5.53 (–CH_2OC(=O)–), 2 H triplet (J = 5 cps) centered at 7.24 (–CH_2S–), 3 H singlet at 8.72 (CH_3C<), broad 3 H triplet centered at 7.24 (–CH_2S–), 3 H singlet at 8.72 (CH_3C<), broad 3 H triplet centered at 9.07 (CH_3CH_2–).

Anal. Calcd for $C_{11}H_{20}O_2S$: C, 61.07; H, 9.33. Found: C, 60.81; H, 9.38.

2-Methyl-2-(3-oxoheptyl)-1,3-dithiolane (XIV).—Butylmagnesium bromide (from 1.26 g (0.056 g-atom) of magnesium), 6.09 g (0.033 mole) of cadmium chloride, and 5.27 g (0.025 mole) of acid chloride XIIIb gave 1.00 g (17%) of ketone XIV: bp 109–113° (0.15 mm); n^{24}D 1.5202; $\lambda_{max}^{CHCl_3}$ 5.85 μ; nmr ($CDCl_3$) 4 H singlet at τ 6.68 (–SCH_2CH_2S–), 3 H singlet at 8.22 (CH_3C<), broad 3 H triplet centered at 9.08 (CH_3CH_2–).

Acid Cleavage of 8-*n*-Butyl-8-methyl-1,4-dioxocan-5-one (II).—A suspension of 0.5196 g of II in 10 ml of 3 N hydrochloric acid was heated on a steam bath for 2 hr. After saturation with salt, the product was extracted with three 15-ml portions of ether. The extract was washed with saturated sodium carbonate solution, dried ($MgSO_4$), concentrated at reduced pressure, and distilled to yield 0.176 g (48%) of γ-butyl-γ-valerolactone (IV): bp 60–65° (0.07 mm); n^{28}D 1.4426; $\lambda_{max}^{CHCl_3}$ 5.67 μ. The infrared and nmr spectra as well as the glpc retention time were identical with those of the authentic compound prepared by the reaction of ethyl levulinate with butylmagnesium bromide.[12]

Base Hydrolysis of 8-*n*-Butyl-8-methyl-1,4-dioxocan-5-one (II).—A suspension of 0.991 g of II and 0.260 g of sodium hydroxide in 10 ml of water was refluxed 30 min. After cooling, the colorless solution was extracted with ether, and the aqueous layer was acidified with 6 N hydrochloric acid. The ether extract was dried ($MgSO_4$) and concentrated at reduced pressure to yield a colorless oil (0.916 g; $\lambda_{max}^{CHCl_3}$ 2.78, 2.84, and 5.83 μ). Treatment with excess ethereal diazomethane gave 0.414 g of hydroxy ester III: bp 88–89° (0.05 mm); $\lambda_{max}^{CHCl_3}$ 2.78 and 5.77 μ; nmr ($CDCl_3$) 3 H singlet at τ 6.33 (–CO_2CH_3), 2 H multiplet centered at 6.37 (–CH_2OH), 2 H multiplet at 6.58 (–OCH_2–), 1 H singlet (exchanged by D_2O) at 7.60 (–OH), 3 H singlet at 8.87 (CH_3C<), broad 3 H triplet centered at 9.08 (CH_3CH_2–).

Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 61.93; H, 10.32.

