Enamine Chemistry. IV. Cycloaddition Reactions of Enamines Derived from Aldehydes and Acyclic Ketones[1,2]

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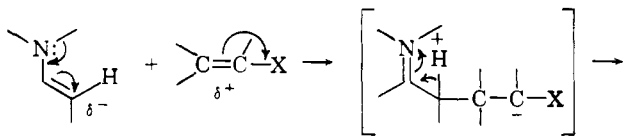
A variety of enamines, both with and without β-hydrogens, react with electrophilic olefins to give cyclobutane derivatives. This reaction is quite sensitive to steric effects, and its scope is discussed. Some further transformations of the cyclobutanes also are discussed.

Since the work of Stork and his co-workers first appeared,[3] enamines have found increasingly important uses in organic syntheses. The Stork alkylation of enamines by electrophilic olefins depends on the presence of a β-hydrogen in the enamine. Thus, the transfer



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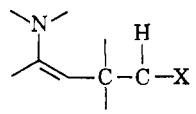
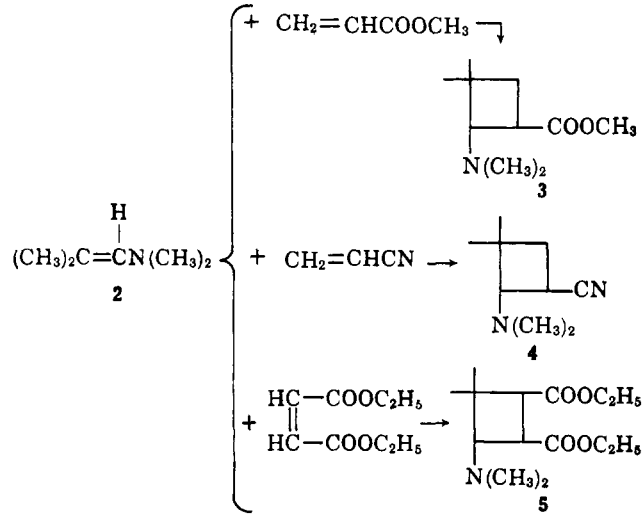


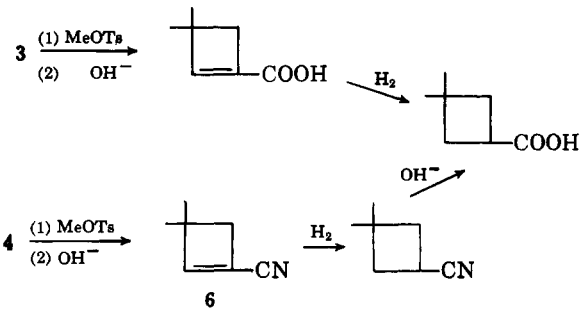
of the proton (which was originally the β-hydrogen of the enamine) in the zwitterionic intermediate (**1**) leads to its stabilization and to the products obtained by Stork. Our original purpose in the work described in this paper was to determine what course the reaction of electrophilic olefins with enamines containing no β-hydrogens would take. We found that reaction did indeed occur, leading to the formation of cyclobutanes, presumably *via* the collapse of a zwitterionic intermediate similar to **1**. We later found that the absence of β-hydrogens was not essential for cycloaddition to occur within certain limitations as to choice of reactants and conditions. The present paper deals with cycloaddition reactions of enamines derived from a variety of aldehydes and one acyclic ketone.

Cycloadditions of Enamines without β-Hydrogens.—We chose as a model compound the first of the series of enamines having no β-hydrogens: N,N-dimethylisobutenylamine (**2**), derived from isobutyraldehyde and dimethylamine. Compound *2* was found to react with methyl acrylate to give the cyclobutane **3** in 75% yield on heating the reactants for 2 hr. at 170° in an autoclave or, better, in 91% yield by refluxing for 2 hr. at 85° in acetonitrile.

Similarly, **4** is obtained from 2 and acrylonitrile in 64% yield after 2 hr. at 170°, and **5** is obtained from 2 and diethyl maleate (or fumarate, since the maleate is rapidly converted to fumarate in the presence of the enamine) in 70% yield after 20 hr. at reflux, beginning at 110° and ending at 170°.[4]



The structures of **3** and **4** were confirmed by their conversion to 3,3-dimethylcyclobutanecarboxylic acid, as shown schematically.[5]



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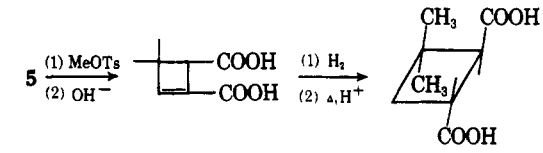
The structure of adduct **5** was confirmed by its conversion to *trans*-norcaryophyllenic acid.



(1) A portion of the material in this paper was presented at the Enamine Chemistry Symposium, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept., 1961.

(2) A preliminary announcement of this work has been made: K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, *J. Org. Chem.*, **26**, 625 (1961).

(3) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954). For a more complete review, see G. Stork, H. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(4) Similar reactions between diethyl maleate and enamines with no β-hydrogens were reported by A. G. Cook, doctoral dissertation, University of Illinois, 1959.

(5) While the unsaturated nitrile **6** can be distilled readily under reduced pressure, attempted distillation at atmospheric pressure leads to a vigorous, exothermic reaction in which the Diels–Alder dimer of the ring-opened product is obtained. Caution should be used when subjecting compounds similar to **6** to elevated temperatures.

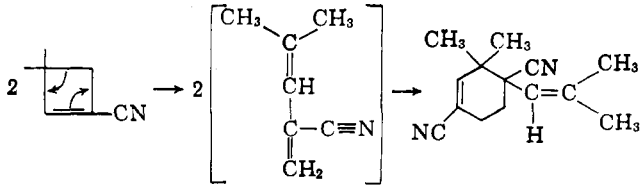
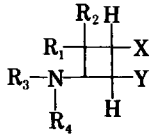
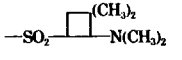
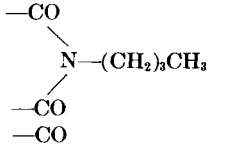
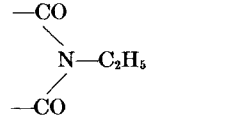


TABLE I

CYCLOBUTANES PREPARED FROM ENAMINES HAVING NO β-HYDROGEN ATOMS

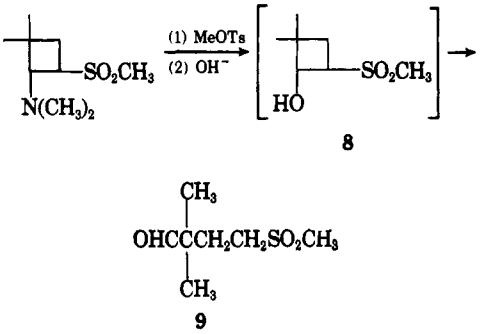


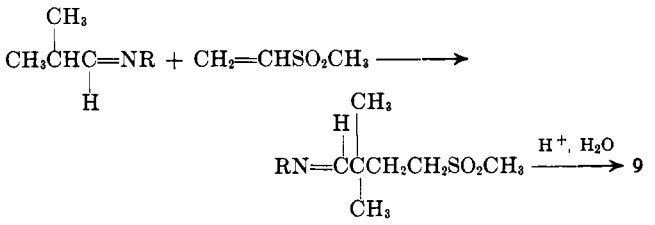
R_1	R_2	R_3	R_4	X	Y	B.p. °C.	B.p. mm.	M.p., °C.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Found C	Found H
CH_3	CH_3	$(CH_2)_5$		H	CN	73–77	1–2		1.4775	62	F	75.0	10.4	75.3	10.5
CH_3	CH_3	CH_3	CH_3	H	CN	44–45	0.5–1		1.4531	64	F	71.0	10.6	70.9	10.6
CH_3	CH_3	$(CH_2)_5$		H	CO_2CH_3	91–92	2		1.4705	72	F	69.3	10.3	69.4	10.5
CH_3	CH_3	CH_3	CH_3	H	$CO_2CH(CH_3)_2$	62–70	2		1.4418	51	F	68.7	11.1	68.7	11.3
CH_3	CH_3	C_2H_5	C_2H_5	H	$CO_2C_2H_5$	56–65	<1		1.4453	30	F	68.7	11.1	68.3	11.5
C_2H_5	C_2H_5	$(CH_2)_5$		H	CO_2CH_3	119–121	2		1.4788	20	F	71.0	10.7	71.1	10.7
CH_3	CH_3	$CH_2CH_2OCH_2CH_2$		H	CO_2CH_3	99–102	2.2		1.4711	35	F	63.5	9.3	63.4	9.2
CH_3	CH_3	*b*		H	CO_2CH_3			148		22	F	65.5	9.4	65.4	9.4
$(CH_2)_5$		$(CH_2)_5$		H	CO_2CH_3	115–120	1.5		1.4963	63	F	72.4	10.3	72.2	10.3
CH_3	CH_3	$CH_3(CH_2)_2CH_2$	$CH_3(CH_2)_2CH_2$	H	CO_2CH_3	98–110	1.5		1.4543	18	F	71.3	11.6	71.8	11.7
CH_3	CH_3	CH_3	$C_6H_5CH_2$	H	CO_2CH_3	96–105	1.5		1.5062	49	F	73.5	8.9	73.3	8.9
CH_3	CH_3	$(CH_2)_5$		$CO_2C_2H_5$	$CO_2C_2H_5$	113–120	1		1.4660	51	F	65.6	9.4	65.4	9.1
CH_3	CH_3	$(CH_2)_5$		C_6H_5	NO_2			71–73		68	E	70.8	8.4	70.6	8.5
CH_3	CH_3	CH_3	CH_3	C_6H_5	NO_2			90–92		94	E	67.7	8.1	67.9	8.3
CH_3	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	C_6H_5	NO_2			95–96.5		50	E	78.0	7.1	77.9	7.2
CH_3	CH_3	CH_3	CH_3	H	SO_2CH_3	100–103	0.5–0.6			91	F	52.7	9.3	52.2	9.2
CH_3	CH_3	CH_3	CH_3	CN	CN	99–100	0.75		1.4705	73	E	67.8	8.5	67.7	8.5
CH_3	CH_3	CH_3	CH_3	H				80–85		85	E	60.6	10.0	60.7	10.0
CH_3	CH_3	CH_3	CH_3	H	$CO_2CH_2CH{=}CH_2$	55.5–58	*ca.* 0.2		1.4528	75	F	68.3	10.0	67.9	10.0
CH_3	CH_3	CH_3	CH_3			110–120	*ca.* 0.5		1.4828	51	E	66.6	9.6	66.7	9.6
CH_3	CH_3	CH_3	CH_2			96–103	*ca.* 0.5		1.4853	53	E	64.2	9.0	63.9	8.6

