure white, granular **3c,** mp 84–86.5 °C, identical with that reported below.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Dimethyl Acetal (9).** A mixture of geometric isomers of **1b** (1.702 g, 10.0 mmol) was dissolved in 15 mL of anhydrous methanol under nitrogen, 5.7 mL (25 mmol) of 25% sodium methoxide in methanol was added, and the mixture was refluxed and stirred for 3 h. After cooling to 15 °C and diluting with 75 mL of ice-cold citrate buffer (1.00 M citric acid in 1.33 M NaOH, pH 4.1),[16] the aqueous solution was extracted with ether (3 × 25 mL), and the combined extracts were

dried. Removal of the solvent on a rotary evaporator gave 1.75 g of yellow semisolid. This crude product, after analysis by NMR, was recrystallized from ether–pentane without heating, yielding 360 mg (19%) of white, granular **9**: mp 87–88.5 °C; IR (KBr) 1670 (C=O), 1231, 1184, and 1141 cm^{-1} (C–O); NMR ($CDCl_3$) 1.23 and 1.35 (6 H, 2 s, ring CH_3), 1.5–1.8 (2 H, m, ring CH), 3.42 and 3.43 (6 H, 2 s, OCH_3), 4.91 (H, d of d, J = 6.5 and 1.5 Hz, OCHO), and 11.75 ppm (H, br s, D_2O exch, CO_2H); CIMS *m/e* 173 ($MH^+ - 16$, parent itself not observed), 157 (base peak), 139, 125, 113, and 57. Anal. Calcd for $C_9H_{16}O_4$; C, 57.43; H, 8.57. Found: C, 57.51; H, 8.58.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Monomethyl Acetal–Lactone (3a).** The mother liquor from the recrystallization of **9** was concentrated on a rotary evaporator, giving a residue which was taken up in 15 mL of dry dimethoxyethane. The solution was refluxed 1 h under N_2, after which the dimethoxyethane was removed by distillation under N_2. Three 15-mL aliquots of dimethoxyethane were added, each one being removed by distillation before addition of the next one. The residue was cooled to 25 °C and diluted with 10 mL of ether. Filtration to remove slight cloudiness, removal of the ether on a rotary evaporator, and bulb-to-bulb distillation [66–71 °C (0.05 torr)] gave 613 mg (45%) of clear, colorless **3a**: IR (film) 1767 (C=O), 1166, 1118, 997, and 938 cm^{-1}; NMR ($CDCl_3$) 1.21 (6 H, s, ring CH_3), 2.03 (2 H, br s, ring CH), 3.55 (3 H, s, OCH_3), and 5.15 ppm (H, s, OCHO); CIMS *m/e* 157 (MH^+), 143, 139, 125, and 57.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Hemiacetal–Lactone (3c).** The procedure described for the preparation of **9** was repeated using 6.81 g (40 mmol) of **1b** (cis–trans mixture) and 0.1 mol of sodium methoxide in 83 mL of anhydrous methanol, providing 6.15 of the crude yellow semisolid product. The crude product was dissolved in 25 mL of tetrahydrofuran, 50 mL of 0.3 M aqueous HCl was added, and the mixture was refluxed under N_2 for 2 h. The hot mixture was then poured onto 75 g of ice, after which 100 mL of brine was added. The aqueous mixture was extracted with ether (3 × 100 mL), and the combined ether fractions were dried and filtered. Solvent removal on a rotary evaporator gave 4.65 g of viscous yellow oil which, after treatment with activated carbon, crystallized from ether–pentane to yield 1.54 g (27%) of white, granular **3c**: mp 83.5–87 °C (lit.[4] 116 °C from diisopropyl ether); IR (KBr) 3286 (OH), 1705 (C=O), 1206, 1183, and 1112 cm^{-1}; NMR ($CDCl_3$) 1.23 and 1.30 (6 H, 2 s, ring CH_3), 2.11 (H, s, ring CH distal to C=O), 2.13 (H, s, ring CH vicinal to C=O), and 6.72 ppm (2 H, br s, exch. D_2O, OCHOH); NMR (^{13}C, $CDCl_3$, 25 MHz) 14.9 (1 C, q, J = 127 Hz, C-7), 25.9 (2 C, br s + q, J = 125 Hz, C-3 and C-6), 31.2 (1 C, br d, J = 160 Hz, C-4), 37.3 (1 C, br d, J = 170 Hz, C-2), 96.3 (1 C, br d, J = 180 Hz, C-5), and 174.2 ppm (1 C, s, C-1); CIMS *m/e* 143 (MH^+), 125, 99, 97, 81, 71, 69, and 57. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.11; H, 7.06.