Acid Cleavage of 9-*n*-Butyl-9-methyl-1,4-dioxocan-5-one (VI).—A suspension of 3.00 g of VI in 60 ml of 3 N hydrochloric acid was stirred and refluxed for 2 hr. Work-up as above for II yielded 0.582 g of δ-butyl-δ-caprolactone: bp 73–76° (0.07 mm); $\lambda_{max}^{CHCl_3}$ 5.82 μ; nmr ($CDCl_3$) 3 H singlet at τ 8.63 (CH_3C<), broad 3 H triplet at 9.17 (CH_3CH_2–). Acidification of the sodium carbonate wash yielded 0.884 g of an unsaturated acid: bp 83–90° (0.18 mm); $\lambda_{max}^{CHCl_3}$ 5.86 μ; nmr ($CDCl_3$) τ 4.83 (broad, >C=CH–CH_2–). The unsaturated acid (56 mg) was stirred and refluxed for 24 hr with 5 ml of 20% sulfuric acid. Ether extraction yielded 36 mg of δ-butyl-δ-caprolactone which was identified by its infrared spectrum and retention time by vapor phase chromatography. Addition of butylmagnesium bromide to ethyl δ-acetylbutyrate at −10° gave authentic δ-butyl-δ-caprolactone: bp 74–75° (0.20 mm); n^{28}D 1.4562; $\lambda_{max}^{CHCl_3}$ 5.82 μ. The nmr spectrum was identical with that of the product obtained by acid cleavage of VI.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.76; H, 10.53.

Acid Cleavage of 9-*n*-Butyl-3-ethyl-9-methyl-3-nitro-1,3-dioxonan-6-one (VIII).—A suspension of 0.973 g of VIII in 20 ml of 3 N hydrochloric acid was stirred and refluxed for 17 hr. Work-up as above yielded 0.103 g γ-butyl-γ-valerolactone (IV): bp 65–70° (0.06 mm); $\lambda_{max}^{CHCl_3}$ 5.68 μ.

Acid Cleavage of 5-*n*-Butyl-5-methyl-1,4-oxathiolan-8-one (XII).—A suspension of 0.500 g of XII in 10 ml of 3 N hydrochloric acid was stirred and refluxed 2 hr. The usual work-up gave 0.037 g of γ-butyl-γ-valerolactone (IV); bp 70° (0.07 mm); $\lambda_{max}^{CHCl_3}$ 5.68 μ. The infrared spectrum and the glpc retention time were identical with those of the authentic compound.

Reaction of Mixed Anhydride I with Dimethylcadmium.—A solution of 5.80 g (0.025 mole) of mixed anhydride I in 12 ml of anhydrous benzene was added dropwise with stirring to 3.5 g (0.025 mole) of pure dimethylcadmium (obtained from Orgmet Inc., Hampstead, N. H.) in 25 ml of anhydrous benzene. After stirring 15 hr at room temperature, the clear colorless solution was cooled in an ice bath during the dropwise addition of dilute sulfuric acid. The organic layer was separated, washed with 5% sodium bicarbonate solution, dried ($MgSO_4$), and concentrated under reduced pressure to yield 4.28 g of a colorless oil. Infrared and glpc analysis showed the product to be the ketal ester I (R = OC_2H_5).

8,8-Dimethyl-1,4-dioxocan-5-one.—Magnesium bromide was prepared by reaction of 14.10 g (0.075 mole) of 1,2-dibromoethane with 1.70 g (0.07 g atom) of magnesium in 40 ml of ether. The ether was removed in a stream of nitrogen and 3.5 g (0.025 mole) of pure dimethylcadmium in 30 ml of anhydrous benzene was added. A solution of 5.78 g (0.025 mole) of mixed anhydride I in 10 ml of benzene was then added dropwise at room temperature over a 15 min period. After stirring overnight at room temperature, the reaction mixture was cooled in an ice bath during the dropwise addition of dilute sulfuric acid. The organic layer was washed with 5% sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation yielded 1.46 g (37%) of a colorless liquid: bp 112–117° (20 mm); $\lambda_{max}^{CHCl_3}$ 5.75 μ; nmr ($CDCl_3$) 2 H multiplet centered at τ 5.66 (–CH_2OC(=O)–), 2 H multiplet centered at 6.42 (–CH_2O–), 6 H singlet at 8.83 (($CH_3)_2$C<)).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.40; H, 8.92.

