Mass Spectra of Certain Cyclobutanecarboxylates

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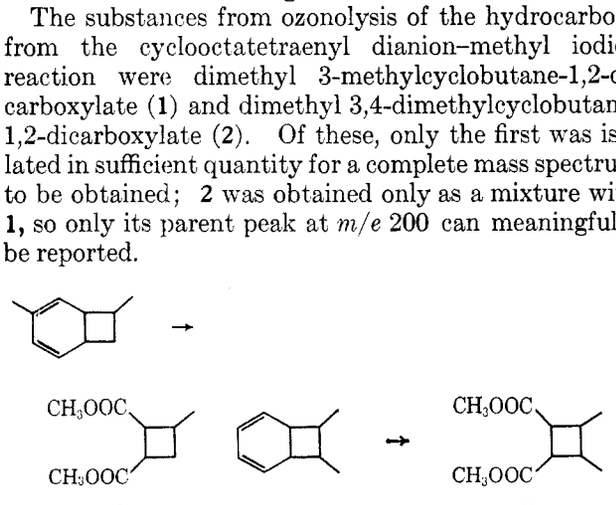
Received May 9, 1966

Cyclobutane derivatives have been shown to give characteristic ring cleavage upon electron impact in a mass spectrometer. In every compound studied, fragment ions which could be attributed to ring cleavage were among those of major abundance. It was noted that *cis* substituents on adjacent carbon atoms caused characteristic cleavage of the ring between the two substituents. Presumably this occurs to relieve steric compression caused by the interaction of the *cis* groups.

The reaction of cyclooctatetraenyl dianion with methyl iodide and the thermal rearrangement of the initial products formed have been reported.[2] Initial evidence that hydrocarbons containing the cyclobutane ring were present was obtained in the form of esters of cyclobutanecarboxylic acids obtained by ozonolysis of the hydrocarbon mixture, oxidative degradation of the ozonides, and esterification of the acids. Because the isolation and purification of these esters were extremely tedious, we turned to mass spectrometry as an effective way to identify them in small quantities. The mass spectral data on the cyclobutane esters permitted assignment of structures to them and, thus, to certain of the rearranged hydrocarbons.

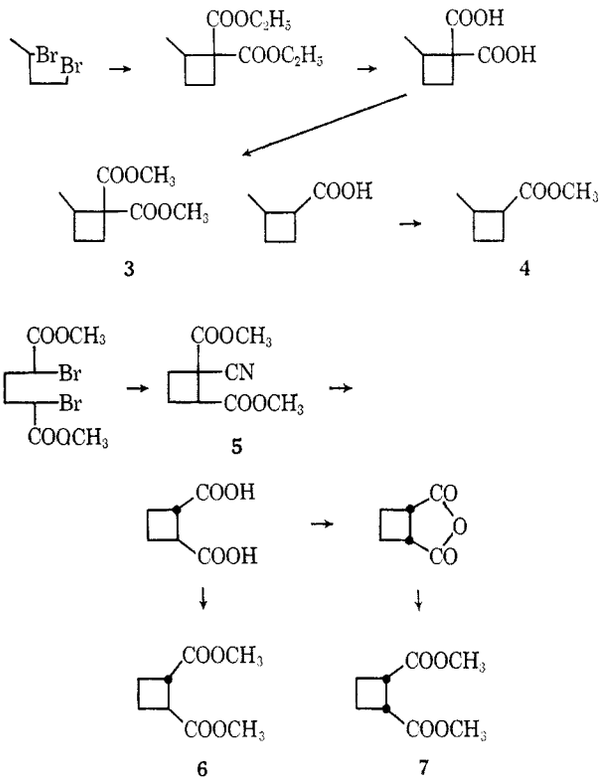
Although the initial identification of the cyclobutane derivatives was done on the basis of mass spectral data, the structures of the hydrocarbon precursors were later secured by infrared, ultraviolet, and nmr spectral analysis and by investigation of their thermal interconversion. Therefore the structures of the cyclobutane degradation products of the hydrocarbons can be regarded as securely established, even though they were previously unknown compounds and classical structure proofs have not been provided. To provide some additional examples of analogous structures for study of fragmentation patterns, we prepared some further cyclobutanecarboxylates, including some unsymmetrically substituted examples to aid in distinguishing alternative modes of fragmentation.