$(CH_2)_5$	CH_3	H	CO_2CH_3			1.4765	83		F	68.9	10.3	69.2	10.0
CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$	H	CO_2CH_3	111–116	0.7–0.69	1.4904	*ca.* 75–80		F	72.4	10.3	72.1	10.4
CH_3	CH_3		$(CH_2)_6$				75		F	70.3	10.5	70.4	10.4
CH_3	CH_3	H	CO_2CH_3	79–84	0.3–0.5								
CH_3	C_6H_5	CH_3											
		H	CO_2CH_3	102–108	0.3	1.5194	33		F	73.0	8.5	72.7	8.7
	$(CH_2)_5$	CH_3											
		H	$CO_2C_2H_5$	116–125	0.5	1.4753	71		F	65.6	9.4	65.9	9.4
CH_3	CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$											
		$CO_2C_2H_5$	$CO_2C_2H_5$	148–154	0.4–0.65	1.4830	72		F	68.3	9.5	68.1	9.4
CH_3	CH_3	$CH_2CH_2N(CH_3)CH_2CH_2$											
		$CO_2C_2H_5$	$CO_2C_2H_5$	120–125	0.5	1.4698	30		F	62.5	9.3	62.1	9.2
CH_3	CH_3	$CH_2CH_2OCH_2CH_2$											
		H	CN	94	0.7		72		G	68.0	9.3	68.2	9.4
CH_3	CH_3							71–72					
		CH_3	$CH(CH_3)_2$				74		E	61.6	10.3	61.7	10.3
CH_3	$CH_2N(CH_2)_4$												
		H	NO_2	123–126	0.3	1.4960	68		G	68.6	10.1	68.9	10.3
	$(CH_2)_4$												
		H	CO_2CH_3	60–61	0.3	1.4519	69		G	67.7	10.8	68.2	10.8
CH_3	$CH_3(CH_2)_2$												
		H	CO_2CH_3	45–47	0.3–0.4	1.4551	45		G	68.3	10.0	68.1	10.1
CH_3	CH_3	CH_2=$CHCH_2$											
		H	CO_2CH_3	120–123	0.1	1.5041	74		G	74.7	9.4	74.9	9.6
CH_3	CH_2	$C_6H_5CH_2CH(CH_3)$											
		H	$CO_2C_2H_5$	92	7×10^{-6}[a]	1.4920	41		F	69.8	8.6	69.6	8.6
CH_3	CH_3	$C_6H_5CH_2CH_2$											
		$CO_2C_2H_5$	$CO_2C_2H_5$	89–96	10^{-4}[a]	1.4979	45		G	70.4	8.9	70.2	8.6
CH_3	CH_3	$C_6H_5CH_2CH(CH_3)$											
		$CO_2C_2H_5$	$CO_2C_2H_5$	93–96	*ca.* 0.1	1.4589	77		G	64.7	9.2	64.2	9.1
CH_3	CH_3	CH_2=$CHCH_2$											
		$CO_2C_2H_5$	$CO_2C_2H_5$	92	9×10^{-6}[a]	1.4848			G	65.6	9.4	65.3	9.4
CH_3	$CH_2N(CH_2)_4$												
		$CO_2C_2H_5$	$CO_2C_2H_5$	103–107	0.3	1.4559	44		F	64.2	9.8	64.1	9.8
CH_3	$CH_3(CH_2)_2$	CH_3											

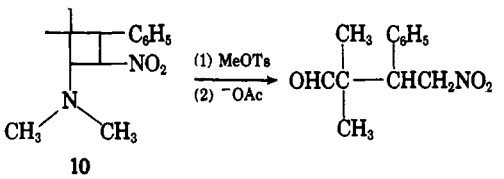
[a] Compound had to be molecularly distilled. [b] $(CH_3)_2$ $COOCH_3$ $-CH_2CH_2NCH_2CH_2$

Compound **2** reacted with methyl vinyl sulfone to give adduct **7** in 91% yield after 1.5 hr. at reflux, beginning at 90° and ending at 160°. Quaternization of **7** and treatment with base led to aldehyde **9**, presumably through dealdolization of **8**. Compound **9** was independently prepared by the reaction of methyl vinyl sulfone with a Schiff base of isobutyraldehyde, followed by hydrolysis.





Compound **2** reacted vigorously with β-nitrostyrene to give adduct **10** in 94% yield. Quaternization of

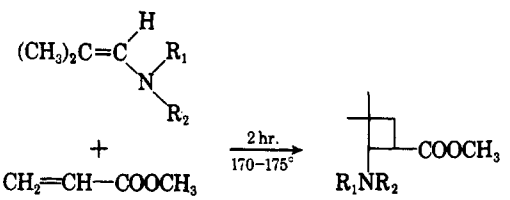


10 and treatment with a weak base, such as sodium acetate or bicarbonate, gave the ring-opened aldehyde in poor yield. A number of other adducts from enamines containing no β-hydrogens are listed in Table I.

Scope of the Reaction.—The effect of structure change in either the aldehyde or secondary amine from which the enamine is prepared is similar. Table II

TABLE II

EFFECT OF AMINE MOIETY ON YIELD OF CYCLOBUTANE



R_1	R_2	Yield %
CH_3	CH_3	75
CH_3	—C=C—C—	45
C_2H_5	C_2H_5	30[a]
C_4H_9	C_4H_9	18
CH_3	$C_6H_5CH_2$	49
$R_1 + R_2$ =	$(CH_2)_5$	72
$R_1 + R_2$ =	$CH_2CH[CH_2CH_2]_2CHCH_2$	75
$R_1 + R_2$ =	$CH_2CH_2OCH_2CH_2$	35

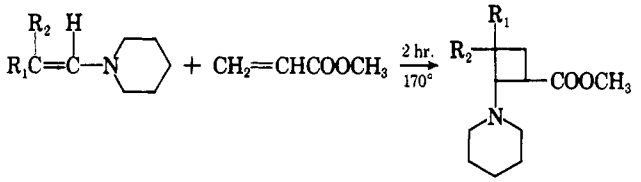
[a] Ethyl acrylate was used instead of methyl acrylate.

shows the yield of cyclobutane obtained from a series of isobutyraldehyde enamines and methyl acrylate under comparable reaction conditions, that is, 2 hr. at 170–175°. The yield falls off rapidly with increasing chain length of the aminoalkyl groups as shown for the first three adducts. The fifth enamine, from benzylmethylamine, is intermediate in reactivity, while the sixth and seventh, from piperidine and azabicyclononane, are comparable to the dimethyl enamine. Finally, the morpholine enamine is considerably less reactive in these cycloaddition reactions.

The effect of the structure of the aldehyde is illustrated in Table III for a series of piperidine enamines. As shown, the yield of adduct drops sharply on going from isobutyraldehyde to 2-ethylbutyraldehyde but rises again when the groups are tied into a ring as with cyclohexanecarboxaldehyde.

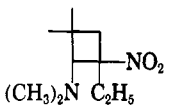
TABLE III

EFFECT OF ALDEHYDE MOIETY ON YIELD OF CYCLOBUTANE



R_1	R_2	Yield %
CH_3	CH_3	72
C_2H_5	C_2H_5	30
$R_1 + R_2$ =	$(CH_2)_5$	63

The effect of the structure of the electrophilic olefin on the cycloaddition reaction is indicated by the following observations. In the reactions involving α,β-unsaturated esters and nitriles, we have never isolated any cyclobutanes from methyl methacrylate, methyl crotonate, methyl cinnamate, or the corresponding nitriles. The reaction is, therefore, highly sensitive to steric effects, which can be overcome by using a more powerful electron-withdrawing group to activate the olefin. Typical of such groups is the nitro group, as in β-nitrostyrene or 2-nitro-1-butene. Like β-nitrostyrene, the latter reacts exothermically with **2** to give an excellent yield of the adduct **11**. This adduct, however, is

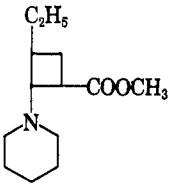


11

extremely sensitive to moisture, a property which appears to be characteristic of cyclobutanes which are derived from similar α-substituted electrophilic olefins. The reaction of **11** with water leads to the loss of dimethylamine and to ring opening, as will be discussed later.

Cycloadditions of β-Hydrogen-Containing Enamines.—We were surprised to find that β-hydrogen-containing enamines derived from aldehydes or the only acyclic ketone studied, 3-pentanone, also undergo cycloaddition reactions. In general, the reaction is carried out under milder conditions than those involving enamines containing no β-hydrogens because of the decreased stability of both the enamines and the cyclobutanes.

For example, the piperidine enamine of butyraldehyde gave, with methyl acrylate, the cyclobutane **12** in 83% yield when the reaction was carried out in acetonitrile for 2 days at room temperature, in 82% yield after 3 hr. of refluxing in acetonitrile, and in 57% yield after standing for 1 day in methanol[6] at room temperature.



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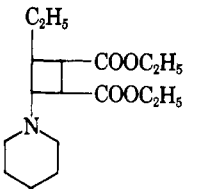
The butyraldehyde piperidine enamine reacted with diethyl maleate to give adduct **14** in 45% yield after standing for 1 day at room temperature in acetonitrile.



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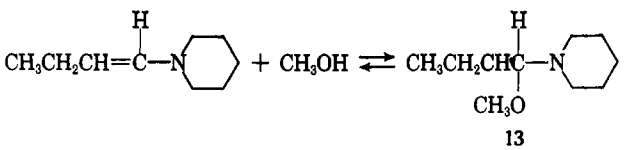
The cycloaddition products derived from the 3-pentanone enamine were perhaps the least stable thermally of any studied. Most of the β-hydrogen enamine adducts begin to dissociate at temperatures roughly in the range of 125–170°, depending on the structure, to the reactants from which they were prepared. Generally, if the reactants are not removed as formed, recombination can occur to give the products derived from the Stork-alkylation reaction. It is, therefore, sometimes necessary to resort to molecular distillation for purification, and sometimes the crude products must be used for further transformations.

The structure proofs of the β-hydrogen enamine adducts were analogous to those used for the no β-hydrogen enamine adducts, though the detailed experimental procedures were frequently different (see Experimental). Table IV lists some typical examples of cyclobutanes prepared from β-hydrogen enamines.

Mechanism of the Reaction.—Little can be said about the detailed mechanism of these cycloaddition reactions, but the following observations are pertinent. Enamines give with diethyl maleate (or fumarate) an orange-red color which fades considerably on completion of the cycloaddition reaction.[7] With the more reactive nitro olefins and acetylenic esters,[8] intense red

(6) As a point of interest, the piperidine enamine of butyraldehyde reacts exothermically with methanol to give the butyraldehyde O,N-acetal (**13**), which can be distilled at low pressure and temperature. The reaction is obviously reversible, however. The isobutyraldehyde enamine (**2**) did not



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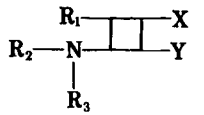
react spontaneously with methanol but did react on the addition of a trace of acid.

(7) This also was observed by A. G. Cook, ref. 4.

