furan solution of [3-(*o*-chlorophenyl)propyl]triphenylsilane, in the same quantities as used in the first run, was added to the magnesium, but after refluxing 24 hr. with intermittent additions of ethyl bromide, Color Test I was negative and the starting material was recovered in a 60% yield.

B. With Lithium in an Ether–Tetrahydrofuran Mixture.—A mixture of 3.48 g. (0.0084 mole) of [3-(*o*-chlorophenyl)propyl]-triphenylsilane and 0.7 g. (0.1 g.-atom) of cut lithium wire in 40 ml. of ether was stirred 30 min. at room temperature and then refluxed 1.5 hr. with no evidence of a reaction. Tetrahydrofuran (25 ml.) was added and the refluxing was continued 1 hr., but there was no change in the mixture. After acid hydrolysis, the aqueous layer was extracted with ether and discarded. The combined organic layer was dried and distilled to remove the solvents. Addition of ethanol to the residue gave 2.9 g. (83.4%) of a solid, m.p. 84–86°. The infrared spectrum of the solid was superimposable on that of the starting material, m.p. 77.5–79.5°. The melting point of the starting material was not depressed when the two solids were admixed. The solid was recrystallized twice from absolute ethanol and once from petroleum ether (b.p. 38–45°) to give fine needles, m.p. 84.5–86.5°.

Anal. Calcd. for $C_{27}H_{25}ClSi$: Si, 6.80. Found: Si, 6.86. The solid melted at 89.5–90° after 18 months.

Reaction of [3-(*o*-Chlorophenyl)propyl]diphenylsilane with Lithium.—To finely cut lithium wire (0.7 g., 0.1 g.-atom) in 50 ml. of tetrahydrofuran (THF) was added 30 ml. of a solution of [3-(*o*-chlorophenyl)propyl]diphenylsilane (14.5 g., 0.043 mole) in 50 ml. of the same solvent. The mixture was cooled to 0.5° and, after 20 min., a green color developed. The addition was completed during which time the color became deep red. After stirring 30 min. at this temperature, the solution was filtered through a glass-wool plug into a second flask. The mixture was stirred overnight. The THF was distilled and 100 ml. of dry toluene was added. Color Test I was negative after refluxing 1 hr. The reaction mixture was hydrolyzed by pouring into iced sulfuric acid. Ether was added, followed by the usual separation, drying, and concentration techniques. The residual material was distilled under reduced pressure to give 2.62 g. of an oil, b.p. 163–182° (0.007 mm.), which partially crystallized upon standing. Recrystallization from ethanol gave 1.27 g. (9.8%) of 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene, m.p. 75–77°, identified by mixture melting point with an authentic sample[1] and by comparison of the infrared spectra.

The distillation residue was taken up in petroleum ether (b.p. 60–70°) and chromatographed on alumina. Cyclohexane eluted a trace of the cyclic compound, whereas benzene and ethyl acetate gave viscous, pale green oils which could not be purified further.

Reaction of [3-(*o*-Chlorophenyl)propyl]triphenylsilane with Sodium.—To a cold suspension of 0.23 g. (0.01 g.-atom) of sodium in 20 ml. of toluene was added 1.91 g. (0.005 mole) of [3-(*o*-chlorophenyl)propyl]triphenylsilane. Although a pink color developed, the reaction appeared to be slow; therefore, the mixture was refluxed 10 hr. and cooled. Ethanol was added and the solution was poured into iced hydrochloric acid. Ether was added and the organic layer was separated and dried. Removal of the solvents gave 1.43 g. of an oil which was dissolved in petroleum ether (b.p. 60–70°) and poured onto a column of alumina. The same solvent eluted 0.45 g. (32.4%) of 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene, m.p. 78.5–80°, identified by a mixture melting point determination and by comparison of the infrared spectra. A mixture melting point with the starting material was depressed to 63°. Further elution of the column with benzene and ethyl acetate gave a viscous yellow oil which could not be purified.

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Conformational Analysis. XLIII. Stereochemical Studies in the Cyclobutane Ring System[1-3]

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The *cis* and *trans* isomers of 1,3-dimethylcyclobutane have been prepared by stereospecific synthesis and the earlier geometric assignments have been found to be reversed. The *cis* isomer is inferred to be of lower enthalpy. The *cis* and *trans* isomers of methyl 3-methylcyclobutanecarboxylate have been prepared by stereospecific reactions and equilibrated. The *cis* isomer predominates over the *trans* at equilibrium; $\Delta F°_{338}$ is 0.3 kcal./mole. The *cis*- and *trans*-dimethyl 1,3-cyclobutanedicarboxylates have been equilibrated and $\Delta F°_{338}$ favors the *trans* isomer by 0.1 kcal./mole. The greater stability of the *trans* isomer here appears to be due to dipole–dipole interactions.

While the conformational aspects of the cyclohexane ring have been studied in great detail, much less is known concerning rings of other sizes.[4] The present paper is concerned with some of the conformational properties of the cyclobutane ring. Cyclobutane has been shown by electron diffraction[5,6] and by spectroscopic and thermodynamic measurements[7] to be puckered. Presumably the relief in torsional strain which results from a modest amount of puckering outweighs the additional bond-angle distortion in the molecule required by this puckering. The chemically interesting consequences of this nonplanarity have been explored to only a very slight extent.[3,8] Scale models show that there are two kinds of positions in cyclobutane, somewhat analogous to the axial–equatorial positions in cyclohexane. If there are two substituents located 1,3 to one another on the cyclobutane ring, the *trans* isomer has an equatorial–axial (ea) arrangement, while the *cis* isomer may be either diequatorial (ee) or diaxial (aa). It would appear from models

(1) Paper XLII: N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *J. Am. Chem. Soc.*, **87**, 1232 (1965).

(2) This research was supported by Grants DA-20-018-ORD 22743 and DA-ARO(D)-31-124-G494 from the Army Research Office.

(3) A preliminary communication describing some of this work was published earlier: J. M. Conia, J. L. Ripoll, L. A. Tushaus, C. L. Neumann, and N. L. Allinger, *J. Am. Chem. Soc.*, **84**, 4982 (1962). Many of the conclusions herein were presented at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963.