Registry No.—II, 14734-32-8; III, 14734-44-2; IV, 3285-00-5; Va, 5694-89-3; VI, 14734-43-1; VIIa, 14734-35-1; VIII, 14734-36-2; X, 14734-37-3; XIa, 14734-38-4; XII, 14746-17-9; XIV, 14734-39-5; δ-butyl-δ-caprolactone, 14734-40-8; 8,8-dimethyl-1,4-dioxocan-5-one, 14734-41-9; di-*n*-butylcadmium, 3431-67-2.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Dr. Floie Vane, Mr. S. Traiman, and Mr. Hubert Jenny for the nuclear magnetic resonance spectra, infrared spectra, and vapor phase chromatography respectively. We wish to thank Drs. K. E. Fahrenholtz, R. W. Kierstead, and P. Rosen and Professor G. Buchi for stimulating discussions and encouragement during the course of this work. It is a pleasure to acknowledge the technical assistance of Mr. Mathew Carson and Mrs. Ann Kahn.

(12) C. Rai and S. Dev, *J. Indian Chem. Soc.*, **34**, 178 (1957).

Nonplanar Cyclobutane. Temperature Dependence of Infrared Spectra of *cis*- and *trans*-Methyl 3-Isopropylcyclobutanecarboxylate

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We have recently reported the basic equilibration of *cis*- and *trans*- methyl 3-isopropylcyclobutanecarboxylate and discussed the conformational implications in terms of cyclohexane analogies.[1] In such terms, the greater thermodynamic stability of the *cis* isomer may be ascribed to the difference between an equatorial and axial carboalkoxy group in a homogeneously puckered cyclobutane. K_{equil} would thus represent a *cis* (e,e) ⇌ *trans* (e,a) ⇌ (a,e) equilibrium. However, a comparison of ΔF and K_{equil} values for this system and its 3-methyl analog[2] with corresponding values for alkyl-

(1) I. Lillien and R. A. Doughty, *Tetrahedron*, **23**, 3321 (1967).
(2) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965).

cyclohexanecarboxylates of more rigid geometry does not support such direct analogy.[1] In the light of reports that "axial" halocyclobutanes may actually prefer a planar conformation[3,4] and that *trans*-1,3-cyclobutanedicarboxylic acid is indeed planar,[5] the possibility must be strongly considered that K_{equil} for the cyclobutane esters reflects the incursion of planar conformers for one or both isomers rather than the former equilibrium. In an effort to assess this possibility, we have studied the temperature dependence of the vapor phase infrared spectra of the 3-isopropylcyclobutanecarboxylate methyl esters and have obtained results which we feel support the latter interpretation.

Infrared-active bands may be invariant with temperature, or they may vary selectively. For a compound of theoretical flexibility (*i.e.*, conformational variance), the first instance is evidence of a single conformer. The second instance corresponds to conformational equilibrium through population of different energy levels with resultant splitting of one or more vibrational transitions into as many different components as there are conformers, each component belonging to one of the conformers only.[6] The resulting spectrum is thus a composite. For two conformers which differ only slightly in conformation, only few such splittings may be expected.[4]

In the case of the halocyclobutanes,[4] Rothschild was able to demonstrate convincingly the temperature dependence of different carbon–halogen stretching frequencies characteristic of equatorial and less stable planar conformers. In the present case, the complexity of the spectrum, with a larger number of vibrational modes, at first appeared relatively formidable; however, the bands of interest proved to be fortuitously accessible.