The substances from ozonolysis of the hydrocarbons from the cyclooctatetraenyl dianion–methyl iodide reaction were dimethyl 3-methylcyclobutane-1,2-dicarboxylate (**1**) and dimethyl 3,4-dimethylcyclobutane-1,2-dicarboxylate (**2**). Of these, only the first was isolated in sufficient quantity for a complete mass spectrum to be obtained; **2** was obtained only as a mixture with **1**, so only its parent peak at *m/e* 200 can meaningfully be reported.



1 **2**

Structures which were prepared for the purpose of providing examples for comparison were from two sources: the Perkin ring closure of 1,3-dibromobutane with malonic ester[3] and the ring closure with sodium cyanide of 2,5-dibromohexanedioate to 1-cyanocyclobutane-1,2-dicarboxylate.[4] Five additional esters, dimethyl 2-methylcyclobutane-1,1-dicarboxylate (**3**), methyl 2-methylcyclobutanecarboxylate (**4**), dimethyl 1-cyanocyclobutane-1,2-dicarboxylate (**5**), and *trans*- and *cis*-dimethyl cyclobutane-1,2-dicarboxylate (**6** and **7**, respectively), were obtained from these sources.



In **4**, the *trans* isomer is probably predominant because it is the more stable isomer. To prepare **6**, the pure *trans* acid was isolated and esterified. In **3**, **5**, and **7** the *cis* relationship of two adjacent groups is ensured, in **3** and **5** by the geminal substitution and in **7** by the isolation of the anhydride which is necessarily *cis* and conversion of it to the ester under conditions which avoid epimerization. In **1** and **2**, the extended exposure to epimerizing conditions during oxidative work-up of the ozonide and subsequent isolation of the diacids is presumed to have effected isomerization to the more stable *trans* isomers.

When searching the literature for mass spectra which would help identify the cyclobutane products we obtained from ozonolysis of dimethylcyclooctatriene mix-

(1) From the dissertation of David A. Bak, submitted in partial fulfillment of the requirements for the Ph.D. degree, Kansas State University, 1966.

(2) David A. Bak and Kenneth Conrow, *J. Org. Chem.*, in press.

(3) A. T. Blomquist and I. Wolinsky, *ibid.*, **21**, 1371 (1956).

(4) E. R. Buchman, A. O. Reims, T. Shei, and M. J. Schlatter, *J. Am. Chem. Soc.*, **64**, 2696 (1942).

tures, we noticed a trend in the fragmentation patterns of all the cyclobutanes. The most abundant fragment always corresponded to the one which arises from splitting of the cyclobutane ring. This was usually the most abundant fragment by far.

The most abundant fragment ion in the mass spectrum of cyclobutane[5] is *m/e* 28 which corresponds to ring splitting to form two fragments of ethylene, one of which retains the charge. This molecule forms two other quite abundant fragments, the parent ion (*m/e* 56) with a relative abundance (ra) of 62.5 and *m/e* 41 (ra 89).

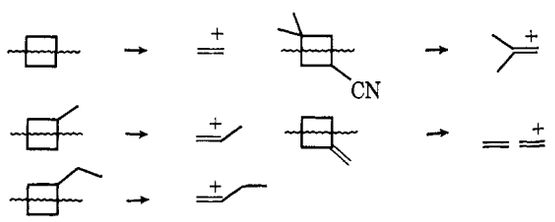
The most abundant fragment ion in the mass spectrum of methylcyclobutane[6] corresponds to a species represented by propene cation, *m/e* 42, arising by ring splitting. The ion of *m/e* 41 (ra 31.5) is the only other fragment ion with relative abundance greater than 20.

The most abundant fragment of the mass spectrum of ethylcyclobutane[5] corresponds again to the ring-splitting fragment represented by butene cation, *m/e* 56. The fragment *m/e* 41 (ra 65) is the only other ion of major intensity.

The most abundant fragment in the mass spectrum of 1-cyano-3,3-dimethylcyclobutane[6] corresponds to ring splitting to give an ion represented by the isobutylene cation, *m/e* 56.