(8) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

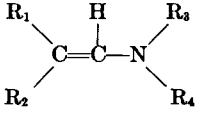
Table IV.—Cyclobutanes Prepared from Enamines Having a β-Hydrogen Atom



R_1	R_2	R_3	X	Y	B.p. °C.	B.p. mm.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_2H_5	$(CH_2)_5$		H	CO_2CH_3	87–89	0.5	1.4734	82	A	69.3	10.3		69.6	10.3	
CH_3	$(CH_2)_5$		H	CO_2CH_3	70–75	0.5	1.4741	67	A			6.6			6.6
C_2H_5	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	95–98	0.8	1.4482	78	B			4.9			5.2
CH_3	CH_3	CH_3	H	CO_2CH_3	55–58	3.0–3.5	1.4437	32	A	63.1	10.0		63.1	10.0	
C_2H_5	CH_3	CH_3	H	CO_2CH_3	52–53	1	1.4454	87	A			7.6			7.6
$(CH_3)_2NCH_2$	CH_3	CH_3	H	CO_2CH_3	78–82	0.75	1.4592	55	B	61.6	10.3		61.7	10.2	
C_5H_{11}	$CH_2CH_2OCH_2CH_2$		H	CO_2CH_3	125–130	1	1.4725	70	A			5.2			5.3
CH_3	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	86–87	0.5	1.4463	30	B	60.7	9.0		60 6	9.2	
C_2H_5	$(CH_2)_5$		$CO_2C_2H_5$	$CO_2C_2H_5$	69–70	10^{-4}[a]	1.4686	45	B			4.5			4.4
$(CH_3)_2NCH_2$	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	42–50	$(6 \times 10^{-6}$–$12 \times 10^{-6})$[a]	1.4562	33	B	60.0	9.4		59.9	9.2	
C_6H_5	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	78–80	10^{-6}[a]	1.5015	32	B	67.8	7.9		68.0	7.9	
C_2H_5	$(CH_2)_5$		H	CN	85–90	*ca.* 0.5	1.4830	53	B	74.9	10.5		74.8	10.4	
C_5H_{11}	$(CH_2)_4$		H	CN	116–120	*ca.* 0.5	1.4783	33	A	76.4	11.0		75.8	11.1	
CH_3	$(CH_2)_5$		H	SO_2CH_3	127–130	0.5	1.4954	57	A			6.6			6.1
$(CH_3)_2N$	CH_3	CH_3	H	CO_2CH_3	63–67	0.3–0.4	1.4586	40	A	60.0	10.0		59.8	10.0	
$CH_2N(CH_2)_5$	$(CH_2)_5$		H	CO_2CH_3	57	8×10^{-6}[a]	1.4990	39	B	69.3	10.3		69.2	10.3	
$CH_2N(CH_2)_5$	$(CH_2)_5$		$CO_2C_2H_5$	$CO_2C_2H_5$	66	6×10^{-6}[a]	1.4857	33	B	66.4	9.9		66.7	9.6	

[a] Compound had to be molecularly distilled.

Table V.—New Enamines Prepared in This Investigation

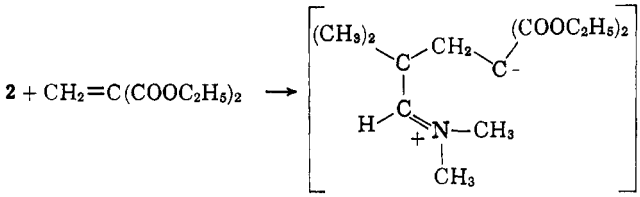


R_1	R_2	R_3	R_4	B.p. °C.	B.p. mm.	$n^{20}D$	Yield %	Method of preparation	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	CH_3	CH_3	CH_3	40–45	200	1.4293	46	B			16.4			16.3
$(CH_2)_5$		CH_3	CH_3	171–172.5	atm.	1.4747	30	A	77.7	12.3		77.2	12.2	
CH_3	C_6H_5	CH_3	CH_3	51–53	0.2		66	A			8.7			8.5
CH_3	$CH_3CH_2CH_2$	CH_3	CH_3	134–136	atm.	1.4332	54	A			11.0			10.5
CH_3	CH_3	C_4H_9	C_4H_9	72	4.5–5.0	1.4409	63	C	78.6	13.7		78.4	13.7	
CH_3	CH_3	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2$	64	5.8	1.4375	57	C	78.7	13.7		78.5	14.1	
CH_3	CH_3	CH_3	$C_6H_5CH_2$	45	*ca.* 0.5	1.5145	80	C	82.3	9.8		82.3	10.0	
CH_3	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	110–114	0.8	1.5591	28	C	85.9	8.4		85.5	8.4	
CH_3	CH_3	$CH_2CH[CH_2CH_2]_2CHCH_2$		70–74	1.3–2.0	1.5008	85	C	80.5	11.7		80.4	11.8	
CH_3	CH_3	$CH_2N(CH_2)_5$		38–40	1	1.4718	82	C	70.2	11.8		70.6	11.6	
$(CH_2)_5$		$(CH_2)_5$		75–88	1.5–3.0	1.5042	85	C	80.3	11.8		80.2	12.1	
C_2H_5	C_2H_5	$(CH_2)_4$		92–97	26–31	1.4773	78	C	78.3	12.5		78.0	12.4	
CH_3	CH_3	$(CH_2)_6$		106–108	48–50	1.4823	67	C			9.1			8.9
CH_3	$CH_2N(CH_2)_4$	$(CH_2)_4$		91	0.2	1.5076	50	D	74.3	11.3		73.8	11.9	
CH_3	CH_3	CH_3	$C_6H_5CH_2CH(CH_3)$	61–64	0.1–0.2	1.5099	94	C	82.8	9.9		83.0	9.9	
CH_3	CH_3	CH_3	$C_6H_5CH_2CH_2$	61–65	0.6	1.5063	88	C	82.4	10.1		82.8	10.0	

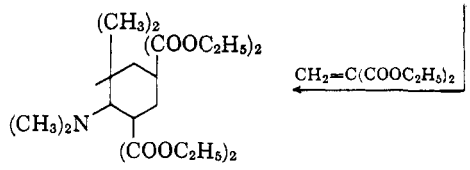
colors of a highly transient nature are observed on admixture with enamines. These colored materials may be charge-transfer complexes, but no further study has been given to them.

Based on our qualitative observations, the enamine cycloadditions are much more polar in nature than the usual Diels–Alder reaction, since they occur at a remarkably faster rate in polar solvents such as acetonitrile.[9]

The polar nature of the intermediate is further illustrated by the fact that **2** (and related enamines) reacts with diethyl methylenemalonate to give the adduct **16** derived from 2 moles of ester and 1 mole of enamine, even when the enamine is used in excess.



15

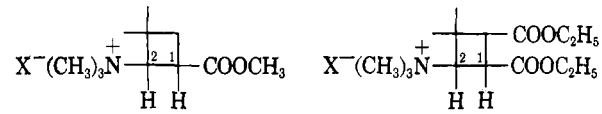


16

Thus, when the anionic center of the intermediate **15** is sufficiently stabilized (as in this malonate anion) and the electrophilic olefin is sufficiently free of steric hinderance (as with a terminal methylene group), intermediate **15** may react with another mole of electrophilic olefin rather than collapse to form the cyclobutane.[10]

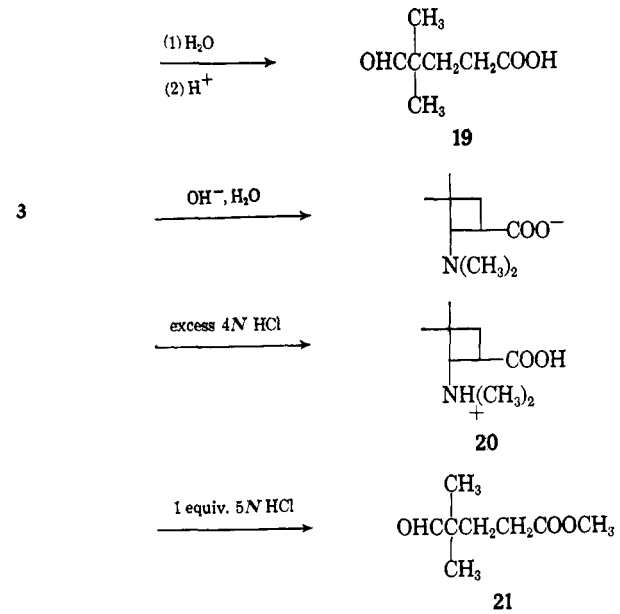
Stereochemistry of the Cyclobutanes.—As with the mechanism of the reaction, little can be said about the stereochemistry of the adducts. We did not observe any isomers of those adducts which are solids. Gas–liquid chromatography (g.l.c.) of adducts **3** and **5** did show the presence of *ca.* 5% of a second component in each adduct. This minor component also was found by g.l.c. to be less stable thermally than the major component and could be cracked almost preferentially to the reactants from which it was derived by raising the temperature of the vaporization chamber of the chromatography unit. The adducts corresponding to **3** and **5** but containing a piperidino group in place of the dimethylamino group showed a similar behavior, but with somewhat more of the less stable component. Whether these less stable isomers were formed in the original cycloaddition or arose by subsequent epimerization is not known.

The ease of elimination of trimethylamine from the quaternary salts of **3** and **5** led us to suspect that the hydrogen at C-1 is *trans* to the amine function at C-2.



Further evidence for this configuration was provided by treatment of **3** and **5** with hydrogen peroxide to prepare the amine oxides. If the hydrogen at C-1 were *cis* to the amine group, Cope elimination should occur quite readily. In both compounds, amine oxide formation took place along with a facile hydrolysis of the adjacent ester function, presumably with anchimeric assistance by the amine oxide. The resulting products (**17** and **18**) were quite stable.[11]

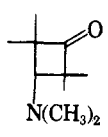
Some Reactions of the Cyclobutane Adducts.—Adduct **3** was found to undergo some remarkable ring-opening reactions. On refluxing with water, it gradually went into solution. Acidification then gave dimethylglutaraldehydic acid (**19**). Saponification with aqueous base apparently took place normally without ring opening, since acidification gave no insoluble material. Treatment of **3** with excess 4 *N* hydrochloric



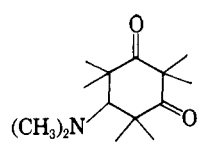
acid gave the amino acid hydrochloride (**20**),[12] while the use of an equivalent of 5 *N* hydrochloric acid gave the methyl ester of dimethylglutaraldehydic acid (**21**).

(9) For a similar observation involving cycloaddition reactions of tetracyanoethylene, see C. A. Stewart, Jr., *J. Am. Chem. Soc.*, **84**, 117 (1962). Unfortunately, nitromethane is not a good solvent for enamine reactions since it reacts with enamines.

(10) A borderline case is that reported by R. H. Hasek and J. C. Martin [*J. Org. Chem.*, **28**, 1468 (1963)] in which **2** reacts in nonpolar solvents with dimethyl ketene to give the cyclobutane, but in polar solvents such as acetonitrile to give the cyclobutane and some 2:1 adduct.



Cyclobutane



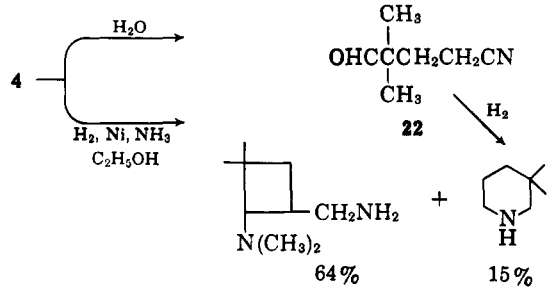
2:1 Adduct

(11) These experiments involving amine oxides were carried out by J. G. Thweatt and H. E. Davis.

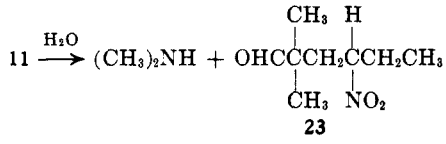
(12) We are indebted to Leonard Weintraub, of the Bristol-Myers Products Division, for disclosing this procedure to us.