The spectrum was scanned from 5000 to 700 cm^{-1} in the temperature range of room temperature (24°) to 150°.[7] The spectra of the two isomers were quite similar at room temperature except in the region 1243–1286 cm^{-1} (Figure 1); this similarity prevailed over the range studied. Note the absence of 1257 and 1286-cm^{-1} bands in the *trans* isomer, while the 1243-cm^{-1} band is negligible in the *cis* isomer at room temperature. In cyclobutane itself,[8] in the vapor phase, bands appear in this region at 1210, 1228, 1246, 1261, and 1277 cm^{-1}. The first two are believed to be branches of the 1220-cm^{-1} τ (CH_2) transition present in the liquid and Raman spectra, but which is infrared forbidden for the D_{4h} (planar) conformer by selection rules. Unfortunately, in the present esters, this possibly diagnostic band was obscured by other intense absorption. The 1261-cm^{-1} band was assigned as ω (CH_2), and very likely corresponds to the present 1257-cm^{-1} band. The 1246- and 1277-cm^{-1} bands were unassigned. However, this is a region of CH_2 modes, and these bands are considered probably to be similar transitions.[9] A computerized assay of a large number of cyclobutane derivatives has appeared;[10] one of the bands with greatest frequency of occurrence was cited at 1335 ± 10 cm^{-1}. It appears reasonable, therefore, to infer that this is a diagnostic ring CH_2 fundamental which corresponds to the present 1243-cm^{-1} band. The present 1286-cm^{-1} band corresponds to a calculated ω (CH_2) frequency which was not observed in cyclobutane,[8] but which may be the unassigned 1277-cm^{-1} band. Thus, as ring methylene fundamentals, these transitions may be expected to be sensitive to changes in ring conformation and dihedral angle.[11] For the *trans* isomer, the 1243-cm^{-1} band remains the same in *relative* intensity throughout the temperature range examined. For the *cis* isomer, however, this band, initially quite small, shows an intensity increase *relative* to the other two. For comparison, band structure in the region of interest for both conformers at different temperatures is shown in Figures 2 and 3.[12]

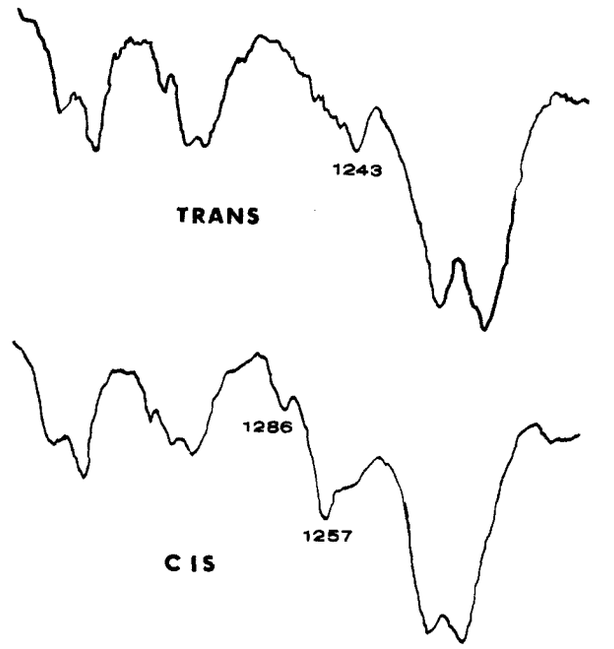

Figure 1.

It may be logically assumed that the 1243-cm^{-1} band represents a less stable conformational species for the *cis* isomer and the only available conformer for the *trans* isomer.[4,6,13] Were the (highly unlikely) condition of (e,e $\rightleftharpoons$ a,a) equilibrium prevalent for the *cis* isomer, one would not expect the considerably less

(3) J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 3884, 3891 (1965).

(4) W. G. Rothschild, *J. Chem. Phys.*, **45**, 1214 (1966).

(5) T. N. Margulis and M. S. Fisher, *J. Am. Chem. Soc.*, **89**, 223 (1967).

(6) K. Kozima and K. Sakashita, *Bull. Chem. Soc. Japan*, **31**, 796 (1958).

(7) Bands of interest could not be observed in low temperature liquid or glass phases because of broad, obscuring absorptions.

(8) G. W. Rathjens, Jr., W. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Am. Chem. Soc.*, **75**, 5634 (1953).

(9) H. A. Szymanski, "Interpreted Infrared Spectra," Vol. 1, Plenum Press, New York, N. Y., 1964, p 164 ff.

(10) H. E. Ulery and J. R. McClenon, *Tetrahedron*, **19**, 749 (1963).