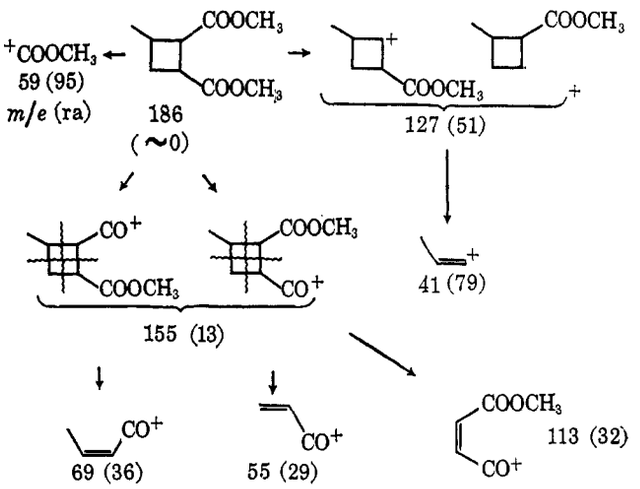
The most abundant ion in the mass spectrum of methylenecyclobutane[5] corresponds to the ring-splitting fragment represented by the allene cation, *m/e* 40.

The principal modes of fragmentation of these substances are summarized in the following scheme.



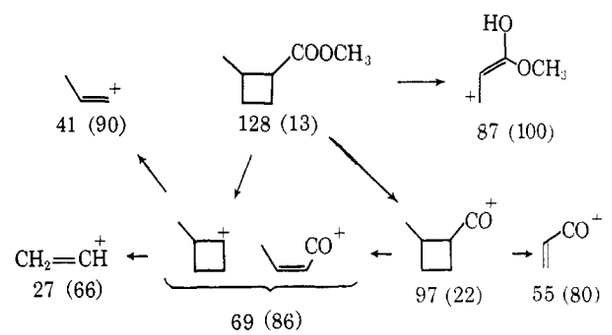
The compounds we had available by ozonolysis of the dimethylbicyclic derivatives and those we could conveniently prepare for comparison purposes gave much more complex mass spectral fragmentation patterns than the simple cyclobutane systems found in the literature. This is due to the presence of the easily fragmented ester group.[7] In the esters, fragment ions other than those from ring cleavage sometimes have larger relative abundances than ring cleavage products. In the discussion which follows, attention is focused on the more abundant fragment ions, especially those of higher mass, since those of lower mass can arise in more than one way and may result from rearrangement. The structures given for the various fragments are merely rationalizations of the presence of a fragment ion of the given mass; no evidence of structure was obtained and isomeric structures may prevail.

Dimethyl 3-methylcyclobutane-1,2-dicarboxylate (**1**) gives four major ring-splitting fragments: *m/e* 69, 55, 113, and 42. The two fragments of *m/e* 127 formulated with an intact ring could just as well be formulated as open-chain isomers instead.



This molecule is an excellent example for showing that ring splitting occurs at both sets of bonds in the absence of compelling steric factors.

Methyl 2-methylcyclobutanecarboxylate (**4**) shows five main fragments which are all ring-cleavage products: *m/e* 41, 27, 69, 55, and 87.



The most abundant peak which is formulated as having an intact ring is that at *m/e* 97; its relative abundance is 22% of the base peak at *m/e* 87. Even this peak might consist of open-chain isomers of the same composition.

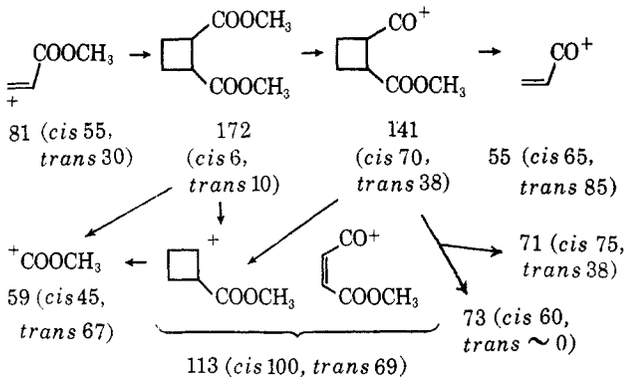
The peak at *m/e* 69, which might be formulated as a ring-intact methylcyclobutyl cation, is likely to consist largely of the ring cleavage fragment $C_4H_5O^+$. It appears that, since steric compression is not a factor here, the two alternative modes of fragmentation of the cyclobutane ring are about equally probable, as witnessed by the high intensity of both the *m/e* 41 and *m/e* 27 peaks which are formulated as arising from the methylcyclobutyl cation. If a similar nonspecific cleavage is assumed for the methylcyclobutylcarbonylium ion, *m/e* 97, then the size of the *m/e* 55 peak implies that most of the *m/e* 69 peak is due to ring cleavage of the carbonylium ion. In addition, the presence of large amounts of the cleavage products of the methylcyclobutyl cation indicates its ready cleavage and thus that it is unlikely to be a large contributor to the *m/e* 69 peak.