(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. B. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p. 189.

(5) A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta Chem. Scand.*, **15**, 711 (1961).

(6) J. D. Dunitz and V. Schomaker, *J. Chem. Phys.*, **20**, 1703 (1952).

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

(8) (a) J. M. Conia and J. Gore, *Tetrahedron Letters*, **No. 21**, 1379 (1963); (b) J. M. Conia and J. L. Ripoll, *Bull. soc. chim. France*, 768 (1963); (c) M. Takahashi, D. R. Davis, and J. D. Roberts, *J. Am. Chem. Soc.*, **84**, 2935 (1962); (d) J. B. Lambert and J. D. Roberts, *ibid.*, **85**, 3710 (1963).

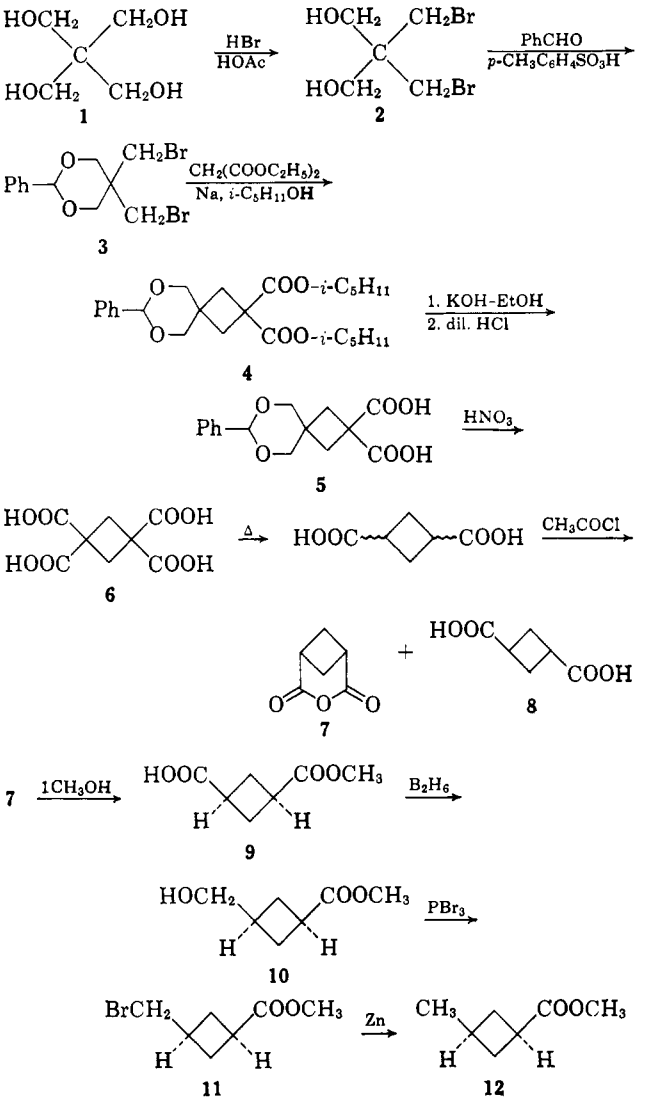
that ordinarily a group in the equatorial position would be of lower enthalpy than one in the axial position, but the distances involved are such that the conformational enthalpy ($H_{axial} - H_{equatorial}$) of most groups would appear to be smaller in the cyclobutane system than for the analogous cyclohexane. If there are two groups located 1,2, they are very nearly eclipsed in the *cis* isomer, so that probably the *trans* isomer would in general be more stable than the *cis*. When the groups are 1,3, it would appear that the *cis* (or diequatorial) isomer might be the more stable.

Among the 1,3-disubstituted cyclobutanes which have been previously prepared are the dimethyl derivatives, both the *cis* and *trans* isomers being known compounds.[9] The stereochemistry of these compounds was assigned on the basis of von Auwer's rule. There is good reason to believe that the conformational rule[10] should be used here, and the original assignment appeared to be in doubt. A consideration of the stereochemical properties of these compounds led to a consideration of other kinds of 1,3-disubstituted cyclobutanes. Specifically, it appeared to us that it would be desirable to investigate the 1,3-dicarbomethoxy and 1-methyl-3-carbomethoxy derivatives. The reason for this particular choice of compounds was that this selection included symmetrical and nonsymmetrical compounds containing both polar and nonpolar groups in various combinations, and all of the stereoisomers were conveniently accessible and their geometries could be established unambiguously.

Synthetic Work

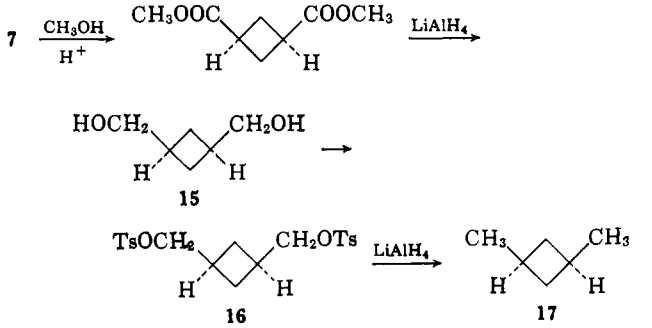
The key compounds in the present study were the *cis* and *trans* isomers of 1,3-cyclobutanedicarboxylic acid. These compounds were incorrectly reported in the early chemical literature many times, and the pure compounds were finally reported by Deutsch and Buchman in 1950.[11] The synthesis is outlined in Scheme I. Pentaerythritol with dry hydrobromic acid in acetic acid gave the dibromo derivative **2** which was converted to the acetal **3** with benzaldehyde. Treatment of this dibromide with the anion of malonic ester, followed by saponification of the condensation product, gave compound **5**, which was hydrolyzed and oxidized to the tetra acid **6**, which was in turn decarboxylated to a mixture of the *cis*- and *trans*-1,3-cyclobutanedicarboxylic acids. Treatment of the mixture of acids with acetyl chloride converted the *cis* isomer to the anhydride without affecting the *trans* isomer. The *cis* anhydride was separated from the *trans* diacid by distillation, and was refluxed with 1 equiv. of methanol[12] to give the *cis* monomethyl ester **9** which was reduced with diborane[13] to the hydroxy ester **10**. Replacement of the hydroxyl by bromine through the action of phosphorus tribromide[14] gave

SCHEME I



the *cis* bromo ester **11**, and reductive debromination of the latter with zinc produced methyl *cis*-methylcyclobutanecarboxylate (**12**).