(11) There is a rather small possibility that these bands may be due to C—C(=O)—O stretch modes; however, the more likely assignment for the latter is at 1178 and 1194 cm^{-1} in the present spectra, especially in view of the former's unique behavior for one isomer and the coincidence with cyclobutane bands.

(12) Because of the difficulty in volatilizing the esters in the gas cell, intensities *increase* with increasing temperature because of increasing vapor concentration. However, the intensities of bands other than the 1243–1286-cm^{-1} group varied uniformly for both isomers.

(13) A referee has objected to this interpretation, stating that the structural change ". . . could well be due to vibrational changes rather than conformational ones" or, if it were conformational, could be due to group transitions not involving the ring. However, this begs the question as to why similar spectral changes are not shown by the *trans* isomer and confounds attempts at conformational rationale. While it is of course not possible to unambiguously assign the 1243- and 1257-cm^{-1} bands, this objection overlooks their *probable* identification as ring CH_2 frequencies, and the *specific* assignment of the former as a *trans* band. In addition, it is not compatible with the similarity of integrated intensities of bands atrributable to group vibrations at room (Figure 1) and elevated (Figures 2 and 3) temperatures.

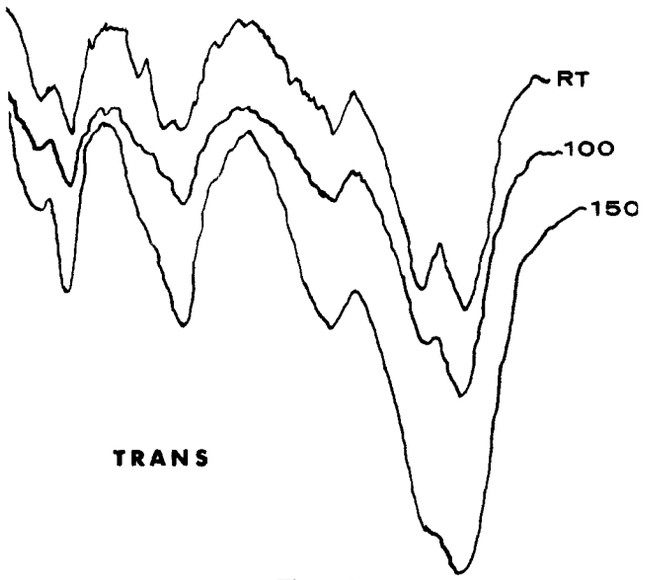

Figure 2.

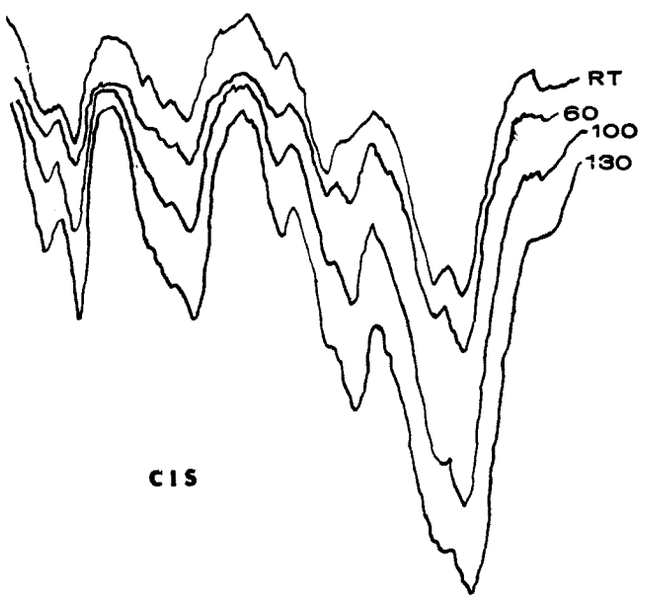

Figure 3.

