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Synthesis and Reactions of 3-Methylcyclobutene

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The synthesis of 3-methylcyclobutene (XII) was accomplished by two different methods, one involving thermal decomposition of N,N-dimethyl-3-methylcyclobutylamine oxide and the other, base detosylation of *trans*-2-tosyloxy-1-methylcyclobutane. In the presence of a sodium–alumina catalyst, at 5°, XII yields an equilibrium mixture containing 1-methylcyclobutene (85.5%), methylenecyclobutane (14.5%), and XII (less than 0.02%). Thermal isomerization of XII proceeds between 160 and 250° giving stereospecifically *trans*-1,3-pentadiene as the sole product. Mechanistic aspects of the ring cleavage and some other reactions of XII are discussed.

In view of the extensive recent work[1] on small ring compounds, it is noteworthy that one of the simplest derivatives of cyclobutene, *i.e.*, 3-methylcyclobutene (XII), has not yet been synthesized. Probable formation of the compound has, however, been reported by the authors,[2] and more recently by Srinivasan.[3] The difficulty of obtaining monosubstituted cyclobutenes with the substituent in the 3-position is illustrated by the reported[4] failure of cyclobutene to undergo Ziegler bromination to an extent useful for preparative purposes.

Synthesis of XII is of particular interest for the study of the stability relationships of cyclic olefins having a four-membered ring. Recent experiments[5] have shown that XII is not produced in more than trace amounts during the base-catalyzed equilibrium isomerization of methylenecyclobutane and 1-methylcyclobutene. The formation of XII appeared, therefore, to be highly unfavorable energetically.

Another interesting aspect of the chemistry of cyclobutenes is thermal isomerization,[2,6,7] which results in the formation of an open-chain diene. In the case of XII, splitting of the ring at the biallylic position should yield 1,3-pentadiene and could conceivably be stereospecific,[7] giving only one of the two possible isomers.

Preparation of XII was accomplished by two different routes, one involving in its final step thermal decomposition of N,N-dimethyl-3-methylcyclobutylamine oxide (XI) and the other, base detosylation of *trans*-2-tosyloxy-1-methylcyclobutane (XIV).

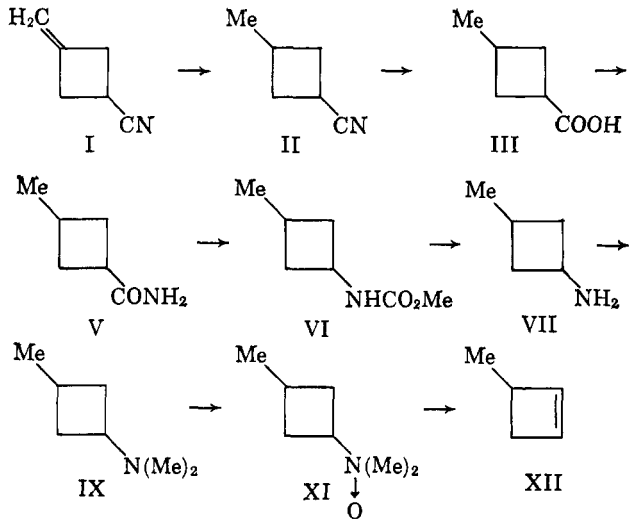
The scheme for the synthesis *via* the amine oxide is given in Chart I. 3-Methylcyclobutanecarboxylic acid (III) was prepared by cycloaddition of allene to acrylonitrile according to Cripps, *et al.*,[8] and selective hydrogenation of the resulting methylenecyclobutanecarbonitrile (I), followed by hydrolysis. Using the procedure of Kazanskii and Lukina,[9] the acid was converted into the amide (V). Hofmann reaction to obtain amine VII has to be carried out by first preparing[10] the urethane (VI), followed by hydrolysis with calcium hydroxide.[11] The amine (VII) was converted to the desired olefin *via* the amine oxide (XI) of the N,N-dimethyl derivative (IX). Decomposition of XI proceeds slowly at 130–135° with a yield of 88%. After washing with dilute hydrochloric acid to eliminate the dimethylhydroxylamine formed in the decomposition, the olefin was examined by gas chromatography and found to be 97% pure. No isomers of XII such as 1-methylcyclobutene or pentadiene were present in the product.

The structure of XII was proved by oxidation[12] to α-methylsuccinic acid, which was identified by conversion to the diphenacyl ester, m.p. 101–102° (lit.[13] m.p. 101–101.5°).

The structure was also confirmed by n.m.r. The spectrum showed (1) a doublet at 1.14 p.p.m. (J = 7 c.p.s.), due to the secondary methyl group; (2) a complex of lines between 1.9 and 2.9 p.p.m., assigned to the allylic protons; and (3) a closely spaced group of lines centered at 6.0 p.p.m., due to the vinylic protons.

(1) E. Vogel, *Angew. Chem.*, **72**, 4 (1960).
(2) J. Herling, J. Shabtai, and E. Gil-Av, *Bull. Res. Council Israel*, **11A**, 20 (1962).
(3) R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962).
(4) E. R. Buchman and D. R. Howton, *ibid.*, **70**, 3510 (1948).
(5) E. Gil-Av and J. Herling, *Tetrahedron Letters*, **No. 1**, 27 (1961).
(6) H. M. Frey, *Trans. Faraday Soc.*, **58**, 957 (1962).
(7) E. Vogel, *Ann.*, **615**, 14 (1958).
(8) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 2723 (1959).
(9) B. A. Kazanskii and M. Yu. Lukina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 47 (1951).
(10) *Cf.* E. S. Wallis and J. F. Lane, "Organic Reactions," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 289.
(11) E. Jeffreys, *Ber.*, **30**, 898 (1897); N. Zelinskii and J. Gutt, *ibid.*; **40**, 4744 (1907).
(12) E. von Rudloff, *Can. J. Chem.*, **34**, 1413 (1956).
(13) I. M. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Vol. III, Eire and Spottiswoode. London. 1953. p. 509.