A sample of pure *cis*-1,3-dimethylcyclobutane (**17**) was prepared according to the scheme shown below. The *cis* anhydride was treated with methanol containing a trace of sulfuric acid and gave the pure



dimethyl ester. When reduced with lithium aluminum hydride, the latter gave *cis*-1,3-bishydroxymethylcyclobutane (**15**). Diol **15** was in turn converted to the ditosylate **16**, which was reduced with lithium aluminum hydride to *cis*-1,3-dimethylcyclobutane (**17**).

The same sequence of reactions was carried out on a mixture of *cis*- and *trans*-1,3-cyclobutanedicarboxylic

(9) B. A. Kazanskii and M. Y. Lukina, *Dokl. Akad. Nauk SSSR*, **65**, 693 (1949); *Chem. Abstr.*, **45**, 2878*i* (1951).

(10) See ref. 4, p. 172.

(11) (a) D. H. Deutsch and E. R. Buchman, *Experientia*, **6**, 462 (1950); (b) Abstracts, 119th National Meeting of the American Chemical Society, Boston, Mass., 1951, p. 35M; (c) Technical Report, California Institute of Technology, 1951.

(12) J. Cason, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 169.

(13) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **82**, 681 (1960).

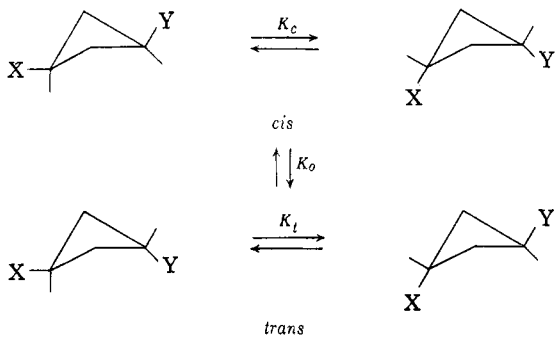
(14) A. T. Blomquist and J. A. Verdol, *ibid.*, **77**, 1806 (1955).

acids, and furnished a mixture of the corresponding *cis*- and *trans*-1,3-dimethylcyclobutanes. It was not necessary for present purposes to separate the mixture.

In addition to the dimethyl esters of the dicarboxylic acids, the diethyl esters and the monomethyl monoethyl esters were also desired as will be discussed below. The diethyl esters were made by Fischer esterification of the appropriate diacids. Gas phase chromatography showed that no epimerization occurred during this process. The monomethyl monoethyl ester was made from the monoethyl ester analogous to **9** by treatment with diazomethane.

Discussion

In any discussion of stability one must in general be careful to separate enthalpy and entropy effects.[15] While such a separation may be made experimentally in various ways (the determination of an equilibrium constant as a function of temperature being the most commonly used[16]), it is almost always possible to estimate the entropy of an epimerization reaction as accurately as it can be conveniently measured,[17] and we have in the present work made use of calculated rather than experimental entropies. For a 1,3-disubstituted cyclobutane ring which is puckered, in general we may write the equilibrium between the *cis* and *trans* isomers in terms of an equilibrium between four conformers. If we consider first the simplest



case where X = Y, the *cis* isomer is a mixture of two conformations (ee and aa), while the *trans* isomer is a single conformation (ea). If the substituent is rather small and nonpolar, a good approximation would seem to be that relative to the enthalpy of the ee form as zero, that of the ea form would be H, while that of the aa form would be $(2H + \delta)$.[18] All of the conformations are optically inactive. The symmetry numbers of both forms of the *cis* isomer are 2, while that of the *trans* form is 1. There is an entropy of mixing in the *cis* form which is absent in the *trans*. The entropy of the isomerization *cis* → *trans* is therefore dependent upon the magnitude of the conformational enthalpy (H), and if $H = 0$, the entropy of isomerization will also equal 0, while, if the value of H is quite large, the entropy of isomerization will tend to a limiting value of +1.4 e.u. Since we will only be concerned with small substituents (methyl and carboalkoxy) here, the entropy of isomerization should always be small for cases in which X = Y.

If we consider now the equilibrium between the *cis* and *trans* isomers where X and Y are not identical, the situation becomes a little more complicated. In this case the symmetry number is 1 for each conformation. Both isomers now have entropies of mixing, which are, however, limited to rather small ranges. If H has the same value for X and Y as for hydrogen, then ΔS for the reaction *cis* → *trans* is 0. If H has the same value for X and for Y, as this value becomes larger, in the limit ΔS tends toward +1.4 e.u. In the present work we are concerned with only small substituents for which H is small and roughly similar for the two groups X and Y. Consequently we expect only small entropy effects, regardless of whether or not X and Y are equal, and regardless of the signs of H for X and for Y.

Unfortunately, the four-membered ring is easily ruptured by hydrogenolysis under the conditions where epimerization would be expected to occur[19] and hence it did not appear feasible to attempt equilibration of 1,3-dimethylcyclobutane. The more volatile isomer was found to be *cis*, however, in agreement with the conformational rule, but contrary to the earlier assignment. Hence the original idea of a stable diequatorial isomer appears to be correct in this case.

The equilibration of methyl 3-methylcyclobutanecarboxylate is possible in the presence of base. The equilibrium constant was measured and found to be 0.63, thus the *cis* isomer has a lower free energy than the *trans* under these conditions by 0.3 kcal./mole. It is known that the methyl group and the carboxylate group have roughly similar "sizes" when on a cyclohexane ring,[20] and the same should also be true here, but because the axial substituent is subject to less repulsion from the 1,3 interaction (because of the greater distance) in the cyclobutane case, the conformational enthalpies of both the methyl and carboxylate groups on the cyclobutane ring of these compounds should be small and similar in magnitude, which is consistent with the observed equilibrium constant.