***trans*-2,2-Dimethyl-3-vinylcyclopropanecarboxylic Acid (10).** A modification of the procedure of Okada et al.[11] was used. Sodium hydride (50% in oil, 6.15 g, 128 mmol) was washed with hexane and 80 mL of dry Me_2SO was added to the residue. The resulting suspension was heated at 75–80 °C for 45 min and was then cooled to 0 °C while 44.0 g (123 mmol) of methyltriphenylphosphonium bromide in 130 mL of dry Me_2SO was added over 15 min. The mixture was stirred at 25 °C for 30 min and was then transferred via a metal cannula to a dropping funnel maintained under N_2. The solution was then added over 30 min to 15.4 g (99 mmol) of *trans*-**1a** in 30 mL of dry Me_2SO held at 0 °C with an ice bath. After completing the addition, the mixture was stirred at 25 °C for 1 h and was then poured into 1 L of ice water. The aqueous mixture was extracted with ether (3 × 250 mL), and the combined extracts were washed with water (3 × 250 mL) and brine (100 mL). Most of the ether was removed, after drying and filtering, by distillation through an 8-cm Vigreux column to prevent loss of the volatile ester. Absolute ethanol (250 mL) was added and distillation was continued until a head temperature of 78 °C was obtained. The mixture was then cooled to 25 °C and 50 mL of 10 M aqueous KOH was added. After stirring 2 h 500 mL of H_2O was added and the mixture was extracted with ether (3 × 100 mL). The *aqueous* solution was acidified to pH 1 with 50 mL of concentrated HCl (ice bath) and was then reextracted with pentane (3 × 100 mL). The combined pentane extracts, after drying and solvent removal, yielded 7.98 g (58%) of viscous oily **10** which solidified on standing: mp 39–43 °C; IR (film) 1684 (C=O) and 1634 cm^{-1} (C=C); NMR[11] ($CDCl_3$) 1.19 and 1.33 (6 H, 2 s, ring CH_3), 1.59 (H, d, J = 5.5 Hz, $CHCO_2H$), 1.9–2.4 (H, m, allylic proton), 4.9–6.1 (3 H, m, vinyl H), and 11.51 ppm (H, s, CO_2H).

***trans*-2,2-Dimethyl-3-vinylcyclopropanecarboxamide (6).** Acid **10** (701 mg, 5.00 mmol) was dissolved in 10 mL of dry pyridine and cooled to 0 °C under N_2. Freshly distilled $SOCl_2$ (0.45 mL, 0.75 g, 6.3 mmol) was added slowly via syringe and the mixture was stirred 1 h at 0 °C before pouring into 25 mL of ice-cold concentrated NH_4OH. The mixture was saturated with NaCl and was extracted with ether (3 × 25 mL). The combined extracts were dried and filtered, and the solvent was removed, yielding 729 mg of pale yellow solid. Recrystallization from ether–pentane provided 430 mg (62%) of floculent, off-white crystals of **6**: mp 119.5–120.5 °C; IR (KBr) 3377 and 3173 (NH_2) and 1630 cm^{-1} (C=O); NMR ($CDCl_3$) 1.17 and 1.27 (6 H, 2 s, ring CH_3), 1.38 (H, d, J = 5.5 Hz, CHCO), 1.9–2.2 (H, m, allylic proton), and 4.9–6.2 ppm (5 H, m, vinyl H and NH_2); CIMS *m/e* 140 (MH^+), 122, and 57. Analytical sample mp 120–121 °C. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.89; H, 9.24; N, 10.13.