stable (a,a) conformer to become preponderant at 60°, as the less stable band appears to do in this case.[14] Further one must expect a similar equilibrium for the *trans* isomer. A situation in which the *trans* spectra represented a uniform composite of two conformers (e,a $\rightleftharpoons$ a,e) over a temperature range of 126° would demand $K_{equil} = 1$ over that entire range, and this is not possible in view of the quite different values of $\Delta G°$ for the two substituents.[15] The spectra are thus not consistent with the concept of (e,e) *cis* and (e,a) *trans* isomers as unique equilibrium partners. The only *cis* conformer less stable than the (e,e) species, which can exhibit the appearance of spectral similarity to an invariant *trans* isomer, is that which can be achieved by flexion toward the plane and creation of an essentially "planar" conformation.[16] This arrangement is one in which the 1,3 diaxial interactions of the puckered (e,e) conformer have been minimized at the expense of adjacent eclipsings and a resolution has been achieved in favor of the latter. This destabilizing effect apparently becomes a predominant influence in determining the conformation of the *trans* isomer, where a well-puckered ring would have to have a substituent much larger than hydrogen in an axial position. This model is in agreement with that deduced for the monohalocyclobutanes and the energetically small order of magnitude ($\Delta E \cong 1$ kcal/mole) for the equatorial–planar transition in these compounds.[4,17] However, such a model contrasts with the conclusions reached by Wiberg and Lampman in their recent study of equilibration of 1,3-dihalocyclobutanes.[18] These authors deduced an (a,e) conformation in well-puckered *trans* isomers on the basis of dipole moment measurements.[19] A possible rationale may be found in the much smaller $\Delta G°$ values for the halogens compared with that of $COOCH_3$.[15a] Halogens are large and polarizable and can more readily accommodate a C–X bond bent away from the axial, possibly reducing the axial tension.

At room temperature, *ca.* 88%[20] of the *cis* ester appears to be the diequatorial conformer (compare with *ca* 80% for equatorial bromocyclobutane[4]). The proportion of the "planar" conformer rises abruptly between ambient and 100° temperatures. Although abrupt transition of this type as a consequence of ring puckering motion has been described,[21] in this instance it appears unexpectedly facile over a rather low temperature range. For the five points which were measured from 80 to 150° for the *cis* isomer, a plot of the logs of the ratios of the intensities of the 1243- and 1257-cm^{-1} bands *vs.* $1/T$ is linear. The slope yields $\Delta E \cong 1.6$ kcal/mole,[20] which may be taken as an estimate of the zero-point energy for the equatorial–"planar" transition in the present case. While not too much significance can be given the accuracy of this value owing to measurement difficulties, it is in the expected direction from that for the bromocyclobutane transition, presuming some substituent dependence. In the case of the *cis* ester, planarization causes a decrease in the isopropyl–carbomethoxy distance as opposed to a decrease in the hydrogen–bromine distance in bromo-

(14) Since diaxial *cis*-1,3-dimethylcyclohexane is destabilized with respect to the diequatorial conformer by at least 3.7 kcal/mole (*cf.* N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961)), diaxial isopropyls in the 1,3 relationship would engender an even greater repulsive energy, probably in excess of 5 kcal/mole, considering the shorter 1,3 distance in cyclobutane

(15) In cyclohexane, $\Delta G°$ for isopropyl = 2.1 kcal/mole, and $\Delta G°$ for carbomethoxy = 1.1 kcal/mole. *Cf.* (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1965, pp 433 ff; also (b) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **31**, 894 (1966).

(16) It is certainly conceivable that this "planar" conformer may still be slightly puckered, with a small dihedral angle.

(17) As a referee has pointed out, conformation can certainly differ in different phases (*i.e.*, solid *vs.* liquid). However, a good many values of conformational energies obtained in both liquid and vapor phases correspond quite well (*cf.* ref 15a, p 433 ff, for examples), and there seems no *a priori* reason to suspect that a conformer detected in the vapor phase will not be present in the liquid.

(18) K. B. Wiberg and G. M. Lampman, *ibid.*, **88**, 4429 (1966).