The *cis* and *trans* isomers of dimethyl 1,3-cyclobutanedicarboxylate were next equilibrated. In this case the equilibrium constant was found to have the value 1.17, and hence the *trans* isomer is of lower free energy by 0.1 kcal./mole under these conditions. Since this situation is qualitatively reversed from the case described above, there is clearly an important difference getween the two sets of compounds. There are two ways in which these diesters appear to differ from the mono esters initially studied. In this case the groups on the two ends of the molecule are the same rather than different, so there is a symmetry difference, and also in this case *both* of the groups are polar, so there is an electrostatic interaction between the dipoles. The effect of symmetry was considered first. Theoretical considerations suggest, and the previous equilibration experiments are consistent with,

(15) (a) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956); (b) R. M. Gascoigne, *J. Chem. Soc.*, 876 (1958).

(16) See ref. 4, p. 141.

(17) The only significant exception to this statement, of which the authors are aware, is that reported by R. L. Augustine and J. A. Caputo [*J. Am. Chem. Soc.*, **86**, 2751 (1964)]. This preliminary communication contains insufficient data to allow us to form any conclusions regarding it.

(18) For the cases considered here, δ would be zero or a small positive number. In the argument given $\delta = 0$ is assumed, but the qualitative conclusions are not changed if δ is a small number.

(19) N. L. Allinger, M. Nakazaki, and V. Zalkow, *J. Am. Chem. Soc.*, **81**, 4074 (1959), and references therein.

(20) See ref. 4, p. 44.

the conformational enthalpy of the carboxylate group being small in these compounds. Accepting for the moment that this is true, and accepting the approximate additivity of the conformational enthalpies of the groups[18] and the permissibility of neglecting dipolar interactions with the diesters at hand, the *cis* isomer has a symmetry number of 2, while that of the *trans* is 1. The amount of diaxial conformation in equilibrium with diequatorial in the *cis* isomer is not sufficient to yield an entropy of mixing large enough to make up for the entropy loss due to symmetry in the *cis* isomer; thus, for the reaction *cis* → *trans*, ΔS has a small positive value. The question, then, is whether or not this favorable entropy effect is sufficient to cause the *trans* isomer to have a lower free energy in this compound, while the *cis* isomer predominated in the methyl-3-methylcyclobutanecarboxylate equilibration. Calculations show that, if the conformational enthalpy of the carboxylate group were zero, and retaining the previous assumptions, the equilibrium constant between the dicarbomethoxycyclobutanes would be unity. If the conformational enthalpy of the carboxylate group were positive (that is if the carboxylate group prefers an equatorial position), then the enthalpy effect (favoring the diequatorial conformation) would invariably outweigh the entropy effect (favoring the *trans* isomer) for any value of H, and the *cis* isomer would predominate in equilibrium.[21] (If the conformational enthalpy of the ester group were negative, then it would not have been possible to have the *cis* isomer predominating in the equilibration of the methyl 3-methylcyclobutanecarboxylates, unless the conformational enthalpy of the methyl were also negative. If that were true, it would again be impossible to have the dimethyl 1,3-cyclobutanecarboxylates in the observed order of stability.) Hence, there is no combination of steric circumstances which will allow us to explain the observed results, as long as the original assumptions made are retained; thus, one or more of these assumptions must be incorrect.

The assumption which seemed to be the least justifiable was to ignore the dipolar interaction between groups in the diesters. In the *trans* isomer the ester groupings have their dipoles oriented the more favorably. This means that in these compounds there is an additional factor tending to stabilize the *trans* isomer, relative to the compounds which contain only one dipolar group.

The energy of the electrostatic interaction of two dipoles in a medium of dielectric constant D was derived by Jeans[22] and is given by eq. 1 where χ is the

$$E = \frac{\mu_1\mu_2}{R^3D}(\cos\chi - 3\cos\alpha_1\cos\alpha_2) \qquad (1)$$

angle between the dipoles, μ_1 and μ_2 are the moments of the two dipoles, R is the distance between the centers of the dipoles, and α_1 and α_2 are the angles the dipole vectors make with a vector joining their centers as defined by Jeans.[23] To use this relationship for the present problem, the relative orientations and distances of the dipoles for the various conformations must be known. The most accurate geometry of a cyclobutane ring available appears to be that of cyclobutyl bromide.[26] Using a dihedral angle of 29.5°, and an H–C_α–C_{CO} angle of 110°, and bond lengths of 1.545 for the C–C bonds in a ring and 1.52 Å. for those connecting the carbonyl carbon to the ring, the values of the necessary constants for use in eq. 1 were found for each conformation as indicated in Table I. Taking the dipole moment of the carboxylate group as 1.8 D.,[27] and assuming the moments are located at the carbonyl carbons, and directed along the C–C bond connecting the carbonyl carbon to the ring,[27] the electrostatic energy was calculated for each of the three conformations *in vacuo*, and these values are also given in the table. The problem then arises as to what value one should assign D for these molecules in ethanol solution. A value of 2 would be a lower limit corresponding to the molecule being in a hydrocarbon solvent. In ethanol the effective dielectric constant would be larger than this, but, since much of the space between the dipoles is taken up by hydrocarbon, even in ethanol solvent, the actual value cannot be estimated with any accuracy. If the lower limit of 2 is considered, the electrostatic interaction of the dipoles would favor the ea conformation by 0.72 kcal./mole over the ee. This energy is obviously quite sufficient to account for the 0.4 kcal./mole by which the *trans* isomer is found to be more stable than the *cis*, relative to the carboxylate–methyl case where there is no dipolar interaction. While it cannot be claimed that these calculations establish that the dipolar interaction is responsible for the observed equilibrium constant here as compared with the case where there is only one dipole in the molecule, it can be seen that the interaction energy is of the right order of magnitude to explain the observed equilibrium.

TABLE I
GEOMETRIC DATA

Conformation	R, Å.	χ, deg.	α_1, deg.	α_2, deg.	E (vacuum), kcal./mole
aa	4.1	41	69.5	10.5	+0.76
ee	5.3	99	40.5	139.5	+0.49
ea	5.3	151	42.5	13.5	−0.95

The only alternative interpretation of the observed data evident to the authors was that, perhaps, symmetry factors were in fact responsible for the difference observed between the equilibria involving diesters and monoesters, in spite of the fact that our analysis of the situation indicated otherwise. While this seemed unlikely, there was a remote possibility that our physical picture of the situation was incorrect. For example, a disubstituted cyclobutane could conceivably have a sufficiently low barrier to ring inversion that the molecule would have sufficient vibrational energy in

(21) This statement would not be true for large δ unless $H > 0.4$ kcal./mole. This possibility is eliminated below.