CHART I



The relative intensities of the three groups of lines were in the ratio 3:3:2, respectively.

It should be pointed out that on hydrogenation of the methylene group of I both the *cis*- and *trans*-3-methylcyclobutanecarbonitrile may be formed.[14] Hence compounds II–XI should be mixtures of two substances. Separation of such geometric isomers could not be achieved in all cases, even though gas chromatography with capillary columns was employed (see Analytical). Resolution into two distinct peaks was observed in the case of compounds VII, IX, and the methyl ester of III.

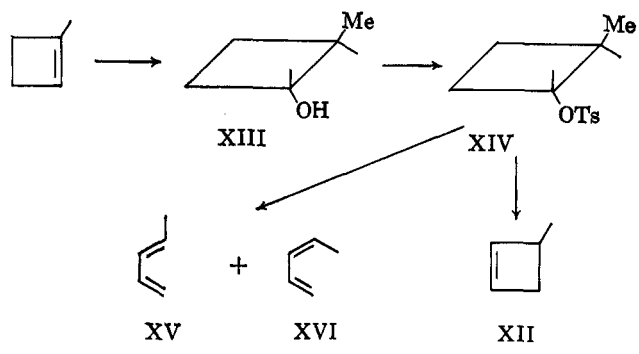
The second approach to XII is outlined in Chart II. It represents an extension of the recently developed method of Brown and Zweifel[15] for the synthesis of 3-alkylcyclenes to four-membered ring derivatives. According to Brown and Zweiel hydroboration of 1-methylcyclobutene should give practically pure *trans*-2-methylcyclobutanol (XIII). Gas chromatography on a capillary column of the alcohol obtained showed indeed a main peak representing 95% of the material. As found[15] in the case of corresponding, larger ring homologs, 3-methylcyclobutene is formed in the detosylation of XIV to the exclusion of any trace of 1-methylcyclobutene. On the other hand, ring opening also takes place yielding *trans*-1,3-pentadiene (XV), as well as a small amount of the *cis* isomer (XVI). This undesirable competing reaction can be reduced in importance by operating at 130–135°, at which temperature a product containing XII (53%), XV (40%), and XVI (7%) was obtained. At 150°, however, the yield of XII already drops to less than 10%. The presence of XII was established by gas chromatography (see Analytical), as well as by oxidation of the reaction mixture and isolation of α-methylsuccinic acid in the form of its diphenacyl ester.

Selective formation[15] of 3-methylcyclenes from the corresponding *trans*-2-tosyloxymethylcyclanes can be understood readily, for instance, in the case of the cyclohexane derivative, where the leaving groups are in the favorable *anti* position. However, in the four-membered ring compound XIV the relative disposition of the bonds involved in the reaction is less favorable for

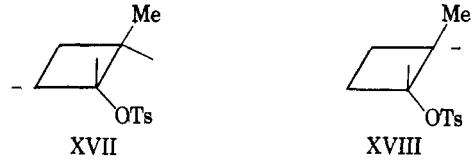
(14) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961).

(15) H. C. Brown and G. Zweifel, *ibid.*, **83**, 2544 (1961).

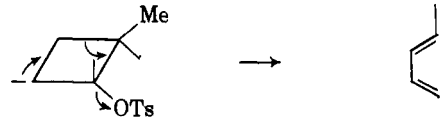
CHART II



E2 elimination. The detosylation of XIV could, therefore, proceed in part or entirely through a nonconcerted mechanism. An intermediate carbanion, such as XVII, arising by the action of the base (sodium isoamylate) on the substrate, will give XII on losing the tosyloxy group, but none of the isomeric 1-methylcyclobutene. It can be argued that the selectivity of the reaction by such a two-step mechanism is due to the higher stability of the secondary carbanion XVII and the lesser steric hindrance to its formation as compared with the alternative tertiary carbanion XVIII.



The competing ring-opening reaction leading to pentadiene may be regarded as a 1,4 elimination, which could equally proceed through the carbanion XVII.



Experiments were carried out with compound XII under the conditions of detosylation, but in the absence of sodium isoamylate. No reaction was observed even when the temperature was raised to 145° and the contact time prolonged up to 10 min. These results exclude the possibility that the 1,3-pentadienes arise by thermal splitting of XII, following detosylation.

As mentioned earlier, *cis*-1,3-pentadiene (XVI) is formed in unimportant amounts compared with the *trans* isomer (XV), ratio, ~1:6, although the former is thermodynamically more stable.[16] Since 1,3-pentadienes were found to isomerize slowly under the conditions of detosylation, it is probable that the small amount of XVI present is essentially a secondary product derived from XV. It thus appears that the ring opening proceeds stereospecifically, as also has been found to be the case for the thermal cleavage of XII (following). The absence of 1-methylcyclobutene and methylenecyclobutane in the product shows that XII does not isomerize under the conditions of detosylation.