cis-Dimethyl cyclobutane-1,2-dicarboxylate (**7**) and *trans*-dimethyl cyclobutane-1,2-dicarboxylate (**6**) both exhibit the same ring-splitting fragment ions, but the

(5) American Petroleum Institute Research Project 44, "Catalog of Mass Spectral Data," Carnegie Institute of Technology, Pittsburgh, Pa., 1953, Spectra 272, 275, and 416.

(6) ASTM Uncertified Spectra, Tennessee Eastman Co. Research Laboratories, Kingsport, Tenn., Spectra 1212 and 1223.

(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, pp 10–16.

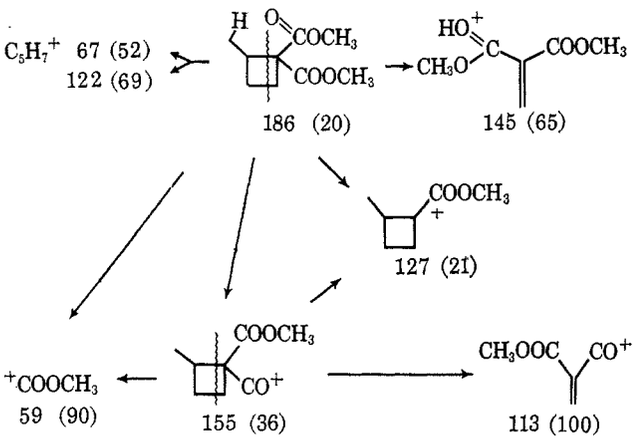


relative abundances differ, as has been reported by D'Or, *et al.*,[8] for other *cis–trans* isomer pairs.

The clearest difference in the two isomers is the intensity of the peaks at *m/e* 71 and 73, which are major peaks in the *cis* isomer, but of less intensity in the *trans* isomer. These peaks must be explained by rearrangement processes which involve ring cleavage. The greater abundance of these ionic fragments in the spectrum of the *cis* isomer is consistent with the greater steric compression and ring cleavage of this isomer.

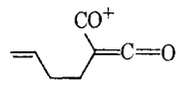
Differences are also apparent in the ratio between the *m/e* 113 and the *m/e* 55 and 59 fragment ions. In the *cis* isomer **7** the *m/e* 113 ion is more abundant than the other two fragments, but the reverse is true in the *trans* isomer **6**. The two sources of an ion of *m/e* 113 make it difficult to interpret these relationships in terms of the difference in steric compression. The most direct indication of a difference in steric compression is the relative size of the peak at *m/e* 81, resulting from scission of the molecule into two fragments of equal masses, but with a relative abundance of 55 in the *cis* isomer where steric compression is greater, and only 30 in the *trans* isomer.

Dimethyl 2-methylcyclobutane-1,1-dicarboxylate (**3**) forms two fragment ions of relatively high mass (*m/e* 145 and 113) owing to ring cleavage, in addition to some prominent ones, *e.g.*, *m/e* 122 and 67, whose status *in re* ring cleavage is less definite.