(22) J. H. Jeans, "Mathematical Theory of Electricity and Magnetism," 5th Ed., Cambridge University Press, London, 1933, p. 377.

(23) As recently pointed out by Lehn and Ourisson,[24] the application of Jeans' formula by Smyth and co-workers,[25] which has guided subsequent workers, incorrectly used the complement of α rather than α itself at one point.

(24) J. Lehn and G. Ourrison, *Bull. soc. chim. France*, 1113 (1963).

(25) C. P. Smyth, R. W. Dornte, and E. B. Wilson, Jr., *J. Am. Chem. Soc.*, **53**, 4242 (1931).

(26) W. G. Rothschild and B. P. Dailey, *J. Chem. Phys.*, **36**, 2931 (1962).

(27) (a) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963; (b) R. F. Curl, Jr., *J. Chem. Phys.*, **30**, 1529 (1959).

the ground state to carry past it and thus become effectively planar (as has been observed for trimethylene oxide).[28] It therefore seemed desirable to carry out one additional experiment to show that no unusual symmetry complications were present in the diesters, and a convenient way to do so appeared to be to determine the experimental equilibrium constant between the epimeric methyl ethyl cyclobutanedicarboxylates (**14**). These molecules have X ≠ Y, and hence the symmetry properties of the methyl methylcyclobutanecarboxylates, but they retain the dipolar interactions of the dimethyl cyclobutanedicarboxylates. An observed equilibrium constant for the unsymmetrical diesters similar to that for the symmetrical ones would be strong support for the idea that dipolar interactions, rather than symmetry, were primarily responsible for determining the position of equilibrium in all of the diesters.

Preliminary experiments indicated that it would be difficult to epimerize esters **14** without simultaneous transesterification to yield the *cis* and *trans* isomers of the dimethyl and diethyl esters of **8**. Fortunately, the two isomers of interest showed different retention times on vapor phase chromatography (v.p.c.) from the various isomeric homologs and from each other, and the equilibrium constant between them was determined without difficulty and had a value within experimental error of those for the diethyl and the dimethyl esters. It is therefore certain that symmetry does not lead to the observed difference between the mono and diesters. Since the dipole interaction is about the right magnitude to explain the observed results, and since there appears to be no alternative explanation, the facts appear to be accounted for adequately.

It would appear that the conformational properties of the cyclobutane ring are qualitatively similar to those of the cyclohexane ring in most respects, but the interactions should in general be less serious. Quantitatively, there will of course be differences, but it seems likely that good predictions about cyclobutane systems can be made by analogy to cyclohexane systems, and many of the methods which have proved so fruitful in the cyclohexane series should prove to be equally useful in cyclobutane series.

Experimental

2,2-Bis(bromomethyl)-1,3-propanediol (2).[29]—In a 5-l. three-necked flask were placed 2470 ml. of glacial acetic acid, 25 ml. of 48% hydrobromic acid, and 408 g. of pentaerythritol (**1**). The mixture was refluxed until the solid had dissolved and then 1360 ml. of 48% of hydrobromic acid was added during 1 hr. Refluxing was continued for an additional 18 hr., and the bulk of the acetic acid and hydrobromic acid was removed by distillation at reduced pressure. Absolute alcohol (2 l.) was added to the residue, and the ethyl acetate, which was formed by transesterification, was removed by distillation through a 12-in. Vigreux column. Additional volatile material was then removed by heating the flask on the steam bath under reduced pressure. About 500 ml. of toluene was added to the residue, and approximately 400 ml. of material was then distilled from the mixture. The remaining toluene was removed by heating the mixture on a steam bath under reduced pressure, and the residue was crystallized once from benzene and once from water. The yield was 369 g. (47%), m.p. 109–110°.

2-Phenyl-5,5-dibromomethyl-1,3-dioxacyclohexane (3).[30]—A mixture of 326 g. of **2**, 140 g. of benzaldehyde, and 1.5 g. of *p*-toluenesulfonic acid in 500 ml. of benzene was heated under reflux, and the water formed in the reaction was removed with the aid of a water separator. After completion of the reaction, the mixture was washed with aqueous sodium carbonate and dried over anhydrous potassium carbonate. After removal of the solvent the residue was crystallized twice from methanol at −15° and gave prisms, m.p. 68.0–68.3°, yield 394 g. (90%).[11]

Isoamyl 7-Phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylate (4).[30]—To a solution prepared by dissolving 25.3 g. of sodium in 1 l. of isoamyl alcohol was added 240 g. of diethyl malonate. The solution was heated, and ethyl alcohol was allowed to distil through a small Vigreux column until the vapor temperature reached 128°. The reaction flask was cooled somewhat, 176 g. of **3** was added, and the resulting mixture was heated under reflux with stirring for 18 hr. The bulk of the isoamyl alcohol was distilled, the residue was cooled and taken up in ether, and the ether phase was washed with water. The water washings were extracted with ether, and the ether solutions were dried over potassium carbonate. After evaporation of the ether, distillation gave a fraction boiling at 190–208° (0.4 mm.), which solidified. The yield was 152 g. (71%), and a sample recrystallized from methyl alcohol at −30° had the reported[11] m.p. 44.5–45.0°.

7-Phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylic Acid (5).[30]—A solution of 0.2 mole of **4** in 200 ml. of absolute alcohol was added to a solution of 37.4 g. of potassium hydroxide in 800 ml. of absolute alcohol, the mixture was heated on a steam bath for 30 min. and then cooled to 0°, and the potassium salt was collected. The salt was washed with absolute alcohol, then with ether, and finally was dried. The yield was quantitative.