Base-Catalyzed Isomerization of 3-Methylcyclobutene (XII).—It has been reported[5] previously that on equilibration of 1-methylcyclobutene and methylenecy-

(16) F. D. Rossini, "Physical Chemistry of the Hydrocarbons," A. Farkas, Ed., Academic Press, New York, N. Y., 1950, p. 425.

clobutane in the presence of a sodium–alumina catalyst[17] not more than a trace of XII was possibly formed. After XII became available, this observation was checked by approaching the equilibrium from this compound. The isomerization was carried out at 5° in pure 2,4-dimethylpentane as solvent, using the above-mentioned catalyst. The reaction was followed by gas chromatography, and it was found that XII is gradually transformed into its double bond isomers. After 5 hr. of reaction time the following constant composition was reached: 1-methylcyclobutene, 85.5%, methylenecyclobutane, 14.5%, and XII, <0.02%.

The difference in the stability of the two endocyclic isomers is in keeping with similar behavior of corresponding pairs of larger ring homologs. Thus, it has been found[18] that at 25° the ratio of the 1-methyl to the 3-methyl isomers is about 30 for the cyclohexene and about 60 for the cyclopentene derivatives. Qualitatively the higher stability of the 1-methyl compounds can be understood in terms of hyperconjugation and weaker nonbonded interaction with adjacent hydrogens. As ring size is decreased, one would also expect a lowering of the relative stability of the 3-methyl isomer due to increased nonbonded interactions of the methyl group. However, the magnitude of the effect observed in the four-membered ring series (ratio of 1-methylcyclobutene to XII > 4000:1) seems higher than would be normally expected on the basis of the preceding considerations.

Thermal Isomerization of 3-Methylcyclobutene (XII).—Compound XII was pyrolyzed at several temperatures between 140–250° in a flow system, and the products were examined by gas chromatography. It was found that *trans*-1,3-pentadiene is formed as the sole product in all experiments.[19] As seen in Table I, XII undergoes reaction to an appreciable extent (8.2%) already at 160° and a contact time of 30 sec. On the basis of available kinetic data,[20] it was calculated that cyclobutene itself will isomerize to the extent of less than 2% under these conditions. Further, isomerization to the corresponding diene is faster for XII than for 1-methylcyclobutene (Table I, footnote *c*).

TABLE I

THERMAL ISOMERIZATION[a] OF 3-METHYLCYCLOBUTENE[b,c] INTO *trans*-1,3-PENTADIENE

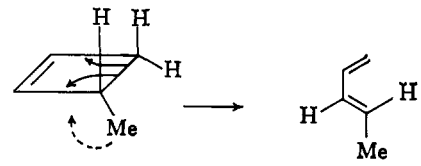
Temperature, °C.	Isomerization, %
140	None
160	8.2
180	55.0
200	90.7
250	100.0

[a] Contact time, 30 ± 2 sec. [b] A 10% solution of 3-methylcyclobutene in 2,4-dimethylpentane (>99% pure) was employed in the experiments; recovery was about 95%. [c] Under the same set of conditions 1-methylcyclobutene isomerizes into isoprene to the extent of 7.6% at 200° and 44.3% at 250°; *cis*-1,3-pentadiene remains unchanged at 250°.

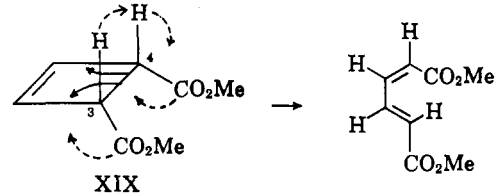
These results indicate that the methyl group in XII increases the ease of ring splitting at the biallylic position. This is in accord with the findings of Vogel,[7] who observed that introduction of allylic substituents in cyclobutene decreases the stability of the ring. It was reported,[7] for instance, that the dimethyl ester of *cis*-3,4-cyclobutenedicarboxylic acid is converted already at 120° to a mucconic acid ester.

The lower thermal stability of XII, as compared with cyclobutene, can be explained by increased Pitzer tension due to the methyl group in the 3-position. Further, if the ring opening at the C-3,C-4 bond proceeds through a transition state incorporating a biradical component,[21] it can be expected that the resonance stabilization of the activated complex is larger in the case of the substituted compound XII as compared with cyclobutene.[7]

The stereospecificity of the ring-opening reaction of XII, as expressed by the exclusive formation of *trans*-1,3-pentadiene, can be explained by preferred outward rotation of the relatively bulky methyl group in the splitting process. Such strain-relieving movement (marked with a dotted arrow) will lead to a *trans* configuration around the newly formed ($\Delta^{3,4}$) double bond in the open-chain product.



Vogel[7] has pointed out that pyrolysis of the dimethyl ester of *cis*-3,4-cyclobutenedicarboxylic acid (XIX) gives only one of the possible open-chain products, *i.e.*, the diester of *cis-trans*-mucconic acid (XX). This observation can likewise be explained by an oriented mode of relief from nonbonded interaction. The outward rotation of one of the ester groups, *e.g.*, at



XIX XX

the 3-carbon, causes a corresponding inward movement of the hydrogen at the same position. The repelling action of the latter hydrogen will then result in an outward movement of the vicinal hydrogen (at carbon 4) and in a corresponding inward rotation of the second ester group.

In extending this reasoning to *trans*-3,4-disubstituted cyclobutenes, it can be predicted that both substituents should turn outwards on ring opening.