***cis*-2,2-Dimethyl-3-vinylcyclopropanecarboxylic Acid (11).** The procedure cited for the preparation of **10** was used, except that 2 equiv of triphenylphosphonium methylide/equiv of **3c** was used. The reaction mixture from 3.55 g (25 mmol) of **3c** was worked up by pouring it into 500 mL of ice-cold H_2O. The aqueous solution was washed with ether (3 × 100 mL) and then brought to pH 1.5 with concentrated HCl (6 mL). The acidic aqueous solution was extracted with three 100-mL portions of pentane which were combined, washed with H_2O and brine, dried, and filtered. Removal of the pentane on a rotary evaporator gave 3.05 g (87%) of pale yellow viscous oil which solidified on standing, yielding **11** as an off-white solid: mp 47–51 °C; IR (film) 1688 cm^{-1} (C=O); NMR[11] ($CDCl_3$) 1.22 and 1.31 (6 H, 2 s, ring CH_3), 1.6–2.4 (2 H, m, ring CH), 5.0–5.5 (2 H, m, C=CH_2), 5.7–6.6 (H, m, –CH=C), and 11.65 ppm (H, br s, CO_2H).

***cis*-2,2-Dimethyl-3-vinylcyclopropanecarboxamide (5).** The procedure reported for the preparation of **6** was used, starting with 2.10 g (15.0 mmol) of **11**. A 59% yield (1.23 g) was obtained of pale yellow crystalline **5**: mp 78.5–80 °C; IR (KBr) 3408, 3316, and 3188 (NH_2), 1633 cm^{-1} (C=O); NMR ($CDCl_3$) 1.18 and 1.31 (6 H, 2 s, ring CH_3), 1.4–2.0 (2 H, m, ring CH), 5.0–5.5 (2 H, m, C=CH_2), and 5.8–6.7 ppm (3 H, m, CCH=C and NH_2); CIMS *m/e* 140 (MH^+), 97, 57. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.86; H, 9.24; N, 9.95.

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Registry No.—*trans*-**1a**, 41301-44-4; *cis*-**1b**, 38692-38-5; *trans*-**1b**, 38692-37-4; *trans*-**1c**, 67528-52-3; **3a**, 67528-53-4; **3b**, 67488-71-5; **3c**, 67528-54-5; **5**, 67506-07-4; **6**, 67488-72-6; *cis*-**7**, 67488-73-7; *trans*-**7**, 67488-74-8; **8a**, 67528-55-6; **8b**, 67488-75-9; **9**, 67528-56-7; **10**, 67528-57-8; **11**, 67528-58-9; *cis*-ethyl chrysanthemate, 7377-84-6; *trans*-ethyl chrysanthemate, 1802-02-4.

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(15) The formation of **1c** instead of diethyl acetal **9** (R = R′ = Et) could also result from the presence of water in the reaction medium. We do not favor this explanation because strictly anhydrous ethanol was used, because a high water content would be required to account for the high yield of **1c**, and because the hydrolysis reaction was not significant under similar conditions in methanol.
(16) The choice of pH is critical. Acidification of the solution to pH 2 results in complete conversion of **9** to **3b**, whereas at a pH of 5 the acetal–acid is not extracted into the organic phase.

Cyclization of Conjugated Azines. Synthesis and Thermal Rearrangements of 1-Oxo-3,4-diaza-2,4,6,7-octatetraenes (Allenyl Azines)

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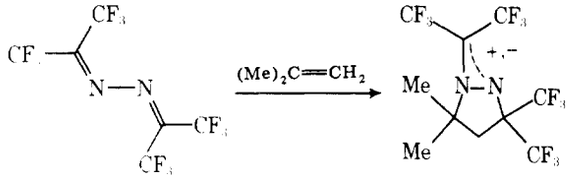
The Wittig reaction of certain 2-(alkylidenehydrazono)propylidenephosphoranes with ketenes provides a general route to 1-oxo-3,4-diaza-2,4,6,7-octatetraenes (allenyl azines). The allenyl azines undergo a facile intramolecular thermal cycloaddition reaction to yield pyrazolo[5,1-*c*]-1,4-oxazines and/or 4,9-dihydropyrazolo[1,5-*b*]isoquinolines depending on the nature of the substituents introduced via the ketene.