With cyclobutanes derived from β-hydrogen enamines, ring-opening reactions analogous to the last one described would lead to the same products as those obtained by the usual Stork-alkylation procedure. This ring opening is not general, however, since adduct **5** does not undergo ring opening on heating with water or dilute acid.

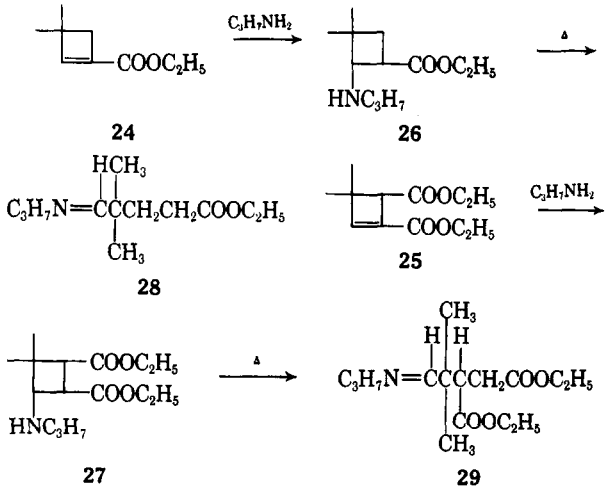
Adduct **4** also undergoes a hydrolytic ring opening to give the aldehydonitrile (**22**), while its hydrogenation over Raney nickel in alcohol and in the presence of anhydrous ammonia gives the expected amine along with some 3,3-dimethylpiperidine, which also is obtained by hydrogenation of **22**.



As mentioned previously, adduct **11** reacted so rapidly with moisture that it could not be purified for analysis. Exposure to air led to the loss of dimethylamine and the ring-opened aldehyde (**23**) was isolated as its 2,4-dinitrophenylhydrazone.



The cyclobutene esters (**24** and **25**) were both found to add primary amines (for example, propylamine) to give the unstable cyclobutanes **26** and **27**, respectively. Compounds **26** and **27** could be trapped as their stable acetyl derivatives, but on attempted distillation they underwent ring opening to **28** and **29**.



Products analogous to **28** and **29** were obtained by heating isobutyraldehyde Schiff bases with methyl acrylate and diethyl maleate, respectively. Although no enamine tautomer could be detected in these Schiff bases by n.m.r. spectroscopy, it is still interesting to consider the admittedly remote possibility that the Schiff bases react with the electrophilic olefins *via* cycloaddition of their enamine tautomers, followed by ring opening. A more plausible explanation, however, is the simple self-catalyzed Michael addition of the Schiff base to the unsaturated esters.

A number of derivatives of the cyclobutane adducts, which were prepared by standard methods and need not be discussed here, are described in the Experimental section.

Enamines.—The enamines used in this investigation are listed in Table V, and representative examples of their preparation are described in the Experimental section. It is of interest to note that 3,3-dimethylcyclobutanecarboxaldehyde reacted normally with piperidine to give the enamine, but cyclopropanecarboxaldehyde and piperidine gave the stable, distillable aminal, or N,N-acetal.[13]

Experimental[14]

Materials.—The following enamines were prepared by methods described in the literature: N,N-dimethyl-1-butenylamine,[15] 1-ethyl-N,N-dimethylpropenylamine,[16] N,N-dimethylstyrylamine,[17] N,N,N′,N′-tetramethyl-1-propene-1,3-diamine and 1,1′-propenylenedipiperidine,[18] 1-propenylpiperidine, 1-(1-butenyl)-piperidine,[19] 1-(1-heptenyl)morpholine,[20] 1-(1-heptenyl)pyrrolidine,[21] N-allyl-N-methylisobutenylamine,[22] N,N-dimethylisobutenylamine,[2] N,N-diethylisobutenylamine and 1-(2-ethyl-1-butenyl)piperidine,[23] 4-isobutenylmorpholine and N,N′-diisobutenylpiperazine,[24] and 1-isobutenylpiperidine.[19]

Table V contains a list of new enamines prepared during this investigation. Four different methods were employed; they are listed below with representative enamines prepared by the method.

Method A.—This method is the same as that previously described for the preparation of N,N-dimethylisobutenylamine.[22]

Method B.—N,N-Dimethylpropenylamine was prepared by adding propionaldehyde (191 g., 3.3 moles) over a 1.25-hr. period to a mixture of anhydrous dimethylamine (300 g., 6.6 moles), ether (250 ml.), and Linde No. 13X Molecular Sieve (300 g.), which had been cooled to −5°. During the addition, the mixture was stirred and its temperature was maintained at 0 ± 5°. The mixture was allowed to stand in a cold bath overnight and then was filtered. Distillation of the filtrate gave 130 g. (46%) of N,N-dimethylpropenylamine, b.p. 40–45° at 200 mm., $n^{20}D$ 1.4293.

Anal. Calcd. for $C_5H_{11}N$: N, 16.4. Found: N, 16.3.

Method C.—The method of Benzing[24] was used. It consists of refluxing a secondary amine with a slight excess of the appropriate aldehyde under a Dean–Stark trap and then recovering the enamine by distillation.

Method D.[25]—An ether solution of acrolein was treated with an excess of the secondary amine in the presence of potassium carbonate, and the enamine was recovered by distillation.

Cycloadditions of Enamines Containing No β-Hydrogen Atom.—A number of cyclobutanes were prepared from various electro-

(13) A similar observation has been made by Dr. Glenn A. Berchtold (private communication).

(14) Melting points were determined using a calibrated Fisher-Johns melting point apparatus. N.m.r. absorptions are reported in parts per million (p.p.m.) relative to tetramethylsilane. All structure assignments were supported by infrared and n.m.r. spectra. Spectral data for specific compounds are included when pertinent.

(15) S. Hünig, K. Hübner, and E. Benzing, *Ber.*, **95**, 92c (1962).

(16) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(17) J. W. Crary, Ph.D. thesis, Emory University, 1955.

(18) C. Mannich, K. Handke, and K. Roth, *Ber.*, **69**, 2112 (1936).

(19) C. Mannich and H. Davidsen, *ibid.*, **69**, 2106 (1936).

(20) P. L. de Benneville and J. H. Macartney, *J. Am. Chem. Soc.*, **72**, 3073 (1950).

(21) R. Dulou, E. Elkik, and A. Veillard, *Bull. soc. chim. France*, 967 (1960).

(22) K. C. Brannock and R. D. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961).

(23) G. Opitz, H. Hellmann, and H. W. Schubert, *Ann.*, **623**, 112 (1959).

(24) E. Benzing, *Angew. Chem.*, **71**, 521 (1959).

(25) C. Mannich and H. Davidsen, *Ber.*, **69**, 2112 (1936).

philic olefins and isobutyraldehyde-type enamines, that is, enamines having no hydrogen atom in the β-position. These cyclobutanes are listed in Table I. The more reactive electrophilic olefins reacted spontaneously with enamines to form cyclobutanes (method E), whereas the less reactive ones required heating to effect cycloaddition. The heating was done without a solvent (method F) at atmospheric pressure or in an autoclave (depending upon the nature of the starting materials) or by refluxing the reactants in the polar solvent acetonitrile (method G) at atmospheric pressure. An example of each is given below.

Method E. 3-Dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarbonitrile.—To fumaronitrile (51 g., 0.65 mole) was added N,N-dimethylisobutenylamine (70 g., 0.71 mole). The temperature of the mixture rose to a maximum of 86° after standing for 45 min. with intermittent swirling. The mixture was heated to 150° over 10 min. and then allowed to stand at room temperature overnight. Distillation through a 6-in. Vigreux column gave a small forerun followed by 84 g. (73%) of 3-dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarbonitrile, b.p. 99–100° at 0.75 mm., $n^{20}D$ 1.4705. On standing, the material crystallized. Recrystallization from hexane gave a solid, m.p. 64–66°.

Anal. Calcd. for $C_{10}H_{15}N_3$: C, 67.8; H, 8.5. Found: C, 67.7; H, 8.5.

Method F. Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate (3).—A mixture of N,N-dimethylisobutenylamine and methyl acrylate was heated for 2 hr. at 170°. Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate, b.p. 49–50° at 1.5 mm., $n^{20}D$ 1.4448, was obtained in 75% yield.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.4; N, 7.6. Found: C, 64.7; H, 10.4; N, 7.5.

Method G. Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate (3).—A mixture of methyl acrylate (129 g., 1.5 moles), N,N-dimethylisobutenylamine (50 g., 0.5 mole), and acetonitrile (200 ml.) was refluxed for 9 hr. An infrared spectrum of the mixture, after 4.5 hr., showed no absorption bands in the >C=C—N= region (6–6.2 μ). The mixture was distilled to give 84 g. (91%) of methyl 3,3-dimethyl-2-dimethylaminocyclobutane-1-carboxylate, b.p. 35–39° at 0.5–1 mm., $n^{20}D$ 1.4438.

Methyl 3,3-Dimethyl-2-piperidinocyclobutanecarboxylate.—A mixture of 1-isobutenylpiperidine (208.5 g., 1.5 moles) and methyl acrylate (158 g., 1.87 moles) containing some hydroquinone was heated in an autoclave for 2 hr. at 175°. Distillation of the reaction product gave 244 g. (72%) of crude methyl 3,3-dimethyl-2-piperidinocyclobutanecarboxylate, b.p. 91–92° at 2 mm. A sample for analysis was obtained by redistillation and had b.p. 103° at 3.6 mm., $n^{20}D$ 1.4705.

Anal. Calcd. for $C_{13}H_{22}NO_2$: C, 69.3; H, 10.3; N, 6.2. Found: C, 69.4; H, 10.5; N, 6.2.

3,3-Dimethyl-1-cyclobutene-1-carboxylic Acid.—Methyl 3,3-dimethyl-2-piperidinocyclobutanecarboxylate (45 g., 0.2 mole) and methyl *p*-toluenesulfonate (40.9 g., 0.22 mole) were combined and heated on the steam bath for 7 hr. and then allowed to stand for 16 hr. at room temperature. A solution of potassium hydroxide (44.8 g.) in water (50 ml.) was added to the solid salt, and the mixture was stirred for 30 min. while being heated on the steam bath. The mixture was cooled, extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. Evaporation of the ether extracts on the steam bath left 20.5 g. (81%) of crude 3,3-dimethyl-1-cyclobutene-1-carboxylic acid, which crystallized on cooling. The crude material was recrystallized from hexane (with Norit treatment) by cooling the hexane solution in a Dry Ice–acetone bath to give 16 g. (63.5%) of the acid, m.p. 70–71°. A sample for analysis, recrystallized from pentane, melted at 71.5–72.5°, lit.[26] m.p. 54–55°.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.4; H, 8.0.

Hydrogenation of the unsaturated acid in pentane over 5% palladium on alumina at 2 atm. gave 3,3-dimethylcyclobutanecarboxylic acid, which gave a *p*-bromophenacyl ester identical with that obtained from the nitrile as described below.

3,3-Dimethyl-2-piperidinocyclobutanecarbonitrile.—A mixture of 1-isobutenylpiperidine (69.5 g., 0.5 mole) and acrylonitrile (26.5 g., 0.5 mole) containing a pinch of hydroquinone was heated for 2 hr. at 175° in an autoclave. Distillation of the reaction mixture gave 17 g. of recovered enamine, b.p. 28–32° at 2.5–3 mm., and 59.5 g. of 3,3-dimethyl-2-piperidinocyclobutanecarbonitrile, b.p. 73–77° at 1–2 mm., $n^{20}D$ 1.4775.