Full support for the outlined mechanism is provided by the work of Criegee and Noll[22] on the pyrolysis at 200° of the *trans* and *cis* isomers of 1,2,3,4-tetramethylcyclobutene (XXI and XXIII, respectively). Both compounds are cleaved stereospecifically. As expected, XXI yields *cis,cis*-1,2,3,4-tetramethylbutadiene (XXII), while XXIII forms *cis,trans*-1,2,3,4-tetramethylbutadiene (XXIV).

(17) H. Pines and W. O. Haag, *J. Org. Chem.*, **23**, 328 (1958); W. O. Haag and H. Pines, *J. Am. Chem. Soc.*, **82**, 387 (1960).

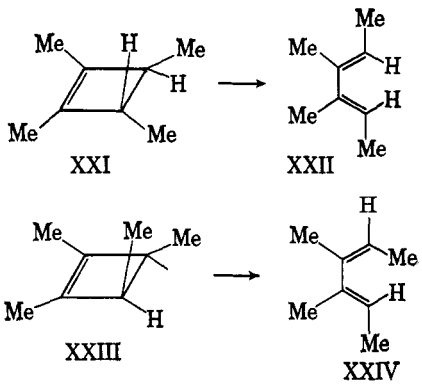
(18) J. Herling, Ph.D. thesis, Hebrew University, Jerusalem, 1961.

(19) This result supports the suggested[3] formation of XII by irradiation of 1,3-pentadiene.

(20) W. Cooper and W. D. Walters, *J. Am. Chem. Soc.*, **80**, 4220 (1958).

(21) C. T. Genaux, F. Kern, and W. D. Walters, *ibid.*, **75**, 6196 (1953).

(22) R. Criegee and K. Noll, *Ann.*, **627**, 1 (1959).



Bromination of 3-Methylcyclobutene (XII).—Compound XII absorbs 1 mole of bromine in carbon tetrachloride solution, giving $C_5H_8Br_2$. Gas chromatography on a capillary column showed the presence of two components in the ratio of 60:40. Since, normally, bromination proceeds by *trans* addition,[23] it can be assumed that the two compounds are 2-*cis*-3-*trans*-dibromomethylcyclobutane and 2-*trans*-3-*cis*-dibromomethylcyclobutane. Two minor peaks, representing about 2% of the total product, also were observed, indicating the possible occurrence of *cis* addition to a limited extent.

Experimental

3-Methylcyclobutanecarbonitrile (II).—A solution of allene (120 g., 3 moles) in toluene (60 ml.) reacted[8] with freshly distilled acrylonitrile (636 g., 12 moles) in a rocking bomb. The temperature was raised from −75° to 200° within 2 hr., resulting in a maximal autogenous pressure of about 3000 p.s.i. The total reaction time was 7 hr. The product was fractionated on a 20 cm. × 12 mm. column, packed with Dixon fillings to give 3-methylenecyclobutanecarbonitrile (I, 168 g., 60% yield), b.p. 66.5–67.5° (25 mm), $n^{25}D$ 1.4596; lit.[8] b.p. 64–65° (21 mm.), $n^{25}D$ 1.4595.

Nitrile I was selectively hydrogenated at 60 p.s.i., over a 10% palladium-on-charcoal catalyst in ethanol, to give compound II in practically quantitative yield. II of about 99% purity was obtained by distillation on the previous column, b.p. 66–67° (25 mm.), $n^{23}D$ 1.4265.

Anal. Calcd. for C_6H_9N: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.52; H, 9.63; N, 14.85.

3-Methylcyclobutanecarboxamide (V).—Compound II (140 g., 1.47 moles) was hydrolyzed by refluxing for 16 hr. with 20% aqueous sodium hydroxide (700 ml.). The product was acidified, saturated with sodium chloride, and continuously extracted with ether for 48 hr. The resulting 3-methylcyclobutanecarboxylic acid (III, 118 g., 70% yield) had b.p. 62–63° (0.5 mm.), $n^{25}D$ 1.4355; lit.[8] b.p. 108–108.5° (18 mm.), $n^{25}D$ 1.4351.

Thionyl chloride (48 g., 0.4 mole) and pyridine (0.1 ml.) were introduced into a flask and warmed at 55–60°. To this was added dropwise and with constant stirring acid III (42 g., 0.4 mole). After completing the addition, the liquid was heated on a water bath for 40 min. The 3-methylcyclobutanecarbonyl chloride (IV) obtained (44 g., 83% yield) had b.p. 147–148° (760 mm.), 74° (70 mm.), $n^{25}D$ 1.4425. The conversion of III to the chloride IV was checked by infrared spectroscopy which showed a shift[24] of the C=O frequency from 1715 cm.$^{-1}$ (in III) to 1798 cm.$^{-1}$ (in IV).

To a saturated solution of ammonia in dry ether (250 ml.), kept at −20°, was added with occasional shaking, a cold solution of chloride IV (20 g., 0.15 mole) in dry ether (40 ml.). After completing the addition, ammonia gas was passed through the reaction mixture for 15 min. The precipitate of 3-methylcyclobutanecarboxamide (V) was filtered, and recrystallized from acetone (14.5 g., 86% yield), m.p. 168°, lit.[9] m.p. 167°.

(23) S. Winstein, *J. Am. Chem. Soc.*, **64**, 2792 (1942).

(24) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1960, p. 125.