(19) Unfortunately, the assumption on which these authors base their dihedral angle calculations, *viz.*, that the dipole moment of bromocyclobutane uniquely defines a conformer with equatorial bromine, is vitiated by the work of Rothschild,[4] who has shown that the calculated dipole moments for the planar, equatorial, and axial conformers of this compound differ by no more than a maximum of ±0.03 D. Further, the assumption that two strong dipoles such as C–Br will not interact at the very short (~2.2 A) transannular distance in cyclobutane is open to question; note the thermodynamically decisive effect of the dipolar interaction of the two $C–COOCH_3$ groups in the 1,3 position (*cf.* ref 2). Thus these authors may have been dealing with relatively planar *trans* isomers. However, note footnote 9 of ref 18.

(20) Because of the fusion of the 1243- and 1257-cm^{-1} bands, integrated intensities are only approximate, and therefore this value likewise represents an approximation only. However, it should be noted in substantiation that it was possible to duplicate integrated intensity measurements for these bands without significant deviation for several runs for each temperature.

(21) W. G. Rothschild, *J. Chem. Phys.*, **44**, 2213 (1966).

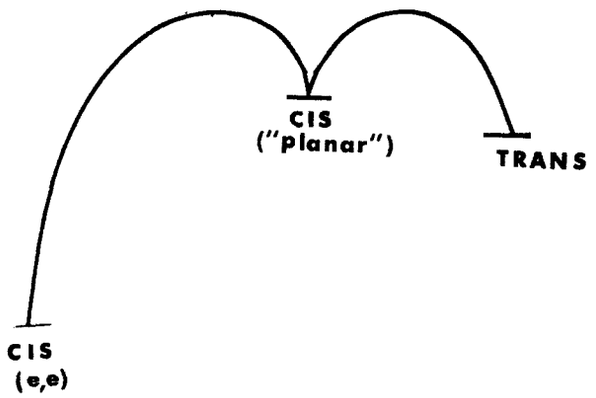

Figure 4.

cyclobutane; the former must require more energy. However, in the present case, the energetic barrier is indeed small, and will be easily overcome by the energy available for most chemical reactions. Planar conformers must therefore be taken into account in considering cyclobutane reactivity even when it is disubstituted.[22] Although this evaluation does not affect the question of conformational distinctions between isomers for certain low-energy reactions such as deamination,[23] it would predict that in other higher energy reactions such as solvolysis, which requires on the order of 20 kcal/mole of activation energy, planarization for both isomers may inhibit the appearance of behavioral disparities possible on the basis of nonplanarity for some cases.

These results allow interpretation of the cyclobutane ester equilibrium in terms of a *cis* (e,e $\rightleftharpoons$ "planar") $\rightleftharpoons$ *trans* (homo "planar") process (Figure 4) and render intelligible the compression of K_{equil} values for the 3-alkyl-substituted esters.[24] It is evident that K_{equil} measures not the thermodynamic difference between isomers differing in the extent of axial substitution, but rather a difference between conformers differing in dihedral angle. The equilibrium constant, reflecting an internal *cis* equilibrium, is thus influenced only slightly by the nature of the substituent.[24]

Experimental Section

Infrared measurements were made in a 5-cm sodium chloride gas cell using the Perkin-Elmer Model 21 double-beam recording spectrophotometer. Samples of liquid ester were inserted onto the cell floor, and the cell atmosphere was saturated with vapor by prolonged periods of moderate heating under evacuation, followed by adjustment to the desired temperature. Heating was accomplished by a transformer-controlled heating tape wound tightly around the outside of the gas cell; temperature was measured by a thermocouple held flush against the cell wall. Several measurements at each temperature were carried out after optimal equilibration was achieved.

Registry No.—Cyclobutane, 287-23-0; *cis*-methyl 3-isopropylcyclobutanecarboxylate, 14721-38-1; *trans*-methyl 3-isopropylcyclobutanecarboxylate, 14746-11-3.