In contrast to all carbon,[2] monoaza,[3] and other diaza[4] dienes, the intra- and intermolecular cycloaddition reactions of acyclic azines (eg., **1** and **8**, Scheme I) or 2,3-diazabutadienes are characterized by the 1,3 reactivity of the C=N—N=C grouping. For example, simple aldehyde and ketone azines (**1**) react with the olefins to yield perhydropyrazolo[1,2-*a*]pyrazoles (**2**), a reaction known as "criss-cross" cycloaddition[5] (Scheme I, eq 1). The intermediacy of azomethinimine 1,3-dipoles has been confirmed by the isolation and characterization[6] of **13** in the reaction of hexafluoroacetone azine (**12**) with isobutylene.

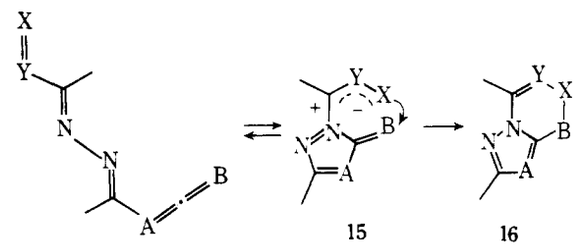


12 **13**

Analogous reactivity has been observed[7,8] with acetylenes, leading to 1,5-dihydropyrazolo[1,2-*a*]pyrazoles (**3**). These azine–acetylene criss-cross cycloadducts are thermally unstable, rearranging to either acyclic azines[7] (e.g., **7**) or N-substituted pyrazoles (e.g., **5** and **6**; Scheme I, eq 2). The key step in these reactions is the ring opening of **3** to a stabilized azomethinimine (**4**).[9] When R = H, **4** can proceed on to the N-substituted pyrazoles (**5**/**6**) by a simple intramolecular proton transfer to the 3-carbon side chain. When R is something other than hydrogen, this proton transfer is not possible and the dipolar intermediate (**4**) decomposes by a second ring opening reaction to yield the acyclic azines **7**.

An analogous intermediate (i.e., **9**) is presumably involved in the thermal rearrangement of certain conjugated azines (**8**) to N-substituted pyrazoles (**10** and **11**). Symmetrical azines derived from α,β-unsaturated aldehydes and ketones[10] (i.e., **8a**) and unsymmetrical azines formed from α-diketone monohydrazones and α,β-unsaturated aldehydes and ketones[11] (i.e., **8b**) rearrange to *N*-propenylpyrazoles (**10a**) and α-pyrazolyl ketones (**11**), respectively (Scheme I, eq 3).

It occurred to us that in a suitably designed system avenues of intramolecular reaction other than proton transfer might be observed in the reactions of azomethinimines such as **4** and **9**. One intriguing system, **14**, has the azine functional group



14 **15** **16**

in conjugation with a cumulene system. If these azines were to react in the same manner as other conjugated azines (**8a** and **8b**), one would expect stabilized azomethinimines such as **15** to be formed. One possible mode of reaction open to **15** would be an internal Michael-type addition to the exocyclic C=B bond, generating bicyclic heterocycles **16**. In theory, a wide variety of heterocyclic systems could be obtained by varying A, B, X, and Y. To establish the feasibility of this reaction concept, we have chosen to study the synthesis and thermal rearrangements of 1-oxo-3,4-diaza-2,4,6,7-octatetraenes (**14**; A = B = Y = carbon, X = oxygen).

Results and Discussion

The required allenyl azines (**14**; A = B = Y = C, X = O) are unknown in the literature. The ready availability[11] of the stabilized phosphorane **17** and the known[12] reaction of phosphonium ylides with ketenes to form allenes suggested the route to the allenyl azines (e.g., **18**) outlined in Scheme II.

As an initial test of the feasibility of this scheme, we investigated the reaction of **17** with diphenylketene (generated in situ by the action of triethylamine on diphenylacetyl chloride,[13] **19**). The reaction proceeds smoothly and rapidly at room temperature in benzene to produce a single product in addition to triphenylphosphine oxide. Although this material proved to be quite thermally labile, by rapidly chromatographing the reaction mixture we were able to isolate it in essentially quantitative yield as an orange solid. Examination of the infrared [1930 (allene) and 1680 cm^{-1} (PhC=O)]

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