Methyl 3-Methylcyclobutylcarbamate (VI).—To a solution of V (11.3 g., 0.1 mole) in absolute methanol (65 g.), kept in a round-bottomed flask, was added a freshly prepared solution of sodium methoxide (4.6 g. of sodium in 115 g. of methanol). This was followed by the dropwise addition with constant stirring of bromine (16 g., 0.1 mole). The resulting solution was warmed for 10 min. on a water bath and, after cooling, brought to about pH 6 by adding glacial acetic acid. The solvent was removed and the methyl 3-methylcyclobutylcarbamate (VI) formed was extracted with ether, dried, and distilled (13.1 g., 92% yield), b.p. 63–64° (0.3 mm.), m.p. 26°, $n^{20}D$ 1.4550.

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.45; H, 9.12; N, 9.78.

The structure of VI was confirmed by infrared spectroscopy. The CO absorption (amide I) band of the compound appears at 1725 cm.$^{-1}$, *i.e.*, in the frequency range characteristic of urethanes,[25] while the NH deformation (amide II) band appears, normally, at 1516 cm.$^{-1}$.

3-Methylcyclobutylamine (VII).—Urethane VI (14.3 g., 0.1 mole) was thoroughly mixed in a vibrating machine with freshly prepared, powdered calcium hydroxide (50 g.). The mixture was transferred to a round-bottomed flask, provided with a reflux condenser, and heated slowly in a metal bath up to a temperature of about 170°, at which point reflux started and the temperature of the mixture gradually dropped to 80–85°. The reflux was maintained for 30 min. and the amine produced was distilled and collected in a Dry Ice–acetone trap. At the end any residual amine was removed from the reaction flask at 25 mm. and collected in a liquid air trap. The product was distilled on the same column to separate the methanol, formed during the hydrolysis, from the 3-methylcyclobutylamine (VII, 6.1 g., 72% yield). Several batches of compound VII were united and redistilled to give a sample of more than 97% purity, as determined by gas chromatography, b.p. 99–100° (760 mm.), $n^{20}D$ 1.4310.

The two NH stretching absorption bands of VII appear in the vicinity of 3350 cm.$^{-1}$ (higher intensity) and 3500 cm.$^{-1}$ (lower intensity), while the NH deformation band appears, also normally,[26] at 1590 cm.$^{-1}$.

A small sample of VII was neutralized with 10% hydrochloric acid and the solution evaporated to dryness. The 3-methylcyclobutylamine hydrochloride (VIII) obtained was recrystallized from dry chloroform and washed with dry *n*-pentane, m.p. 166–167°.

Anal. Calcd. for $C_5H_{12}NCl$: C, 49.38; H, 9.95; N, 11.52; Cl, 29.16. Found: C, 49.43; H, 9.85; N, 11.30; Cl, 28.82.

N,N-Dimethyl-3-methylcyclobutylamine (IX).—Amine VII (8.5 g., 0.1 mole) was added dropwise to a 90% solution of formic acid (25.6 g., 0.5 mole) in a three-necked flask provided with a stirrer and a reflux condenser. To the resulting mixture was added a 37% solution of formaldehyde (22.5 ml., 0.3 mole) and the flask heated on a water bath until vigorous evolution of gas started. The flask was removed to allow the reaction to subside (20 min.) and then heated again at 95–100° for 8 hr. To the product was added 4 *N* hydrochloric acid (50 ml.) and the solution evaporated to dryness at 25 mm. The crystalline residue was dissolved in water and the amine liberated by the addition of aqueous sodium hydroxide and then extracted with ether. After removing the solvent, the N,N-dimethyl-3-methylcyclobutylamine (IX) was distilled on the same column (7.6 g., 67% yield), b.p. 111–112° (760 mm.), $n^{20}D$ 1.4194. The equivalent weight of IX, as determined by nonaqueous titration with perchloric acid, was 118 (theoretical, 113).

A small portion of IX was converted into N,N-dimethyl-3-methylcyclobutylamine hydrochloride (X) by the procedure given before. The compound, which was highly hygroscopic, was recrystallized from a mixture of dry chloroform and *n*-pentane and dried for a prolonged period.

Anal. Calcd. for $C_7H_{16}NCl$: C, 56.18; H, 10.78; N, 9.36; Cl, 23.68. Found: C, 55.90; H, 10.61; N, 9.49; Cl, 23.44.

N,N-Dimethyl-3-methylcyclobutylamine Oxide (XI).—To compound IX (5.1 g., 0.05 mole), dissolved in absolute methanol (30 ml.), was added 30% aqueous hydrogen peroxide (15 ml.) and the solution obtained was stirred at room temperature for 6 hr. An additional 8 ml. of the hydrogen peroxide was added and the stirring continued for another 18 hr., at which point a drop of the solution gave a negative test for free amine with phenol-

(25) Ref. 24, pp. 221–222.

(26) Ref. 24, p. 249.

phthalein. The excess of hydrogen peroxide was subsequently decomposed by stirring the solution for 24 hr. in the presence of a small amount of platinum black. The mixture was filtered and the filtrate concentrated at 35°, initially at 20 mm. and then at 1 mm. The N,N-dimethyl-3-methylcyclobutylamine oxide (XI, 5.4 g., 84% yield) was obtained completely dry by heating at 20 mm. and 100°. A small sample of XI was sublimed at 130° (20 mm.) to a white crystalline substance.