Acknowledgment.—The author wishes to express his thanks to Dr. R. A. Doughty for the preparation of the esters employed in this work and to Dr. E. Brill for his assistance in obtaining the infrared spectra. The author is appreciative of the disclosure of pertinent data by Dr. G. Lampman prior to publication. This work was supported by Grant AFOSR-123-63 from the Directorate of Chemical Sciences, U. S. Air Force.

(22) Some modification of conformational conclusions reached for *cis*- and *trans*-3-isopropylcyclobutylamine on the basis of room temperature nmr measurements (I. Lillien and R. A. Doughty, *J. Am. Chem. Soc.*, **89**, 155 (1967)) may be called for by the present conclusions. It is evident that the preponderance of *cis* isomer will be diequatorial under these conditions. However, to the extent that axial carbomethoxy and amino groups resemble each other in this system, the *trans* isomer should probably be considered less puckered than had been thought likely.

(23) A quite large difference in product composition in this reaction for each isomer in ref 22 has been interpreted in terms of conformational control, with a *trans* isomer of smaller dihedral angle than the *cis* fitting quite well into the scheme presented: I. Lillien and R. A. Doughty, *Tetrahedron Letters*, 3953 (1967).

(24) The value of K_{equil} for the *cis*- and *trans*-3-*t*-butylcyclobutanecarboxylates is only slightly larger than that which we have reported[1] for the 3-isopropyl esters (Dr. G. Lampman, private communication). The unlikely alternative rationale that both groups, which differ greatly in steric effectivity, are equally able to maintain conformational homogeneity in the cyclobutane ring is untenable in the light of the present results.

Cyclization of Aniline–Acetylenedicarboxylate Adducts. An Improved Synthesis of 8-Nitro-2-carbomethoxy-4(1H)-quinolones[1]

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As a route to the synthesis of 4,8-diaminoquinolines as potential antimalarials, an attractive synthetic pathway appeared to involve 8-nitro-2-carbomethoxy-4(1H)-quinolones (IV). The traditional Conrad–Limpach–Knorr quinolone synthesis is generally unsuccessful however, for generation of the anilinocrotonates or acetoacetanilides of aromatic nitro amines,[2,3] presumably because of the reduced basicity of the amine function. In our hands, the condensation of diethyl oxaloacetate with *o*-nitroanilines has also been unsuccessful.

We have found that formation of the required anils or enamino esters (III) by the Michael condensation of *o*-nitroanilines (I) and dimethyl acetylenedicarboxylate (II) proceeds smoothly and in high yield (eq 1). Previous publications have demonstrated the generality of the reaction of (II) with *o*-aminonitriles,[4] phenones,[5] amides,[6] or esters[7] as a highly versatile heterocyclic synthesis.

Although difficulties have been reported in the saponification–decarboxylation of nitro-substituted quinoline-3-carboxylates,[8] we have encountered little difficulty with the 2-substituted carboxylates available by our method.

The cyclization of these adducts (III) to the 4(1H)-

(1) This work has supported in part by Contract No. DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command, and represents Contribution No. 255 from the Army Research Program on Malaria.

(2) S. Coffey, J. K. Thompson, and F. J. Wilson, *J. Chem. Soc.*, 856 (1936).

(3) F. Misani and M. T. Bogert, *J. Org. Chem.*, **10**, 347 (1945).

(4) N. D. Heindel, T. A. Brodof, and J. E. Kogelschatz, *J. Heterocyclic Chem.*, **3**, 222 (1966).

(5) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 1666 (1967).

(6) N. D. Heindel and T. F. Lemke, *J. Heterocyclic Chem.*, **3**, 389 (1966).

(7) E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, **32**, 3339 (1967).

(8) See R. H. Baker, G. R. Lappin, C. J. Albisetti, Jr., and B. Riegel, *J. Am. Chem. Soc.*, **68**, 1267 (1946), in which the use of the silver salts of nitroquinoline carboxylic acids is suggested.