Anal. Calcd. for $C_{12}H_{20}N_2$: C, 75.0; H, 10.4; N, 14.6. Found: C, 75.3; H, 10.5; N, 14.6.

Gas chromatography of the product on a Carbowax column at 200°, with the preheater at 200°, showed two components in approximately a 2:1 ratio. When the preheater temperature was raised to 300°, the second and smaller of the components was decomposed and appeared as two low-boiling components which were eluted rapidly from the column.

3,3-Dimethyl-1-cyclobutene-1-carbonitrile (6).—3,3-Dimethyl-2-piperidinocyclobutanecarbonitrile (108 g., 0.56 mole) and methyl *p*-toluenesulfonate (111 g., 0.6 mole) were combined and heated on the steam bath for 24 hr. Ethyl alcohol (100 ml.) was added to the glassy solid, and then a solution of potassium hydroxide (56 g., 1 mole) in 100 ml. of water was added. The mixture was stirred manually at 40–50° for 20 min. and then poured into 1 l. of water. The mixture was extracted with ether, which was then backwashed with dilute hydrochloric acid to remove the amine. Finally, after being washed with water, the ether layer was distilled to give 38.5 g. (64%) of 3,3-dimethyl-1-cyclobutene-1-carbonitrile, b.p. 52–53° at 20 mm., $n^{20}D$ 1.4440.

Anal. Calcd. for C_7H_9N: C, 78.5; H, 8.5; N, 13.1. Found: C, 78.2; H, 8.7; N, 12.9.

3,3-Dimethylcyclobutanecarbonitrile.—3,3-Dimethyl-1-cyclobutene-1-carbonitrile (9.8 g., 0.09 mole) in 50 ml. of pentane was hydrogenated over 0.1 g. of 5% palladium on alumina at 5–7° and 2 atm. After 15 min., 0.08 mole of hydrogen was absorbed. The reaction mixture was filtered and distilled to give 7.3 g. (74%) of 3,3-dimethylcyclobutanecarbonitrile, b.p. 85–86° at 53 mm., $n^{20}D$ 1.4289.

Anal. Calcd. for $C_7H_{11}N$: C, 77.0; H, 10.2. Found: C, 77.3; H, 10.3.

3,3-Dimethylcyclobutanecarboxylic Acid.—3,3-Dimethylcyclobutanecarbonitrile (6.5 g.) was combined with a solution of 10 g. of potassium hydroxide in 50 ml. of water and 25 ml. of ethyl alcohol and heated under reflux for 15 hr. An additional 25 ml. of water was added, and the alcohol was removed by distillation. The residue was acidified with concentrated hydrochloric acid and extracted with ether. The extract was distilled to give 6.8 g. of 3,3-dimethylcyclobutanecarboxylic acid, b.p. 98–99° at 9.5–10 mm., $n^{20}D$ 1.4363.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.9; H, 9.4.

The acid gave a *p*-bromophenacyl ester, m.p. 89–90°.

Anal. Calcd. for $C_{15}H_{17}BrO_3$: C, 55.4; H, 5.3. Found: C, 55.2; H, 5.3.

An authentic sample of 3,3-dimethylcyclobutanecarboxylic acid was prepared according to the method of Campbell and Rydon.[26] It gave an infrared spectrum identical with that obtained from the cyclobutane degradation product, as well as a *p*-bromophenacyl ester identical with the one above. Campbell and Rydon reported that the *p*-bromophenacyl ester melted at 93°.

Quaternization of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate with methyl *p*-toluenesulfonate, followed by treatment with potassium hydroxide, gave 3,3-dimethyl-1-cyclobutene-1-carboxylic acid in 81% yield.

2-Dimethylamino-3,3-dimethylcyclobutanecarbonitrile (4).—N,N-Dimethylisobutenylamine and acrylonitrile gave in 2 hr. at 170° a 64% yield of 2-dimethylamino-3,3-dimethylcyclobutanecarbonitrile, b.p. 44–45° at 0.5–1 mm., $n^{20}D$ 1.4531.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.0; H, 10.6; N, 18.4. Found: C, 70.9; H, 10.6; N, 18.1.

Quaternization of this product with methyl *p*-toluenesulfonate and treatment with base as previously described gave 3,3-dimethyl-1-cyclobutene-1-carbonitrile in 66% yield.

Rearrangement of 3,3-Dimethyl-1-cyclobutene-1-carbonitrile (6).—3,3-Dimethyl-1-cyclobutene-1-carbonitrile (22.5 g., 0.21 mole) was placed in a distillation flask and heated at atmospheric pressure under a reflux condenser. When the temperature reached *ca.* 190°, an exothermic reaction occurred and the temperature rose rapidly to 224°. Upon cooling, the contents of the flask crystallized. Recrystallization from hexane gave 18.6 g. (83%) of 2,2-dimethyl-1-(2-methyl-1-propenyl)-3-cyclohexene-1,4-dicarbonitrile, m.p. 83–84°.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.5; H, 8.5; N, 13.1; mol. wt., 214. Found: C, 78.8; H, 8.6; N, 12.7; mol. wt., 208.

(26) A. Campbell and H. R. Rydon, *J. Chem. Soc.*, 3002 (1953).

The n.m.r. spectrum showed absorption for the ring olefinic proton at 6.80 (weakly split triplet), the side-chain olefinic proton at 5.70 (broad), and the side-chain methyl at 1.6 and 1.8 p.p.m. The broad, complex absorption due to the ring methylene protons indicated that these were on adjacent carbon atoms.

Rearrangement of Ethyl 3,3-Dimethyl-1-cyclobutene-1-carboxylate.—Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate (60 g., 0.39 mole) was heated as previously described for the 3,3-dimethyl-1-cyclobutene-1-carbonitrile. When the temperature reached *ca.* 210°, an exothermic reaction occurred and the temperature rose rapidly to 240°. After being cooled to room temperature, the material was distilled to give 50.5 g. (85%) of diethyl 2,2-dimethyl-1-(2-methyl-1-propenyl)-3-cyclohexene-1,4-dicarboxylate, b.p. 121–123° at *ca.* 0.1 mm., $n^{20}D$ 1.4913.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.2; H, 9.1. Found: C, 70.2; H, 9.2.

Diethyl 3,3-Dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate.—1-Isobutenylpiperidine (208.5 g., 1.5 moles) and diethyl maleate (322.5 g., 1.87 moles) were combined and heated for 5.5 hr. at 150°. Distillation gave 241 g. (51%) of diethyl 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate, b.p. 113–120° at *ca.* 1 mm., $n^{20}D$ 1.4660.

Anal. Calcd. for $C_{17}H_{29}NO_4$: C, 65.6; H, 9.4. Found: C, 65.4; H, 9.1.

Diethyl 4-Dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (5).—N,N-Dimethylisobutenylamine (82 g., 0.83 mole) and diethyl maleate (172 g., 1 mole) were combined. The temperature of the mixture rose slowly to 40° and then dropped back to room temperature (this heat effect is due to isomerization of the maleate to the fumarate). The mixture was then refluxed. It was held at 105–110° for 12 hr. by control of the Glascol heater voltage, then at reflux the temperature rose to 144° over the next 3.5 hr. At this point, an additional 35 g. of diethyl maleate was added and reflux was continued. Over the next 2.5 hr., the temperature rose to 162°. The mixture then was distilled to give 97.5 g. of diethyl fumarate, b.p. 59–60° at *ca.* 1.5 mm. (the infrared spectrum was practically identical with that of authentic diethyl fumarate), an 11.8-g. intermediate cut, and 150.5 g. (67%) of diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate, b.p. 93–94° at *ca.* 1.5 mm., $n^{20}D$ 1.4502. N,N-Dimethylisobutenylamine (19 g.) was present in the Dry Ice trap.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3; N, 5.2. Found: C, 61.8; H, 9.3; N, 5.0.

A product identical with that obtained from diethyl maleate was obtained in 78% yield when diethyl fumarate and N,N-dimethylisobutenylamine were refluxed for 11.5 hr.

4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylic Acid.—Diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (90 g., 0.33 mole) and methyl *p*-toluenesulfonate (65 g., 0.35 mole) were combined and heated on a steam bath for 16 hr. Over a 0.5-hr. period, a solution of potassium hydroxide (84 g., 1.5 moles) in 100 ml. of water was added with manual stirring and cooling to keep the temperature at *ca.* 50°. The mixture was heated for 1 hr. on the steam bath and acidified with hydrochloric acid. It was extracted ten times with 150-ml. portions of ether (evaporation of the tenth extract gave 0.5 g. of product), and the ether was removed by evaporation on the steam bath to leave a residue of 40 g. (71%) of crude 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylic acid. The acid was recrystallized from an ethyl acetate–hexane mixture with Darco treatment to give 25 g. (44%), m.p. 153–155°. A sample for analysis was recrystallized from an ethyl acetate–cyclohexane mixture, m.p. 154–155°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.5; H, 6.0.

***trans*-Norcaryophyllenic Acid.**—4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylic acid (5.1 g., 0.03 mole) in ethyl acetate (75 ml.) was subjected to hydrogenation over 0.25 g. of 5% palladium on alumina at 25° and 3 atm. Reduction was complete in less than 1 hr. The catalyst was removed by filtration, and the solvent was evaporated to give 5 g. of a solid, m.p. 106–115°, which was a mixture of *cis*- and *trans*-norcaryophyllenic acid. This mixture (4.5 g.) was combined with 15 ml. of 30% (by volume) sulfuric acid solution and heated in an autoclave for 12 hr. at 150°. The mixture was filtered, and the solid was dissolved in acetone and treated with Norit. This solution was filtered, the acetone was removed by evaporation, and the residue was recrystallized from benzene to give 4 g. of *trans*-norcaryophyllenic acid, m.p. 149–150°, lit.[27] m.p. 148–149°.

The dianilide was prepared and was found to melt at 239–240°, lit.[27] m.p. 238°.

N,N,2,2-Tetramethyl-4-(methylsulfonyl)cyclobutylamine (7).—N,N-Dimethylisobutenylamine (28 g., 0.28 mole) and methyl vinyl sulfone (28 g., 0.26 mole) were combined. The immiscible mixture was refluxed, and when the temperature reached 90°, the mixture became homogeneous. Reflux was continued for 1.5 hr. while the temperature rose from 90 to 160°. Distillation of the reaction mixture gave 49 g. (91%) of N,N,2,2-tetramethyl-4-(methylsulfonyl)cyclobutylamine, b.p. 100–103° at 0.5–0.6 mm., which crystallized in the receiver, m.p. 85–86°.

Anal. Calcd. for $C_9H_{19}NO_2S$: C, 52.7; H, 9.3. Found: C, 52.2; H, 9.2.

2,2-Dimethyl-4-(methylsulfonyl)butyraldehyde (9).—N,N,2,2-Tetramethyl-4-(methylsulfonyl)cyclobutylamine (23 g., 0.11 mole) and methyl *p*-toluenesulfonate (23 g., 0.12 mole) were combined and heated on the steam bath for 2.5 hr. Water (50 ml.) was added, followed by a solution of 10 g. of potassium hydroxide in 10 ml. of water, and the mixture was heated on the steam bath for 1 hr. The water-soluble degradation product was extracted twice with 50-ml. portions of chloroform. The chloroform was removed by evaporation, and the residue was distilled to give 5.5 g. of 2,2-dimethyl-4-(methylsulfonyl)butyraldehyde, b.p. 149–153° at 1 mm., $n^{20}D$ 1.4853.