Anal. Calcd. for C_7H_5ON: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.69; H, 11.92; N, 10.84.

3-Methylcyclobutene (XII).—The dried compound XI (5.2 g., 0.04 mole) was mixed with Pyrex beads (2-mm. diameter) and heated at 20-mm. pressure in a 50-ml. round-bottomed flask connected to a series of two traps, the first cooled with Dry Ice–acetone and the second with liquid air. The temperature was raised gradually to 130° at which point slow decomposition of the amine oxide takes place. As sublimation tends to compete with the decomposition, it was necessary to interrupt the reaction several times and scrape down any white crystalline material accumulated around the neck of the flask. Decomposition into volatile products was complete in 4 hr., care being taken to keep the temperature below 135°.

The liquid condensed in the traps was washed several times with cold 5% hydrochloric acid, then with ice-cold water and finally dried over anhydrous magnesium sulfate. The 3-methylcyclobutene (XII) so obtained (2.4 g., 88% yield) had $n^{20}D$ 1.4005. The boiling point of XII, as determined by extrapolation of gas chromatographic data on a 10% silicone column, was 32.0°; the retention volume of XII relative to 2,4-dimethylpentane, at 30°, on the same column, was 0.26.

Oxidation of 3-Methylcyclobutene (XII).—Compound XII (68 mg., 1 mmole) and potassium carbonate (150 mg.) were added to 100 ml. of aqueous 60% *t*-butyl alcohol and stirred at 0–2° for 30 hr. with 90 ml. of the oxidant[12] (containing 98.3 mmoles of $NaIO_4$ and 1.7 mmoles of $KMnO_4$ per liter of solution). The product was acidified with dilute sulfuric acid and, after reducing the excess oxidant, continuously extracted with ether. The extract was evaporated to dryness and the crude acid obtained (120 mg.) was examined by infrared spectroscopy. The spectrum was essentially identical with that of a pure sample of α-methylsuccinic acid. A 100-mg. sample of the acid was esterified[27] with phenacyl bromide to give the diphenacyl ester (198 mg., 73% yield), which after recrystallization from ethanol had m.p. 101–102°, lit.[13] m.p. 101–101.5°; the derivative when mixed with an authentic sample showed no melting point depression.

***trans*-2-Methylcyclobutanol (XIII).**—Pure 1-methylcyclobutene[28] (13.6 g., 0.2 mole) and tetrahydrofuran (130 g.) were placed in a three-necked flask, equipped with a condenser, a thermometer, and a sintered glass dispersion tube. The latter was connected to a diborane generator.[15] A solution of boron trifluoride etherate (43 g., 0.3 mole) in diglyme (40 ml.) was placed in the generator flask and a suspension of sodium borohydride (6.8 g., 0.18 mole) in diglyme (200 ml.) added dropwise. The hydroboration[15] was carried out at 0–1°, and the flask was then allowed to stand for 2 hr. at room temperature. Excess hydride was destroyed by the addition of water (20 ml.) and, subsequently, the organoborane was oxidized by first adding 3 *N* aqueous sodium hydroxide (30 ml.), followed by 30% hydrogen peroxide (30 ml.). The warm reaction mixture was stirred for 1 hr. and then continuously extracted with ether. The extract was washed, dried, and the solvent removed. The *trans*-2-methylcyclobutanol (XIII) obtained was distilled on the same column (13.8 g., 80% yield), b.p. 137–138° (760 mm.), 83–84° (100 mm.) $n^{25}D$ 1.4284.

Anal. Calcd. for $C_5H_{10}O$: C, 69.72; H, 11.70. Found: C, 69.56; H, 11.46.

Characteristically[29] for a cyclobutanol, the C–O stretching absorption of compound XIII appears at 1087 cm.$^{-1}$ (cyclobutanol, 1090 cm.$^{-1}$).

***trans*-2-Tosyloxy-1-methylcyclobutane (XIV).**—A solution of *p*-toluenesulfonyl chloride (20.9 g., 0.11 mole) in warm pyridine (10 g.) was introduced into a three-necked flask and cooled rapidly in an ice–water bath to obtain small crystals.[30] *trans*-2-Methylcyclobutanol (9 g., 0.105 mole) was then added dropwise and with constant stirring while keeping the reaction temperature below 20°. After completing the addition and allowing the mixture to stand for 18 hr. at room temperature, water (30 ml.) was added to the externally cooled flask. The liquid was neutralized with ice-cold 8% hydrochloric acid and the ester formed taken up in ether. The ether solution was washed, dried, and the solvent removed; the tosylate was then freed from any volatile impurities by warming at 100° (20 mm.). The slightly yellow *trans*-2-tosyloxy-1-methylcyclobutane (XIV) so obtained (17 g., 68% yield) had $n^{25}D$ 1.5150; it was prepared in slightly better yield (75%) by an alternative procedure.[31]

The infrared spectrum of XIV showed the following bands (cm.$^{-1}$) characteristic[32] for *p*-toluenesulfonates: 1610 (w), 1364 (s), 1191 (m), 1179 (s), 815 (m).