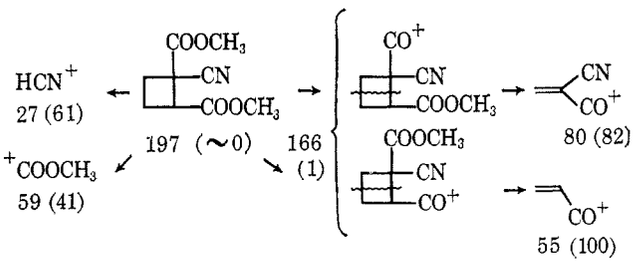
The direction of fragmentation was such that ring cleavage occurs only between the substituted carbon atoms: although the *m/e* 145 peak was prominent the *m/e* 159 peak expected from the other sense of ring cleavage was absent; although the *m/e* 113 peak was the base peak, the *m/e* 127 peak is weak (ra 21), and that is probably derived from an alternate route, the net loss of a carbomethoxy group. A postulated explanation of this specificity of cleavage takes into account the steric compression which arises from the necessarily *cis* relationship of the methyl group and one of the carbomethoxy groups. The bonds of the cyclobutane ring are all expected to be about equally easily cleaved in the absence of this steric compression, but when it is present one would expect that the cyclobutane bond between the substituent groups would have a greater tendency to cleave, as observed.

The presence of the *m/e* 122 fragment is of especial interest because it can be formulated as arising by the loss of the elements of two molecules of methanol with formation of an unusual but probably highly stabilized α-ketenylacylium ion.



122 (69)

Dimethyl 1-cyanocyclobutane-1,2-dicarboxylate (**5**) shows ring cleavage only in one set of bands. As in the preceding case, this can be explained by steric compression between the *cis* groups on the adjacent carbon atoms, so that we observe fragments represented by cyanoacrylate and acrylate moieties.



This work definitely showed that mass spectroscopy can be used to advantage in identification of cyclobutane derivatives since peaks which arise from ring cleavage are always present in large relative abundances. By knowing the functional groups and a few basic principles of fragmentation as set forth by Biemann,[7] one should be able to assign with certainty the structure of unknown unsymmetrical cyclobutane derivatives. The observation that steric compression seems to play a role in determining the relative amount of fragmentation in each of the two possible senses might, with proper care, be useful in making stereochemical assignments in this series when the spectra of all the isomers are compared.

Experimental Section

The mass spectra were obtained on a Bendix time-of-flight Model 12-100 mass spectrometer operating at a nominal 70 ev.[9]

The dimethyl 3-methylcyclobutane-1,2-dicarboxylate (**1**) was obtained as described in the accompanying paper. Dimethyl 1-cyanocyclobutane-1,2-dicarboxylate (**5**) prepared according to the method of Buchman, *et al.*,[4] was kindly provided by Dr. C. E. Reineke.[10]

Preparation of Dimethyl 2-Methylcyclobutane-1,1-dicarboxylate (3).—A sample of 2-methylcyclobutane-1,1-dicarboxylic acid (0.25 g, 1.58 moles) was combined with 15 ml of boron trifluo-

(8) L. D'Or, J. Momigny, and P. Natailis in "Advances in Mass Spectroscopy," R. M. Elliot, Ed., The Macmillan Co., New York, N. Y., 1963, pp 370–376.

(9) E. J. Gallegos and R. W. Kiser, *J. Am. Chem. Soc.*, **83**, 773 (1961).

(10) C. E. Reineke, Ph.D. Thesis, Kansas State University, 1966.