After dissolving the salt in 500 ml. of water, the solution was acidified to congo red with 3 *N* hydrochloric acid. The voluminous precipitate of the dicarboxylic acid was taken up in ether. Benzene was added to the ether, and the ether was evaporated. The pure acid was obtained in quantitative yield, m.p. 185–186° dec., as reported.[11]

1,1,3,3-Cyclobutanetetracarboxylic Acid (6).[30]—A mixture of 58.4 g. of **5** and 50 ml. of 2 *N* nitric acid was heated under reflux for 5 min. The benzaldehyde layer was removed, and the aqueous solution was extracted with ether. The residual aqueous solution was boiled briefly to expel traces of ether and was then added dropwise to 200 ml. of hot concentrated nitric acid (containing a trace of fuming nitric acid) in a 2-l. flask provided with a reflux condenser. A vigorous reaction ensued and oxides of nitrogen were evolved. After the addition was completed, the solution was heated under reflux until nearly colorless and the gas evolution had ceased. The bulk of the excess nitric acid was removed under reduced pressure by heating on a steam bath, and the residual traces of nitric acid were destroyed by the addition of 50 ml. of formic acid. After the resultant mixture was reduced to dryness, it was dissolved in ether and the tetra acid was precipitated by the addition of benzene and evaporation of the ether. The yield was 40.95 g. (88.5%), m.p. 205° dec., lit.[11] m.p. 205° dec.

***cis*- and *trans*-1,3-Cyclobutanedicarboxylic Acids.**[30]—Compound **6** was decarboxylated by heating at 220° for 15 min. The melt was cooled, 56 g. of acetyl chloride was added, and the resulting solution was heated under reflux for 2 hr. The excess acetyl chloride and acetic anhydride was removed under reduced pressure, and then the anhydride of *cis*-1,3-cyclobutanedicarboxylic acid (**7**) was distilled at a pressure of 2 mm. and a bath temperature of about 125°. The solidified distillate was crystallized from benzene and gave large needles of the reported melting point[11] (131–132°), 9.16 g. (43%).

The *cis* anhydride **7** was converted to the corresponding acid by refluxing with an equal weight of 6 *N* hydrochloric acid for 10 min. The hydrochloric acid was removed on a steam bath, and the *cis* acid was crystallized from acetone–benzene and gave needles,[11] m.p. 131–132°.

trans-1,3-Cyclobutanedicarboxylic acid (**8**) was isolated from the residue which remained after the distillation of the *cis* anhydride. The residue was refluxed with 6 *N* hydrochloric acid for a few minutes and then evaporated to dryness. Repeated extraction of the black residue with hot xylene yielded 17.0 g. (27%) of colorless crude *trans* acid, which was recrystallized from 6 *N* hydrochloric acid to give needles,[11] m.p. 192–193°.

(28) S. I. Chan, J. Zinn, and W. D. Gwinn, *J. Chem. Phys.*, **34**, 1319 (1961).

(29) M. Beyaert and M. Hansens, *Natuurw. Tijdschr.* (Ghent), **22**, 249 (1940); *Chem. Abstr.*, **37**, 5373 (1944).

(30) The synthesis of this compound follows a procedure kindly furnished us by Dr. E. R. Buchman.

Dimethyl and Diethyl Esters of *cis*- and *trans*-1,3-Cyclobutanedicarboxylic Acids.—*cis*-Dimethyl 1,3-cyclobutanedicarboxylate was prepared by refluxing 1.0 g. of the diacid with 40 ml. of methyl alcohol and 0.2 g. of sulfuric acid for 5 hr. The yield was 0.9 g., b.p. 91.0–91.5° (3.0 mm.), $n^{25}D$ 1.4443.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.92; H, 7.29.

trans-Dimethyl 1,3-cyclobutanedicarboxylate was prepared as described for the *cis* isomer; b.p. 83.0–83.5° (3.0 mm.), $n^{25}D$ 1.4433.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.80; H, 7.17.

cis-Diethyl 1,3-cyclobutanedicarboxylate was similarly prepared with absolute ethanol and sulfuric acid; b.p. 106° (3.1 mm.), $n^{25}D$ 1.4399.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.06; H, 8.29.

trans-Diethyl 1,3-cyclobutanedicarboxylate was likewise prepared; b.p. 100–100.5° (3.2 mm.), $n^{25}D$ 1.4390.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.86; H, 7.98.

***cis*-Cyclobutane-1,3-dicarboxylic Acid Monomethyl Ester (9).**—This ester was prepared by a procedure described by Cason.[12] *cis*-Cyclobutanedicarboxylic acid anhydride was refluxed for 1 hr. on a steam bath with a slight excess of methanol. The monoester was distilled at 147–150° (3.7 mm.); $n^{25}D$ 1.4603.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.93; H, 6.24.

***cis*-Methyl 3-Hydroxylmethylcyclobutanecarboxylate (10).**—The carboxyl group was reduced according to the procedure of Brown and Subba Rao.[13] Diborane generated in another reaction flask by the dropwise addition of a solution of 1 g. of sodium borohydride in 25 ml. of diglyme to 4 g. of 47% boron trifluoride etherate in 10 ml. of diglyme, was bubbled into a solution of *cis*-cyclobutane-1,3-dicarboxylic acid monomethyl ester (0.6 g.) in 25 ml. of tetrahydrofuran. After a short time the solution became turbid, then cleared again. The diborane was allowed to bubble in for a few more minutes, and then the bubbler was replaced with a magnetic stirring bar. Stirring was stopped after 1 hr. and then methanol was added to destroy the excess diborane. The mixture was distilled, giving the alcohol ester, b.p. 110–111° (3 mm.), $n^{25}D$ 1.4575. Yields range from 50 to 60%. The length of time during which the diborane is passed into the monoester is critical and varies with the amount of monoester. If the reaction is allowed to proceed too long, a considerable amount of diol is formed owing to reduction of the ester group as well as the acid group. If the reaction time is not enough, only the salt of the acid will be formed and will revert to the acid upon addition of methanol.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.31. Found: C, 58.47; H, 8.54.

***cis*-Methyl 3-Bromomethylcyclobutanecarboxylate (11).**—The bromo ester was prepared in a way similar to that described by Blomquist and Verdol.[14] To a solution of 260 mg. of methyl 3-hydroxymethylcyclobutane in 0.4 ml. of benzene was added 490 mg. of phosphorus tribromide. The mixture was allowed to come to room temperature slowly and was then refluxed for 20 hr. After this time it was poured onto ice and the mixture was extracted five times with chloroform. After drying over sodium sulfate, the solvent was evaporated and the product was distilled; b.p. 110–111° (12 mm.), $n^{25}D$ 1.4825, yield 232 mg. (62%).