Detosylation of *trans*-2-Tosyloxy-1-methylcyclobutane (XIV).—The allglass apparatus employed for the elimination reaction consisted of a three-necked flask, provided with a thermometer, a dropping funnel, and a magnetic mixer, and connected to a series of two traps cooled in liquid air. Isoamyl alcohol (120 ml.) and diglyme (120 ml.), dried and freshly distilled over lithium aluminum hydride, were introduced into the flask, and to this was added sodium hydride (7.2 g., 0.3 mole, 50% suspension in oil). The mixture was brought with constant stirring to a temperature of 115°, at which point the tosylate XIV (8 g., 0.033 mole) was added dropwise to the flask and, subsequently, the temperature carefully raised to 135° (1 hr.). No condensate was observed in the traps below this temperature. The reaction mixture was kept at 135° for 3 hr. and the distillate collected (1.9 g., 84% yield) was examined by gas chromatography; it contained XII (53%), *trans*-1,3-pentadiene (40%), and *cis*-1,3-pentadiene (7%).

Catalytic Isomerization of 3-Methylcyclobutene (XII).—The apparatus, catalyst preparation, and isomerization procedure were essentially the same as described in previous work.[28] A 3-g. sample of pretreated[28] alumina (Alcoa, grade F-1, 100 mesh) and 0.5 g. of sodium were employed for the preparation of the catalyst in a 50-ml. three-necked flask, and to this was added XII (0.5 g.), dissolved in pure (Phillips, 99%) 2,4-dimethylpentane (8 g.). The mixture was stirred at 5° under nitrogen for 5 hr. and the product distilled at 20 mm. into a liquid air trap. The recovery was 92%. The product, as determined by gas chromatography, contained methylenecyclobutane (14.5%), 1-methylcyclobutene (85.5%), and XII (<0.02%).

Thermal Isomerization of 3-Methylcyclobutene (XII).—The decomposition experiments were carried out in a flow system which consisted essentially of a vertical 30 cm. × 1 cm. Pyrex tube, packed with Pyrex beads, 2 mm. in diameter; the tube was equipped with a constant rate dropping funnel and was connected to a series of coolers and traps. Heat was supplied by a well-insulated furnace and the temperature was measured with a thermocouple at points 5 cm. apart along the entire length of the tube. The isothermal zone (±3°) had a length of about 15 cm. Prior to every experiment the system was purged with dry nitrogen and the temperature adjusted and stabilized for a period of at least 2 hr. The flow of nitrogen was reduced to a minimum during the experiments.

Samples (1–2 ml.) of a 10% solution of 3-methylcyclobutene in 2,4-dimethylpentane (>99.0% pure) were employed in all runs. The same solvent and concentration were used in the comparative experiments with 1-methylcyclobutene and *cis*-1,3-pentadiene.

Bromination of 3-Methylcyclobutene (XII).—To a solution of XII (136 mg., 2 mmoles) in dry carbon tetrachloride, cooled at 0°, was added dropwise and with constant mixing a 5% solution of bromine in the same solvent until a yellow color persisted. The solvent was then removed by microdistillation. The remaining yellow 1,2-dibromo-3-methylcyclobutane (XV, 425 mg., 93% yield) had $n^{25}D$ 1.5210.

Anal. Calcd. for $C_5H_8Br_2$: C, 26.35; H, 3.54; Br, 70.12. Found: C, 26.06; H, 3.90; Br, 70.25.

Gas chromatographic examination of XV showed the presence of two components in the ratio of about 60:40. The retention volumes of the two compounds relative to *n*-pentane, at 96°, on a capillary column coated with polypropylene glycol, were 3.2 and 4.3, respectively.

Analytical.—Olefin samples were analyzed by gas chromatography on a 2-m. column containing 30% silver nitrate–glycol

(27) *Cf.* R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 157.

(28) J. Shabtai and E. Gil-Av, *J. Org. Chem.*, **28**, 2893 (1963).

(29) Ref. 24, p. 109.

(30) G. Eglinton and M. C. Whiting, *J. Chem. Soc.*, 3650 (1950).

(31) F. Drahowzal and D. Klamann, *Monatsh.*, **82**, 460 (1951).

(32) R. S. Tipson, *J. Am. Chem. Soc.*, **74**, 1354 (1952).

solution as the stationary phase.[33] The presence of XII in the detosylation product was confirmed by blending with a sample of the pure compound, obtained by the decomposition of XI. The blending technique was employed for identification purposes also in the case of the *cis*- and *trans*-1,3-pentadiene. The identity of the latter was further established by partial subtraction chromatography on a column containing chloromaleic anhydride.[34]

Geometric isomers of disubstituted cyclobutanes were separated on a capillary column, 150 ft. long and 0.01 in. wide, coated with squalane. 2-Methylcyclobutanol, as well as the dibromo derivatives of XII, was analyzed on a capillary column of the same dimensions, coated with polypropylene glycol.

A Varian A-60 spectrometer was employed for the measurement of the n.m.r. spectrum of XII, using carbon tetrachloride as a solvent and tetramethylsilane as the reference compound.

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(33) J. Shabtai, J. Herling, and E. Gil-Av, *J. Chromatog.*, **11**, 32 (1963).

(34) Y. Herzberg-Minzly and E. Gil-Av, *Bull. Res. Council Israel*, **10A**, 86 (1961); E. Gil-Av and Y. Herzberg-Minzly, *J. Chromatog.*, in press.