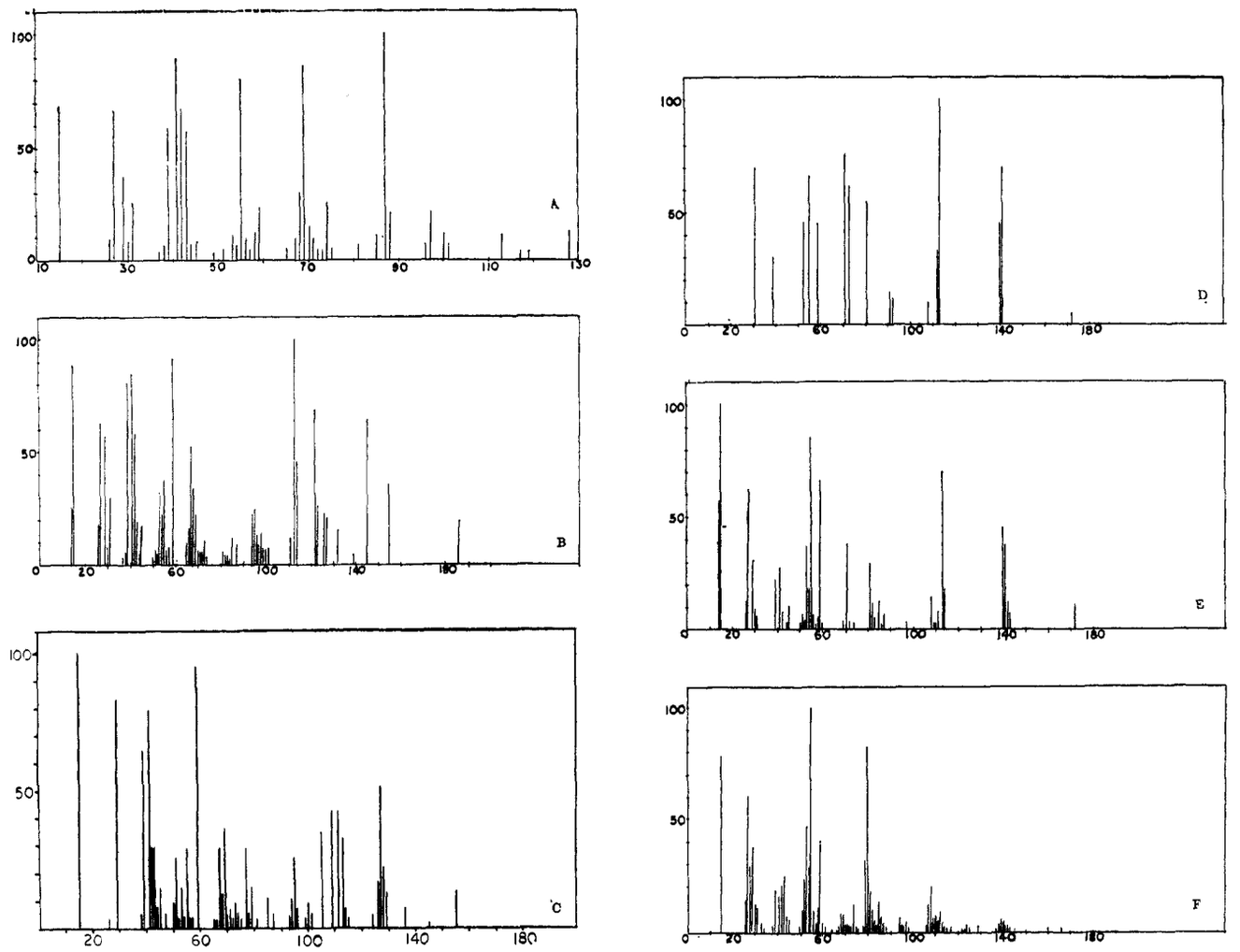


Figure 1.—Mass spectra of (A) methyl 2-methylcyclobutane carboxylate (**4**), (B) dimethyl 2-methylcyclobutane-1,1,dicarboxylate (**3**), (C) dimethyl 3-methylcyclobutane-1,2-dicarboxylate (**1**), (D) *cis*-dimethyl cyclobutane-1,2-dicarboxylate (only the major fragments are shown) (**7**), (E) *trans*-dimethyl cyclobutane-1,2-dicarboxylate (**6**), and (F) dimethyl 1-cyanocyclobutane-1,2-dicarboxylate (**5**).

ride–methanol reagent[11] and heated for 1 hr on a steam bath. A mixture of 20 ml of water and 10 ml of ether was added and the ether layer was separated, washed with 10 ml of 5% sodium bicarbonate solution, dried over magnesium sulfate, and distilled. A water-white liquid sample of **1** was obtained: 0.2 g, 69% yield, bp 83–85° (6 mm), $n^{21.5}$D 1.4389.

Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 57.89; H, 7.84.

Preparation of Methyl 2-Methylcyclobutanecarboxylate (4).—A sample containing 2-methylcyclobutanecarboxylic acid and 2-methylcyclobutane-1,1-dicarboxylic acid, obtained from the mother liquors from crystallization of the latter,[4] was distilled through a 5-in. Vigreux column at atmospheric pressure to effect decarboxylation. The bath temperature was 220–230°. A water-white liquid sample (0.33 g) of 2-methylcyclobutanecarboxylic acid, bp 197–199 (lit.[12] 200°), was obtained.