Anal. Calcd. for $C_7H_{11}BrO_2$: C, 40.60; H, 5.36; Br, 38.59. Found: C, 40.69; H, 5.59; Br, 38.41.

***cis*-Methyl 3-Methylcyclobutanecarboxylate (12).**—*cis*-Methyl 3-bromomethylcyclobutanecarboxylate (200 mg.) was refluxed overnight with an excess (*ca.* 0.5 g.) of zinc dust and 5 ml. of water. The reaction mixture was cooled and extracted with pentane, and the pentane extracts were dried over sodium sulfate. Most of the pentane was removed by distillation and on v.p.c. analysis the residue was found to give only one peak aside from that due to the pentane.

Equilibration of Methyl 3-Methylcyclobutanecarboxylate.—3-Methylcyclobutanecarboxylic acid was obtained[3] as a mixture of isomers. This acid was esterified in the usual way with methanol and a catalytic amount of sulfuric acid. Work-up and distillation yielded the isomeric mixture of esters, b.p. 146–147°, $n^{25}D$ 1.4213.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.30; H, 9.50.

A 0.5-g. sample of this ester mixture was equilibrated with 10 ml. of a solution of sodium methoxide made by dissolving 0.2 g. of sodium in 40 ml. of methanol. The equilibration was carried out at 65° under nitrogen. Samples removed after 119 and 165 hr. were analyzed. The retention times on a 6-ft. Tide column at 44° at 5-p.s.i. pressure were 36 and 40 min. It was found that the first and larger peak was due to the *cis* isomer by a comparison with **12**. Calculations based on height times half-band-width measurements and weighing cutout models of the peaks showed the equilibrium concentration to be 62% *cis* and 38% *trans*, corresponding to an equilibrium constant of 1.60 ± 0.1 and a $\Delta F°$ of 0.32 ± 0.04 kcal./mole.

Equilibration of the Dimethyl 1,3-Cyclobutanedicarboxylates.—Samples (0.5 g.) of *cis* and *trans* dimethyl 1,3-cyclobutanedicarboxylates were placed in separate flasks and refluxed with 10 ml. of a solution of sodium methoxide in methanol made by dissolving 0.2 g. of sodium in 40 ml. of methanol. The equilibration was carried out at 65° under nitrogen. Samples were removed periodically and analyzed. They were found to have been equilibrated after 15 min. A 6-ft. Dow polyglycol E 9000 (15%) column at 175° and 10 p.s.i. cleanly separated the *cis* and *trans* isomers, the *trans* isomer being eluted first. The equilibrium concentrations were found to be 54% *trans* and 46% *cis*, corresponding to an equilibrium constant of 1.16 ± 0.1 and a $\Delta F°$ of 0.10 kcal./mole.

Equilibration of the Diethyl 1,3-Cyclobutanedicarboxylates.—The equilibration of the diethyl esters was carried out in a similar fashion in refluxing ethanol at 80.5°. Analysis on the same polyglycol column under the same conditions showed the equilibrium concentration to be 53% *trans* and 47% *cis*, corresponding to an equilibrium constant of 1.14 ± 0.05 and a $\Delta F°$ of 0.09 kcal./mole. The *trans* ester again was eluted first.

Synthesis and Equilibration of Methyl Ethyl Cyclobutanedicarboxylate (14).—The anhydride of *cis*-1,3-cyclobutanedicarboxylic acid (2 g.) was refluxed for 1 hr. with 0.8 g. of absolute ethanol to yield 1.2 g. of the monoethyl ester of *cis*-1,3-cyclobutanedicarboxylic acid (**13**), b.p. 136–137° (1.7 mm.), $n^{25}D$ 1.4555.

Anal. Calcd. for $C_8H_{13}O_4$: C, 55.80; H, 7.03. Found: C, 55.81; H, 6.98.

Esterification of the monoethyl ester of the diacid with diazomethane yielded 1-methyl 3-ethyl *cis*-1,3-cyclobutanedicarboxylate (**14**), b.p. 98–99° (2.9 mm.), $n^{25}D$ 1.4411, 85% yield.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.34; H, 7.70.

Equilibration was carried out in a solution containing absolute ethanol and methanol in a 1:1 molar ratio. To a mixture of 21.6 g. of ethanol and 15.0 g. of methanol was added 0.1 g. of sodium. Five-milliliter aliquots of this sodium alkoxide solution were placed in four separate flasks containing 0.3 g. of dimethyl *cis*-1,3-cyclobutanedicarboxylate, diethyl *cis*-1,3-cyclobutanedicarboxylate, diethyl *trans*-1,3-cyclobutanedicarboxylate, and 1-methyl 3-ethyl *cis*-1,3-cyclobutanedicarboxylate, respectively. These esters were equilibrated under reflux at 73° for 12–15 hr. These samples were analyzed directly by removing a portion of the equilibrated solution and immediately injecting it into a v.p.c. column. The column in this case was a 12 ft. × 7 mm. glass column packed with Dow polyglycol E 9000 on 40–100-mesh nonacid-washed Chromosorb P. The column temperature was 192°; the helium pressure was 10 p.s.i. The cyclobutane esters began coming off the column after about 40 min.

The manner of experimentation was designed so as to achieve an equilibrium between all six of the possible esters that could arise by ethyl–methyl interchange. These esters were almost cleanly separable by v.p.c. and it was possible to obtain a good estimate of the *cis–trans* ratio in the case of the 1-methyl 3-ethyl cyclobutanedicarboxylates by employing the method of half-band width. Results obtained from the four different samples gave 57.2 ± 1.1% *trans* ester.

The order of elution of the esters was as follows: *trans* dimethyl, *trans* methyl ethyl, *trans* diethyl and *cis* dimethyl (same retention times), *cis* methyl ethyl, and *cis* diethyl.