Anal. Calcd. for $C_7H_{14}O_3S$: C, 47.2; H, 7.9. Found: C, 47.5; H, 8.0.

The 2,4-dinitrophenylhydrazone melted at 153°.

Anal. Calcd. for $C_{13}H_{18}N_4O_6S$: C, 43.6; H, 5.1. Found: C, 43.7; H, 5.3.

2,2-Dimethyl-4-(methylsulfonyl)butyraldehyde.—Methyl vinyl sulfone (15.9 g., 0.15 mole) and N-isobutylideneethylamine (16 g., 0.16 mole) were combined and heated for 1.5 hr. After the first hour, the temperature had risen to 150–160°, where it remained for the last 30 min. of heating. The mixture was cooled, and a solution of concentrated hydrochloric acid (20 ml.) in water (20 ml.) was added. The clear solution was allowed to stand overnight. The mixture was extracted twice with an equal volume of chloroform to remove the heavier-than-water oily layer which had separated. The chloroform was removed by evaporation on the steam bath, and the residue was distilled through a 6-in. Vigreux column to give 17.7 g. (66%) of 2,2-dimethyl-4-(methylsulfonyl)-butyraldehyde, b.p. 126–129° at *ca.* 0.5 mm., $n^{20}D$ 1.4710. The infrared spectrum of this material was identical with that of the aldehyde derived from N,N,2,2-tetramethyl-4-(methylsulfonyl)cyclobutylamine as described above.

The 2,4-dinitrophenylhydrazone melted at 153–154°.

N,N,2,2-Tetramethyl-4-nitro-3-phenylcyclobutylamine (10).—N,N-Dimethylisobutenylamine (33 g., 0.33 mole) was added to β-nitrostyrene (47.5 g., 0.32 mole) in an erlenmeyer flask, and the mixture was stirred manually. The temperature rose to 92° rapidly and then dropped slowly. On standing, crystallization occurred. The solid was stirred in hexane, filtered, and washed with hexane to give 74.5 g. (94%) of crude N,N,2,2-tetramethyl-4-nitro-3-phenylcyclobutylamine, m.p. 86–91°. A sample for analysis was recrystallized from hexane and had m.p. 90–92°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.7; H, 8.1; N, 11.3. Found: C, 67.9; H, 8.3; N, 11.5.

The structure of this material was confirmed by chemical degradation as follows.

N,N,2,2-Tetramethyl-4-nitro-3-phenylcyclobutylamine (167 g., 0.67 mole) and methyl *p*-toluenesulfonate (130 g., 0.7 mole) were combined and heated on a steam bath for 19 hr. Water (400 ml.) was added to the reaction mixture, and it was extracted three times with 150-ml. portions of ether. Evaporation of the ether left 95 g. of nonquaternized material. The remaining aqueous phase was split into two equal portions, A and B.

Sodium bicarbonate (28 g., 0.33 mole) was added to A, and the mixture was heated for 15 min. on a steam bath. The oil which separated was dissolved in ether; the ether was evaporated to leave 26 g. of residue which crystallized to a slush. A good solvent for recrystallization was not found. By dissolving the residue in 150 ml. of ethyl alcohol and chilling the solution in Dry Ice, 4 g. of 2,2-dimethyl-4-nitro-3-phenylbutyraldehyde, m.p. 72°, was obtained.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 64.9; H, 7.1; N, 6.5.

Sodium acetate (28 g., 0.33 mole) was added to B, and the mixture was treated in the same way A was treated to give 27 g.

(27) T. L. Dawson and G. R. Ramage, *J. Chem. Soc.*, 3382 (1957).

of crude aldehyde. Reaction of 1 g. of the crude aldehyde with 2,4-dinitrophenylhydrazine gave 1.3 g. (70%) of the 2,4-dinitrophenylhydrazone of 2,2-dimethyl-4-nitro-3-phenylbutyraldehyde, m.p. 191.5–192.5°.

Anal. Calcd. for $C_{18}H_{19}N_5O_6$: C, 53.9; H, 4.8. Found: C, 53.6; H, 4.9.

Reaction of N,N-Dimethylisobutenylamine with 2-Nitro-1-butene.—N,N-Dimethylisobutenylamine (91 g., 0.92 mole) was added portionwise to 2-nitro-1-butene (91 g., 0.9 mole) with cooling to maintain the temperature at 40–50°. The entire reaction mixture crystallized on cooling, and the product was presumably 2-ethyl-N,N,4,4-tetramethyl-2-nitrocyclobutylamine (11). Pentane was added to the solid, then was removed by filtration. The product began evolving dimethylamine immediately on exposure to air and became gummy. It dissolved in water rapidly with the evolution of dimethylamine, and the solution gave a strong, positive 2,4-dinitrophenylhydrazine test for a carbonyl group. The product was allowed to stand exposed to air for one week, after which time it was completely liquid. Distillation of 83 g. of this material gave 19 g. of a product, b.p. 80–82° at 4 mm., which was apparently impure 2,2-dimethyl-4-nitrohexanal. A satisfactory analysis was not obtained, but it gave a 2,4-dinitrophenylhydrazone, m.p. 116–117°.

Anal. Calcd. for $C_{14}H_{19}N_5O_6$: C, 47.6; H, 5.4. Found: C, 47.4; H, 5.5.

N,N-Dibenzyl-2,2-dimethyl-4-nitro-3-phenylcyclobutylamine.—N-Isobutenyldibenzylamine (12.5 g., 0.05 mole) and β-nitrostyrene (7.4 g., 0.05 mole) were combined. There was a moderate evolution of heat, and the temperature rose to 34°. The mixture was allowed to stand 1 hr., at which time it had partially crystallized. Hexane was added, and the mixture was filtered. The solid was recrystallized from hexane to give 10 g. (50%) of N,N-dibenzyl-2,2-dimethyl-4-nitro-3-phenylcyclobutylamine, m.p. 95–96.5°.

Anal. Calcd. for $C_{26}H_{28}N_2O_2$: C, 78.0; H, 7.1. Found: C, 77.9; H, 7.2.

Cycloadditions of Enamines Containing a β-Hydrogen Atom.—Enamines containing a β-hydrogen atom were found to give cyclobutanes on reaction with electrophilic olefins under mild conditions, that is, standing without external heating in the polar solvent acetonitrile or refluxing in acetonitrile. The cyclobutanes prepared are listed in Table V. The following examples are illustrative.

Methyl 3-Ethyl-2-piperidinocyclobutanecarboxylate (12).—Methyl acrylate (43 g., 0.5 mole), N-(1-butenyl)piperidine (69 g., 0.5 mole), and acetonitrile (150 ml.) containing a pinch of hydroquinone were combined, refluxed for 3 hr., and then allowed to stand overnight. Distillation of the mixture through a 6-in. Vigreux column gave 92 g. (82%) of methyl 3-ethyl-2-piperidinocyclobutanecarboxylate, b.p. 87–89° at *ca.* 0.5 mm., $n^{20}D$ 1.4734.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.3; H, 10.3. Found: C, 69.6; H, 10.3.

This compound was also prepared in 83% yield by allowing the reactants to stand at room temperature in acetonitrile for 3 days.

3-Ethyl-1-cyclobutene-1-carboxylic Acid.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (56 g., 0.25 mole) and methyl *p*-toluenesulfonate (93 g., 0.5 mole) were combined and heated on a steam bath for 16 hr. Water (150 ml.) was added, the mixture was extracted once with ether, and the ether layer then was discarded. Potassium hydroxide (80 g., 1.4 moles) was added to the aqueous layer, and the solution was heated on a steam bath for 4 hr. The mixture was cooled, extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. Distillation of the latter extract gave 20 g. (64%) of 3-ethyl-1-cyclobutene-1-carboxylic acid, b.p. 79–80° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4694.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.3; H, 7.7.

The n.m.r. spectrum showed absorption due to one olefinic proton as a single peak at 7.05 p.p.m.

3-Ethylcyclobutanecarboxylic Acid.—3-Ethyl-1-cyclobutene-1-carboxylic acid (15 g., 0.12 mole) was hydrogenated in pentane (200 ml.) at 25° and 40 p.s.i. over 5% palladium on alumina. Distillation gave 12.4 g. (81%) of 3-ethylcyclobutanecarboxylic acid, b.p. 78–79° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4415.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.6; H, 9.4. Found: C, 65.5; H, 9.5.

Thermal Decomposition of Methyl 3-Ethyl-2-piperidinocyclobutanecarboxylate.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (22.5 g., 0.1 mole) was heated at atmospheric pressure under a 3-in. Vigreux column. When the temperature reached 170–180°, methyl acrylate began distilling. By continuing the heating and by reducing the pressure in the system slightly, a total of 6 g. (70%) of methyl acrylate was obtained. The system then was evacuated to 5–6 mm., and the heating was continued to give 5 g. (36%) of 1-isobutenylpiperidine, b.p. 60–65° at 5–6 mm., $n^{20}D$ 1.4792. There was 3.5 g. of material in the trap, and the residue weighed 8 g.

Methyl 3-Methyl-2-piperidinocyclobutanecarboxylate.—In a manner analogous to that described above for methyl 3-ethyl-2-piperidinocyclobutanecarboxylate, methyl 3-methyl-2-piperidinocyclobutanecarboxylate was prepared in 67% yield from 1-(1-propenyl)piperidine and methyl acrylate, b.p. 70–75° at 0.5 mm., $n^{20}D$ 1.4741.

Anal. Calcd. for $C_{12}H_{21}NO_2$: N, 6.6. Found: N, 6.6.

3-Methyl-1-cyclobutene-1-carboxylic Acid.—Quaternization of methyl 3-methyl-2-piperidinocyclobutanecarboxylate with methyl *p*-toluenesulfonate and treatment of the resulting salt with aqueous potassium hydroxide, followed by acidification with hydrochloric acid, gave a 55% yield of 3-methyl-1-cyclobutene-1-carboxylic acid, b.p. 68–70° at *ca.* 1–1.5 mm., $n^{20}D$ 1.4682. The infrared and n.m.r. spectra of this compound supported the assigned structure. This compound was unstable and on standing at room temperature for several days changed into a polymer-like material.

Anal. Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.1; H, 7.4.

3-Methylcyclobutanecarboxylic Acid.—Hydrogenation of 3-methyl-1-cyclobutene-1-carboxylic acid at 25° and 40 p.s.i. over 5% palladium on alumina gave an 80% yield of 3-methylcyclobutanecarboxylic acid, b.p. 62.5–63° at 1 mm., $n^{20}D$ 1.4376, lit.[28] $n^{25}D$ 1.4351. The amide derivative melted at 162–163°, lit.[28] m.p. 163–164°, and the anilide melted at 129–131°, lit.[28] m.p. 127–128°.

Diethyl 3-Dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate.—N,N-Dimethyl-1-butenylamine (43 g., 0.434 mole), diethyl maleate (74 g., 0.43 mole), and acetonitrile (100 ml.) were combined and allowed to stand at room tmeperature for 22 hr. Distillation gave 91 g. (78%) of diethyl 3-dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate, b.p. 95–98° at *ca.* 0.8 mm., $n^{20}D$ 1.4482.