The 2-methylcyclobutanecarboxylic acid (0.33 g, 2.9 moles) was combined with 8 ml of boron trifluoride–methanol reagent.[11] The mixture was boiled for 5 min. A mixture of 20 ml of water and 10 ml of ether was added, and the ether layer was separated, dried over magnesium sulfate, and distilled. A water-white liquid sample of **4** was obtained: 0.35 g, 94.5% yield, bp 143–145° (1 atm), $n^{21.5}$D 1.4241.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.63; H, 9.38. Found: C, 65.43; H, 9.39.

Preparation of *trans*-Dimethyl Cyclobutane-1,2-dicarboxylate (6).—The liquid isomer of dimethyl 1-cyanocyclobutane-1,2-dicarboxylate (14.45 g, 73.4 mmoles) was refluxed with 40 ml of 6 *N* hydrochloric acid for 24 hr. The aqueous solution was concentrated under water vacuum, washed twice with ether, and continuously extracted with ether. Evaporation of the combined ether layers gave a white, crystalline solid: 7.93 g, 75% crude yield.

The 1,1,2-cyclobutanetricarboxylic acid was heated at 170–180° (20 mm) for 3 hr. One-half of the 1,2-cyclobutanedicarboxylic acid thus obtained was removed and chromatographed through a wet silica gel column,[13] eluting with chloroform–*t*-butyl alcohol mixtures. The *trans* acid obtained in the first two fractions was recrystallized from 20:1 benzene–dioxane, mp 129–130° (lit.[14] 131°). The acid was esterified using an ether solution of diazomethane. The excess diazomethane was destroyed with acetic acid. The ether was removed through a rotary evaporator and the residue was put under a 5-mm vacuum at room temperature to remove the excess acetic acid. The *trans* ester was distilled through a 5-in. Vigreux column, bp 45–46° (0.15 mm).

Preparation of *cis*-Dimethyl Cyclobutane-1,2-dicarboxylate (7).—The remaining half of the decarboxylation reaction was refluxed overnight with 50 ml of acetyl chloride. The excess acetyl chloride and the acetic acid formed were distilled from the anhydride. Cyclobutane-1,2-dicarboxylic acid anhydride (2.03 g, 16.1 moles) and water (1.62 g, 90 moles) were brought to boiling. The mixture was poured into a beaker and cooled in an ice bath to promote crystallization. The first crop of crystals, 1.26 g, mp 136–138° (lit.[14] 137–138°), was esterified with an ether solution of diazomethane. The ether was washed with 5% sodium carbonate solution, dried over magnesium sulfate, and evaporated.

(11) L. D. Metcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961).
(12) N. Rabjohn, M. F. Drumm, and R. L. Elliott, *J. Am. Chem. Soc.*, **78**, 1631 (1956).
(13) C. S. Marvel and R. C. Rands, Jr., *ibid.*, **72**, 2642 (1950).
(14) W. H. Perkin, Jr., *J. Chem. Soc.*, **65**, 572 (1894).

The ester was distilled to give 1.31 g of water-white liquid: 87.5% yield, $n^{20.5}D$ 1.4450 (lit.[15] $n^{20}D$ 1.4430).

Mass Spectra.—The mass spectra of the six cyclobutanes are presented in Figure 1. In the spectrum of dimethyl 3-methylcyclobutane-1,2-dicarboxylate, peaks at *m/e* 172, 184, 185, and 186, were apparent only at low voltage. Similarly in the spectrum of dimethyl 1-cyanocyclobutane-1,2-dicarboxylate, peaks at *m/e* 172 and 182 were present only as traces, and the parent *m/e* 197 was not observed at 70 ev.

(15) G. J. Ostling, *J. Chem. Soc.*, **101**, 457 (1912).

Acknowledgment.—This work was supported by a grant (1324) from the Petroleum Research Fund. We gratefully acknowledge the support provided by the donors of this fund. We are indebted to Mr. D. L. Dugger and Drs. L. A. Shadoff and R. E. Winters who determined the spectra for us.