***cis*-1,3-Bis(hydroxymethyl)cyclobutane (15).**—Dimethyl *cis*-1,3-cyclobutanedicarboxylate, 4.1 g., in 10 ml. of anhydrous ether was added dropwise to a flask containing 1.9 g. of lithium aluminum hydride in 150 ml. of anhydrous ether. The mixture was stirred for 9 hr. and then hydrolyzed. The ether layer was dried and distillation yielded 1.8 g. (62%) of the *cis*-diol, b.p. 107–108° (1.3 mm.), $n^{25}D$ 1.4761.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.42. Found: C, 62.35; H, 10.55.

Ditosylate of *cis*-1,3-Bis(hydroxymethyl)cyclobutane (16).—To a cold solution of 6.9 g. of *p*-toluenesulfonyl chloride in 20 ml. of pyridine was added 1.8 g. of diol **15**. After standing overnight at room temperature, the mixture was poured onto ice–water and the crystals of ditosylate were collected. Recrystallization from hexane–acetone yielded 4.2 g. (77%), m.p. 76.5–77.5°.

Anal. Calcd. for $C_{20}H_{24}O_6S_2$: C, 56.58; H, 5.70. Found: C, 56.66; H, 5.72.

***cis*-1,3-Dimethylcyclobutane (17).**—A solution of 4.2 g. of the ditosylate of *cis*-1,3-bis(hydroxymethyl)cyclobutane in 15 ml. of anhydrous ether was added dropwise to a stirred solution of 5.7 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. Stirring was continued for 5 hr. and the solution was hydrolyzed with dilute hydrochloric acid. The ether layer was dried and most of the ether was carefully removed by slow distillation through a 14-cm. Vigreux column.

A sample consisting of a mixture of *cis*- and *trans*-1,3-dimethylcyclobutane was prepared in analogous fashion by utilizing a mixture of *cis*- and *trans*-dimethyl 1,3-cyclobutanedicarboxylate as starting material. This hydrocarbon mixture was found to be partially separated by v.p.c. (1,2,3-β-cyanoethoxypropane) at 25°. The material which was eluted first was found to be the *cis* isomer by comparison with that obtained in the previously described stereospecific syntheses. This indicates that the *cis*-1,3-dimethylcyclobutane is in fact the lower boiling isomer, and the previously reported *cis* and *trans* structures assigned earlier should be reversed. (Kazanskii and Lukina[9] give *trans*, b.p. 57.4–57.6°, $n^{20}D$ 1.3896, d^{20}_4 0.7016; *cis*, b.p. 60.5–60.6°, $n^{20}D$ 1.3933, d^{20}_4 0.7106.)

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Nucleophilic Ring-Opening Additions to 1,1-Disubstituted Cyclopropanes

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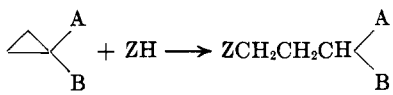
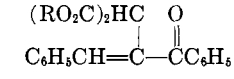
Ring-opening addition reactions have been found to take place between various nucleophilic reagents and a series of cyclopropane compounds substituted at one carbon of the ring by two electron-withdrawing groups. These reactions result in 1,1,3-trisubstituted propanes.

As part of a general study of the ring-opening addition reactions of nucleophilic reagents with cyclopropane compounds having one or more electron-withdrawing substituents on the ring, initial investigations were carried out with cyclopropanes substituted at the same ring carbon by *two* such groups. The cyclopropane ring behaves in a manner analogous to that of an alkene linkage substituted on one carbon by one or more electron-withdrawing groups; ring cleavage occurs adjacent to the substituted carbon, and addition of the nucleophile leads to 1,1,3-trisubstituted propanes as follows. Although a few isolated



instances of such behavior have been reported,[1-5] there have been no reported systematic studies of reactions of this type, and the universal nature of such reactions has not been recognized. Bone and Perkin,[1] in the preparation of diethyl cyclopropane-1,1-dicarboxylate by condensation of ethylene bromide and diethyl malonate in the presence of sodium ethoxide, demonstrated clearly that a by-product, tetraethyl 1,1,4,4-butanetetracarboxylate, was formed by a ring-opening reaction between the desired product and the malonate anion. Kierstad, *et al.*,[2] observed the same reaction and described an analogous reaction between diethyl 2-vinylcyclopropane-1,1-dicarboxylate and diethyl sodiomalonate. Kohler and Conant[3] reported that various anhydrous basic solutions reacted with compounds of the type, 1-$(CO_2R)_2$-2-C_6H_5-3-COC_6H_5-*c*-C_3H_2 (*c*-C_3H_n refers to a cyclopropane ring), to form the isomeric unsaturated structure that is shown.



However, they described only a reaction involving sodium methoxide in methanol in which they proposed that an addition reaction first occurred, with ring opening between C-1 and 2, followed by loss of methyl alcohol to form the unsaturated product. (It has been pointed out by a referee, however, that this product could have been formed by an alternate route involving a base-catalyzed abstraction of a proton from position 3, followed by a conjugate shift of electrons from that position to position 1.) Truce and Lindy[4] reported ring opening of methyl cyclopropyl ketone by sodium benzene thiolate to give $C_6H_5SCH_2CH_2CH_2COCH_3$, and Regan[5] assigned the propenide structure, $[(CN)_2C{=}C(CO_2Et)C(CN)_2]^-NH_4$, to the product formed on reaction of diethyl 2,2,3,3,-tetracyanocyclopropane-1,1-dicarboxylate with ammonia in ether solution.

The cyclopropane compounds used in this investigation were diethyl cyclopropane-1,1-dicarboxylate, ethyl 1-cyanocyclopropane-1-carboxylate, 1-cyanocyclopropane-1-carboxamide, cyclopropane-1,1-dicarboxamide, and cyclopropane-1,1-dicarbonitrile. All are previously reported compounds except cyclopropane-1,1-dicarbonitrile, which was prepared by dehydration of either cyclopropane-1,1-dicarboxamide or 1-cyanocyclopropane-1-carboxamide with phosphorus pentoxide. A number of attempts were made to prepare cyclopropane-1,1-dicarbonitrile by a Perkin-type ring-closure condensation between malononitrile and ethylene bromide in the presence of the basic catalysts, sodium ethoxide or methoxide or sodium

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