Anal. Calcd. for $C_{14}H_{25}NO_4$: N, 5.0. Found: N, 5.2.

4-Ethyl-2-cyclobutene-1,2-dicarboxylic Acid.—Diethyl 3-dimethylamino-4-ethyl-1,2-cyclobutanedicarboxylate (27 g., 0.1 mole) and methyl *p*-toluenesulfonate (20 g., 0.11 mole) were combined and heated on the steam bath for 5 hr. and then allowed to stand overnight. A solution of potassium hydroxide (30 g., 0.53 mole) in water (75 ml.) was added, and the resulting mixture was heated for 2 hr. on a steam bath. The mixture was cooled, acidified with concentrated hydrochloric acid, and extracted three times with ether (125 ml.). The ether was evaporated, leaving 15 g. (88%) of crude 4-ethyl-1-cyclobutene-1,2-dicarboxylic acid as an oil which crystallized on standing. A sample recrystallized from ethyl acetate and hexane melted at 128–129.5°.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.4; H, 6.2.

1-Ethyl-N,N-dimethylpropenylamine with Methyl Acrylate.—1-Ethyl-N,N-dimethylpropenylamine (33 g., 0.29 mole), methyl acrylate (25 g., 0.29 mole), and acetonitrile (50 ml.) containing a pinch of hydroquinone were combined. A mild exothermic reaction took place, and the temperature was maintained below 30° by intermittent cooling. After the mixture had stood for 3 hr., an infrared spectrum of the material showed only a very weak absorption band in the double bond region (6–6.1 μ). An n.m.r. spectrum of this material showed weak absorption in the olefinic proton regions, apparently due to an unsaturated impurity.

This compound was thermally unstable. Distillation of one-half of the above reaction product gave 21 g. (73%) of what appeared to be methyl 5-dimethylamino-4-methyl-5(and possibly 4)-heptenoate, the Stork-type adduct, b.p. 63–65° at *ca.* 0.3 mm., $n^{20}D$ 1.4598. The infrared spectrum showed increased absorption at 6.1 μ, and the n.m.r. spectrum showed olefinic proton absorption as a quartet centered at 4.6 p.p.m.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.5; N, 7.0. Found: C, 66.0; H, 10.8; N, 6.8.

Methyl 2-Ethyl-3-methyl-1-cyclobutene-1-carboxylate.—Methyl 2-dimethylamino-2-ethyl-3-methylcyclobutanecarboxylate (one-

(28) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 2723 (1959).

half of the product obtained above—*ca.* 28 g., 0.14 mole—in 25 ml. of acetonitrile) was treated with methyl iodide (40 g., 0.28 mole) and allowed to stand for 1.5 hr. The solvent and excess methyl iodide were removed under reduced pressure; the solid residue was dissolved in water (150 ml.) and extracted once with ether. A solution of sodium hydroxide (20 g., 0.5 mole) in water (50 ml.) was added, and the oil layer which separated was removed by extraction with ether. The ether extract on distillation gave 11 g. (49% based on the starting methyl acrylate) of methyl 2-ethyl-3-methyl-1-cyclobutene-1-carboxylate, b.p. 60–61° at 5 mm., $n^{20}D$ 1.4586.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.6; H, 9.1.

1-Ethyl-N,N-dimethylpropenylamine with Diethyl Maleate.—1-Ethyl-N,N-dimethylpropenylamine (20 g., 0.177 mole), diethyl maleate (30.5 g., 0.177 mole), and acetonitrile (50 ml.) containing a pinch of hydroquinone were combined. The temperature of the mixture rose to 54° within 18 min. The mixture was allowed to stand at room temperature for 3 days, after which it was heated to 75° at 0.5 mm. There was left 23 g. (46%) of crude diethyl 3-dimethylamino-3-ethyl-4-methylcyclobutanecarboxylate, $n^{20}D$ 1.4602. The infrared spectrum showed no enamine C=C absorption between 5.9 and 6.5 μ., and no olefinic proton absorption was detected in the n.m.r. spectrum.

3-Ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylic Acid.—Crude diethyl 3-dimethylamino-3-ethyl-4-methyl-1,2-cyclobutanedicarboxylate (20.5 g., 0.072 mole) was combined with methyl *p*-toluenesulfonate (13.5 g., 0.073 mole) and allowed to stand overnight at room temperature. Water (50 ml.) was added, and the solution was extracted once with ether. Potassium hydroxide (25 g., 0.45 mole) was added, and the mixture was heated on a steam bath for 2 hr. It was then cooled, acidified with concentrated hydrochloric acid, and extracted twice with ether (75-ml. portions). Evaporation of the combined extracts on the steam bath left 9 g. (68%) of 3-ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylic acid as an oil which crystallized rapidly. A small sample, recrystallized twice from water, melted at 147.5–149°.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.7; H, 6.6; neut. equiv., 92. Found: C, 58.6; H, 6.7; neut. equiv., 91.4.

Diethyl 3-Ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylate.—1-Ethyl-N,N-dimethylpropenylamine (30 g., 0.265 mole) and diethyl maleate (45.5 g., 0.265 mole) were allowed to react as described above to give diethyl 3-dimethylamino-3-ethyl-4-methyl-1,2-cyclobutanedicarboxylate. This crude compound was dissolved in acetonitrile (100 ml.) and treated with methyl iodide (50 g., 0.35 mole), and the mixture was refluxed for 2 hr. at 70°. The solvent and excess methyl iodide were removed under reduced pressure, and the residue was dissolved in 250 ml. of water. The resulting aqueous solution was extracted with ether to remove unquaternized material. Potassium hydroxide (56 g., 1 mole) was added slowly with cooling, and the oil which separated was removed by extraction with ether. Distillation of the extract gave 37 g. (58% yield based on 0.265 mole of starting material) of diethyl 3-ethyl-4-methyl-2-cyclobutene-1,2-dicarboxylate, b.p. 93.5–96° at 0.7–0.8 mm., $n^{20}D$ 1.4581.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.0; H, 8.4. Found: C, 65.0; H, 8.4.

Tetraethyl 6-Dimethylamino-5,5-dimethyl-1,1,3,3-cyclohexanetetracarboxylate (16).—N,N-Dimethylisobutenylamine (30 g., 0.3 mole) was combined with diethyl methylenemalonate (96 g., 0.56 mole) which had been inhibited with hydroquinone. The temperature of the mixture rose to 110° after standing for 15 min. The mixture was heated under a reflux condenser, and at 150° the mixture began to reflux. The temperature of the mixture rose rapidly to 168°, and the refluxing virtually stopped. Distillation of the reaction mixture through a 4-in. Vigreux column gave 101 g. (81%) of tetraethyl 6-dimethylamine-5,5-dimethyl-1,1,3,3-cyclohexanetetracarboxylate (16), b.p. 165–173° at 1 mm., $n^{20}D$ 1.4696.

Anal. Calcd. for $C_{22}H_{37}NO_8$: C, 59.7; H, 8.4; mol. wt., 443. Found: C, 59.8; H, 8.8; mol. wt., 446.

The structure assigned to this compound was based on the elemental analysis, the absence of C=C absorption in the infrared spectrum, and the mode of formation.

Tetraethyl 6-Dimethylamino-5-ethyl-1,1,3,3-cyclohexanetetracarboxylate.—To N,N-dimethyl-1-butenylamine (20 g., 0.202 mole) was added diethyl methylenemalonate (64 g., 0.37 mole) portionwise with stirring. The temperature of the mixture rose rapidly to 80–85° during the addition. The mixture was allowed to stand overnight. Distillation of the mixture gave 32 g. (64%) of tetraethyl 6-dimethylamino-5-ethyl-1,1,3,3-cyclohexanetetracarboxylate, b.p. 165–170° at *ca.* 0.8 mm., $n^{20}D$ 1.4644.

Anal. Calcd. for $C_{22}H_{37}NO_8$: C, 59.7; H, 8.4. Found: C, 59.6; H, 8.7.

2-Dimethylamino-3,3-dimethylcyclobutanecarboxylic Acid, N-Oxide (17).—To a solution of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (93 g., 0.5 mole) in methanol (275 ml.) which was chilled to 0° was added dropwise 30% hydrogen peroxide (170 g.). The temperature of the mixture was maintained at 0 ± 5° during the addition; then it was allowed to come to room temperature. After standing overnight, a slurry of 15 ml. of water containing 2 g. of 5% platinum on charcoal was added to destroy the peroxide, and the mixture again was allowed to stand overnight. The mixture was filtered, and the alcohol and water were removed under reduced pressure, keeping the temperature below 40°. The residue, upon treatment with acetone, gave a white solid which was filtered and dried in a vacuum oven. There was obtained 61 g. (65%) of 2-dimethylamino-3,3-dimethylcyclobutanecarboxylic acid, N-oxide, m.p. 168–170°.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.7; H, 9.2; neut. equiv., 187.2. Found: C, 57.8; H, 9.4, neut. equiv., 187.9.

3,3-Dimethyl-4-dimethylamino-1,2-cyclobutanedicarboxylic Acid, 2-Ethyl Ester, N-Oxide (18).—This compound was prepared in a similar manner from diethyl 3-dimethylamino-4,4-dimethyl-1,2-cyclobutanedicarboxylate.

There was obtained from 54.2 g. (0.2 mole) of the diester 23 g. (45%) of the amine oxide, m.p. 157°.

Anal. Calcd. for $C_{12}H_{21}NO_5$: neut. equiv., 259.3. Found: neut. equiv., 258.1.

Hydrolysis of the Cyclobutane Adducts. A. 4,4-Dimethylglutaraldehydic Acid.—A mixture of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (100 g., 0.54 mole) and water (125 ml.) was refluxed for 1.5 hr. The resulting solution was acidified with concentrated hydrochloric acid and then extracted with ether. The extract was distilled to give 48 g. (68%) of 4,4-dimethylglutaraldehydic acid, b.p. 98–105° at *ca.* 1 mm., $n^{20}D$ 1.4457.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.1; H, 8.4.

The 2,4-dinitrophenylhydrazone melted at 151–151.5°, lit.[29] m.p. 147°.

B. Alkaline Hydrolysis of Methyl 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylate.—Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (97 g., 0.5 mole) was refluxed with a solution of sodium hydroxide (20 g., 0.5 mole) in 150 ml. of water for 4 hr. No dimethylamine was evolved, and the ester had dissolved completely after 1.5 hr. Acidification of the solution with concentrated hydrochloric acid gave no insoluble material, showing that only saponification had occurred.

C. 2-Dimethylamino-3,3-dimethylcyclobutanecarboxylic Acid Hydrochloride (20).—Methyl 3,3-dimethyl-2-dimethylaminocyclobutanecarboxylate (50 g., 0.27 mole) was combined with 250 ml. of 4 *N* hydrochloric acid, and the resulting solution was refluxed for 4 hr. The mixture was evaporated to dryness on a steam bath, 100 ml. of water was added then, and the evaporation was repeated. Ethyl alcohol (100 ml.) was added, and the mixture was evaporated for a third time to dryness. The crystalline residue was triturated with cold 95% ethyl alcohol to give 35 g. of crude product. Recrystallization from ethyl alcohol gave, after drying, 27 g. (49%) of 2-dimethylamino-3,3-dimethylcyclobutanecarboxylic acid hydrochloride, m.p. 196–197°.