Heterocyclic Ring-Closure Reactions. I. A Novel Oxazole Synthesis from S,S'-Dialkyl or -Diaryl Dithiooxaldiimidates and Aromatic Aldehydes[1a]

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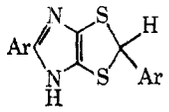
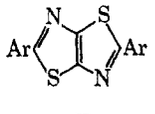
Received May 24, 1966

S,S'-Diaryl or -dialkyl dithiooxaldiimidates were found to react with aromatic aldehydes to give 5-benzylideneamino-4-aryl- or -alkylmercapto-2-aryloxazoles. In some cases *p*-nitrobenzaldehyde afforded the free amine. Mild acid hydrolysis converted the Schiff bases to α-alkylmercaptohippuronitriles. More vigorous conditions gave the α-alkylmercaptohippuramides. These were desulfurized to the known hippuronitriles and hippuramide.

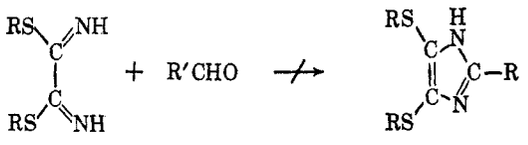
One possible *a priori* product of the thermal condensation of dithiooxamide and an aromatic aldehyde is the unsymmetrical structure I. The reaction, in fact, afforded symmetrical, fully aromatized diarylthiazolothiazoles[2] (II). As part of an investigation of possible methods for preparing structures of type I, we studied the condensations of S,S'-disubstituted dithiooxaldiimidates III with aldehydes. Elemental analyses of the yellow, crystalline substances obtained from aromatic aldehydes indicated that the expected products IV were not obtained. The sulfur:nitrogen ratio was 1:2 rather than the expected 1:1, thus indicating the loss of one sulfur function from III. It was further apparent that 2 moles of aldehyde had reacted with 1 mole of III, accompanied by loss of 1 mole each of mercaptan and water.



I



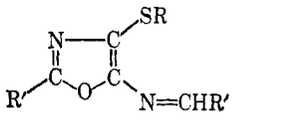
II



IIIa, R = CH_3
b, R = $C_6H_5CH_3$
c, R = C_6H_5

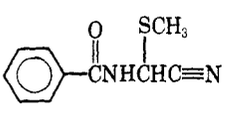
IV

These observations were best explained by structural formula V.[3] The nmr and ultraviolet spectra (the latter were very similar to the spectra of diphenylthiazolothiazoles II) are consistent with the proposed structures.

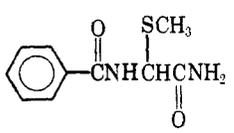


Va, R = CH_3; R' = C_6H_5
b, R = $C_6H_5CH_2$; R' = C_6H_5
c, R = C_6H_5; R' = C_6H_5
d, R = CH_3; R' = *p*-$MeOC_6H_4$
e, R = C_6H_5; R' = *p*-$O_2NC_6H_4$

The condensation product Va was rapidly and irreversibly destroyed by acid. The hydrolysis products were benzaldehyde and α-methylmercaptohippuronitrile (VI) or α-methylmercaptohippuramide (VII). These structures were converted by desulfurization to the known hippuric acid derivatives. The *nmr* spectrum of the nitrile VI is consistent with this structural assignment. These uniquely substituted glycine derivatives would appear to be unavailable by any direct route.

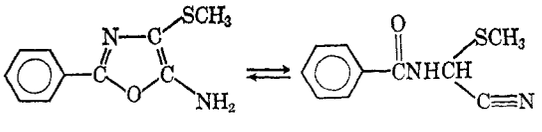


VI



VII

An effort was made to prepare the aminooxazole VIII, a suspected intermediate in the formation of Va. When benzaldehyde was added to a slight excess of S,S'-dimethyl dithiooxaldiimidate, a mixture of Va and the nitrile VI was isolated. The nitrile thus appears to be the more stable member of the ring–chain tautomeric system, VIII ↔ VI, if indeed, the free amine is ever formed.



VIII VI

(1) (a) Supported by National Institutes of Health Training Grant 5 TI GM 728 and National Institutes of Mental Health Grant MH 08787. The nmr spectra were determined on an instrument purchased with funds supplied by the National Science Foundation (NSF-G-21268). (b) A portion of the Ph.D. thesis of A. R. M. (c) To whom inquiries should be sent.

(2) J. R. Johnson and R. Ketcham, *J. Am. Chem. Soc.*, **82**, 2719 (1960).

(3) This structure was first suggested by Dr. J. F. Oneto of this department.