Jervine. XI. The Structure and Stereochemistry of Isojervine

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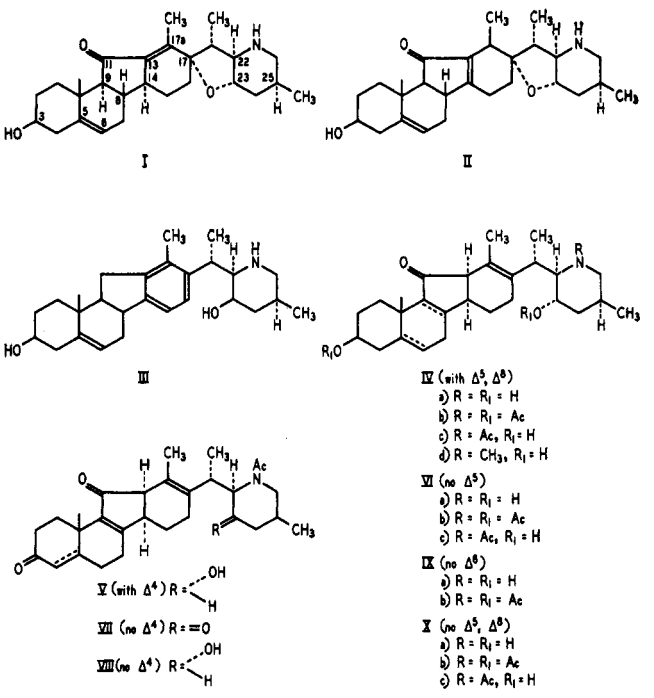
The structure of isojervine has been established as IVa by transformations which lead through its N-acetyl 5,6,8,9-tetrahydro derivative (Xc) and the latter's 17β,17aβ-oxide (XIa) to the enone (XIV) and thence to 5,6-dihydrojervisine 17-monoacetate (XIX) and to triacetyl-5,6-dihydro-11-ketoveratramine (XVII). The abnormal ultraviolet spectrum of isojervine is due to inhibition of resonance in the $\Delta^{8,9}$-11-keto system by the 5,6-double bond, an effect also exerted by the 4,5-double bond in N-acetyl-Δ^4-isojervone (V). Configurational assignments have been made for the asymmetric carbon atoms in rings C and D of isojervine, 5,6,8,9-tetrahydroisojervine, and the latter's derivatives, XI, XII, XIV, and XVIII.

In 1944, Jacobs and Craig[1] recorded the observation that the native veratrum alkaloid jervine, on treatment with hydrochloric acid or methanolic hydrogen chloride, is transformed into an isomer, isojervine, which markedly differs in its properties from the native alkaloid. Thus the hydrochloride and sulfate of isojervine are far more soluble in water or ethanol than the corresponding salts of jervine; in contrast to jervine the isomer is unstable to caustic alkali at room temperature (immediate formation of red pigment); in its ultraviolet absorption spectrum the high maximum at 250 mμ (ε 15,000) characteristic for jervine is replaced by strong end absorption showing only a shoulder of much lower ε (~3000) in that region, while the low intensity maximum at 360 mμ (ε ~60) is hypsochromically shifted to 330 mμ (ε ~250).[2] On short warming with acetic anhydride isojervine formed a N-acetyl derivative and, on more prolonged heating with this reagent, a triacetate.[2]

Concurrently with the investigation which led to the establishment in 1951 of structure I[3] for jervine, a limited amount of work on isojervine was carried out in this laboratory. The results, supplemented by more recent findings, have led us to assign to isojervine, structure IVa. In this paper we present the facts immediately relevant to the structure proof,[4] while other, more tangential aspects of the work will be presented in the following two papers of this series.

Isojervine conforming in its properties with the description of Jacobs and Craig[1] showed in its infrared spectrum a strong carbonyl band at 5.92 μ and a medium high band at 6.10 μ indicative of a conjugated C=C bond. In this respect isojervine resembles Δ^{13}-jervine (II)[5] which exhibits a corresponding band at 5.94 and



(1) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **155**, 565 (1944).

(2) W. A. Jacobs and C. F. Huebner, *ibid.*, **170**, 635 (1947).

(3) The stereochemical features of formula I derive from evidence adduced in the following papers: (a) C-17, C-23, ref. 9; (b) C-22:C-23, J. Sicher and M. Tichy, *Tetrahedron Letters*, **12**, 6 (1959); (c) C-25, S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961); (d) C-22:C-25, R. L. Augustine, *ibid.*, 1448 (1961); (e) C-8, C-9, C-14, H. Mitsuhashi and Y. Shimizu, *Tetrahedron Letters*, **21**, 777 (1961); *Tetrahedron*, **19**, 1027 (1963).

(4) A brief account of this phase of the work has been published [O. Wintersteiner and M. Moore, *Tetrahedron Letters*, **18**, 795 (1962)]. T. Masamune, M. Takasugi, H. Swzuki, S. Kawahar, M. Godha, and T. Irie [*Bull. Chem. Soc. Japan*, **35**, 1749 (1962)] and W. G. Dauben, W. W. Epstein, M. Tanabe, and B. Weinstein [*J. Org. Chem.*, **28**, 293 (1963)] have independently arrived at the same conclusion regarding the structure of isojervine. We are indebted to Professor Masamune and Professor Dauben for making available to us prepublication copies of their manuscripts.

The communication by R. Ikan and H. Conroy [*Bull. Res. Council Israel*, **11A**, 33 (April, 1962)] postulating the same structure is based almost entirely on our own data to which R. Ikan had access in 1960 through Professor Conroy, who has meanwhile informed us that he never authorized the use of these data and of his name for publication.

(5) B. M. Iselin and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 5318 (1955).