Anal. Calcd. for $C_9H_{18}ClNO_2$: neut. equiv., 207.7. Found: neut. equiv., 208.3.

D. Methyl 4,4-Dimethylglutaraldehydate (21).—Methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (97 g., 0.5 mole) was combined with a solution of 42 ml. of concentrated hydrochloric acid in 50 ml. of water and refluxed for 3.5 hr. An oil layer began separating soon after the mixture began refluxing. The oil was collected and distilled to give 70.5 g. (89%) of methyl 4,4-dimethylglutaraldehydate, b.p. 40–42° at 0.5 mm., $n^{20}D$ 1.4306.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 61.0; H, 8.9.

E. Acid Hydrolysis of 3,3-Dimethyl-1-cyclobutene-1-carboxylic Acid.—3,3-Dimethyl-1-cyclobutene-1-carboxylic acid (41 g., 0.33 mole) was refluxed, with vigorous stirring, with 33 ml. of concentrated hydrochloric acid and 150 ml. of water for 15 hr. The oil was dissolved in ether and distilled to give 19 g. of mostly

(29) R. H. Wiley and P. Veeravagu, *J. Org. Chem.*, **23**, 297 (1958).

3,3-dimethyl-1-cyclobutene-1-carboxylic acid, b.p. 77–100° at *ca.* 1 mm., which crystallized in the head and receiver, and 11 g. of 4,4-dimethylglutaraldehydic acid, b.p. 103–105° at *ca.* 1 mm., $n^{20}D$ 1.4467, which was identical with that of an authentic sample.

Methyl 4-Ethylglutaraldehydate.—Methyl 3-ethyl-2-piperidinocyclobutanecarboxylate (20 g., 0.089 mole) was combined with a solution of concentrated hydrochloric acid (8 ml.) and water (25 ml.) and refluxed for 2 hr. An oil began separating soon after the mixture began refluxing. The oil was collected and distilled to give 10 g. (72%) of methyl 4-ethylglutaraldehydate, b.p. 57–58° at 1 mm., $n^{20}D$ 1.4321.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.3; H, 9.0.

Attempted Hydrolytic Ring Opening of Diethyl 4-Dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate.—Diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (76 g., 0.28 mole) and water (250 ml.) were combined and refluxed for 23 hr. The mixture then was acidified with hydrochloric acid and extracted twice with 100-ml. portions of ether. Evaporation of the ether left only 5 g. of residue, which gave a weak test for carbonyl groups on treatment with 2,4-dinitrophenylhydrazine reagent.

Refluxing the diester (135 g., 0.5 mole) with 100 ml. of water and 42 ml. of concentrated hydrochloric acid for 18 hr. gave no acid-insoluble material.

3,3-Dimethyl-4-piperidino-1,2-cyclobutanedicarboxylic Acid Hydrochloride.—Diethyl 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylate (31 g., 0.1 mole) and 100 ml. of concentrated hydrochloric acid were refluxed for 6 hr. The mixture then was evaporated to dryness on the steam bath. The residue was triturated with hot butyl alcohol to give 17 g. (58%) of 3,3-dimethyl-4-piperidino-1,2-cyclobutanedicarboxylic acid hydrochloride, m.p. 234–235°.

Anal. Calcd. for $C_{13}H_{22}ClNO_4$: C, 53.5; H, 7.6. Found: C, 53.2; H, 7.6.

4-Cyano-2,2-dimethylbutyraldehyde (22).—2-Dimethylamino-3,3-dimethylcyclobutanecarbonitrile (38 g., 0.25 mole) and water (75 ml.) were refluxed for 5 hr., during which time dimethylamine was evolved through the condenser. The mixture was acidified with concentrated hydrochloric acid, extracted with ether, and the extract was distilled to give 18.5 g. (59%) of 4-cyano-2,2-dimethylbutyraldehyde, b.p. 55–56° at *ca.* 1 mm., $n^{20}D$ 1.4371.

Anal. Calcd. for $C_7H_{11}NO$: C, 67.2; H, 8.9. Found: C, 67.4; H, 9.1.

The 2,4-dinitrophenylhydrazone melted at 140–142°, lit.[30] m.p. 139–140°.

2-Dimethylamino-3,3-dimethylcyclobutanemethylamine.—3,3-Dimethyl-2-dimethylaminocyclobutanecarbonitrile (331 g., 2.2 moles) was dissolved in ethyl alcohol (250 ml.) and hydrogenated in the presence of anhydrous liquid ammonia (125 g.) and alcoholic Raney nickel (36 g.). The catalyst was removed by filtration, and the filtrate was distilled to give 39.5 g. (16%) of 3,3-dimethylpiperidine, b.p. 51–54° at 39–40 mm. The distillation was continued to give 21.9 g. (64%) of 2-dimethylamino-3,3-dimethylcyclobutanemethylamine, b.p. 102.5–104° at 39 mm., $n^{20}D$ 1.4598.

The infrared spectrum of the 3,3-dimethylpiperidine obtained was identical with that of an authentic sample.

Ethyl 3,3-Dimethyl-2-(N-propylacetamido)cyclobutanecarboxylate.—Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate (11.5 g., 0.075 mole) was treated with 9 g. (0.15 mole) of propylamine. After standing overnight at room temperature, the mixture was dissolved in pyridine (50 ml.). The resulting solution was treated with acetyl chloride (12 g., 0.15 mole) with stirring and cooling to keep the temperature below 30°. The reaction mixture was poured into 150 ml. of ice–water, and the resulting mixture was extracted with two 100-ml. portions of ether. The combined extracts were washed with water (25 ml.), and the ether was evaporated on the steam bath. The residue was distilled to give, after removal of a 6-g. forerun boiling from 47–100° at 0.25–0.1 mm., 4.5 g. (24%) of ethyl 3,3-dimethyl-2-(N-propylacetamido)-cyclobutanecarboxylate, b.p. 100–103° at 0.1 mm., $n^{20}D$ 1.4648.

Anal. Calcd. for $C_{14}H_{25}NO_3$: C, 65.8; H, 9.9. Found: C, 65.5; H, 9.9.

Ethyl 4,4-Dimethyl-5-propyliminovalerate.—Crude ethyl 3,3-dimethyl-2-(propylamino)cyclobutanecarboxylate (obtained from 30.4 g. (0.2 mole) of ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate) was distilled to give 25.3 g. (59%) of ethyl 4,4-dimethyl-5-propyliminovalerate (**28**), b.p. 64–65° at 0.2 mm., $n^{20}D$ 1.4407.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.6; H, 10.8. Found: C, 67.6; H, 10.9.

The compound was hydrolyzed by dilute hydrochloric acid to give an aldehyde whose 2,4-dinitrophenylhydrazone (m.p. 105–106°) was identical with that of a derivative of authentic ethyl 4,4-dimethylglutaraldehydate.

Diethyl 3,3-Dimethyl-4-(N-propylacetamido)-1,2-cyclobutanedicarboxylate.—In a manner similar to that described above, the adduct from diethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate (24 g., 0.106 mole) and propylamine gave, upon treatment with acetyl chloride (8.4 g.) in pyridine, 10.0 g. (29%) of diethyl 3,3-dimethyl-4-(N-propylacetamido)-1,2-cyclobutanedicarboxylate, b.p. 123–127° at 0.15–0.2 mm., $n^{20}D$ 1.4655.

Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.4; H, 8.9. Found: C, 62.2; H, 8.9.

Diethyl (1,1-Dimethyl-2-propyliminoethyl)succinate.—The adduct from diethyl 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylate (22.6 g., 0.1 mole) and propylamine (6.4 g., 0.11 mole) was distilled to give 20 g. (70%) of diethyl (1,1-dimethyl-2-propyliminoethyl)succinate (**29**), b.p. 110–113° at 0.7–0.8 mm., $n^{20}D$ 1.4493.

Anal. Calcd. for $C_{15}H_{27}NO_4$: C, 63.2; H, 9.5. Found: C, 63.3; H, 9.6.

The compound gave a 2,4-dinitrophenylhydrazone, m.p. 111–112°.

Anal. Calcd. for $C_{18}H_{24}N_4O_8$: C, 50.9; H, 5.6. Found: C, 51.0; H, 5.7.

Methyl 5-Ethylimino-4,4-dimethylvalerate.—Toluene (100 ml.), N-ethylisobutylideneamine (99 g., 1.0 mole), and methyl acrylate (86 g., 1.0 mole) were combined and heated under a reflux condenser. When the temperature reached *ca.* 78°, an exothermic reaction began; the heat source was removed and the mixture refluxed spontaneously for 5 min. at 88–89°. Heating then was resumed and continued for a total of 21 hr. The final temperature was 107°. Distillation gave 66 g. (36%) of methyl 5-ethylimino-4,4-dimethylvalerate, b.p. 52–53° at 1 mm., $n^{20}D$ 1.4379. A polymeric residue (60 g.) was left.

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3. Found: C, 64.6; H, 10.3.

Diethyl (2-Ethylimino-1,1-dimethylethyl)succinate.—N-Ethylisobutylideneamine (50 g., 0.5 mole) and diethyl maleate (86 g., 0.5 mole) were combined and heated under reflux for 8 hr., during which time the temperature rose from 109° to 184°. Distillation of the reaction mixture gave 117.5 g. (87%) of diethyl (2-ethylimino-1,1-dimethylethyl)succinate, b.p. 90–92° at 0.5 mm., $n^{20}D$ 1.4478.

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3. Found: C, 62.4; H, 9.0.

The 2,4-dinitrophenylhydrazone m.p. 111–112° was identical with that obtained from **29**.

Derivatives of Cyclobutanes Prepared by Standard Methods During This Investigation. A. Alcohols.—The following amino alcohols were prepared by the lithium aluminum hydride reduction of the corresponding esters.

3,3-Dimethyl-2-morpholino-1-cyclobutanemethanol in 76% yield had b.p. 99–103° at 1.5–1.8 mm., $n^{20}D$ 1.4832.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.3; H, 10.6. Found: C, 66.1; H, 10.7.

1-Piperidinospiro[3.5]nonane-1-methanol had m.p. 105–106.5°.

Anal. Calcd. for $C_{15}H_{27}NO$: C, 76.0; H, 11.5. Found: C, 76.2; H, 11.4.

3-Dimethylamino-4,4-dimethyl-1,2-cyclobutanedimethanol in 52% yield had b.p. 133–136° at 1 mm., $n^{20}D$ 1.4821.

Anal. Calcd. for $C_{10}H_{21}NO_2$: C, 64.1; H, 11.3. Found: C, 63.7; H, 10.9.

B. Amides.—3,3-Dimethyl-1-cyclobutanecarboxamide, m.p. 170–171°, was prepared in 86% yield by treating the corresponding acid chloride with ammonia.

Anal. Calcd. for $C_7H_{13}NO_4$: C, 66.1; H, 10.3. Found: C, 65.9; H, 10.4.

C. Esters.—Ethyl 3,3-dimethyl-1-cyclobutene-1-carboxylate, b.p. 50–54° at 5.5–6.5 mm., $n^{20}D$ 1.4418, was prepared in 77% yield by refluxing the corresponding acid with excess ethyl alcohol and removing the water formed by azeotropic distillation.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 69.8; H, 9.1.

(30) G. Tschudi and H. Schinz, *Helv. Chim. Acta*, **33**, 1879 (1950).