

Preparation of [1-¹³C], [3-¹³C], [1-D] and [3-D] Enriched Cyclobutenes

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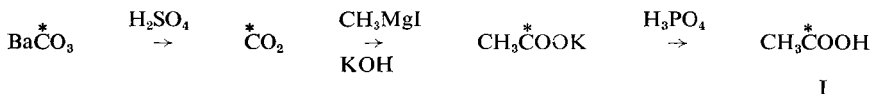
SUMMARY

Three isotopically enriched samples of cyclobutene have been prepared, namely, a mixture containing 20 % [1-¹³C]cyclobutene, 20 % [3-¹³C]cyclobutene and 60 % parent molecule; a second mixture of 75 % [1-D]cyclobutene and 25 % parent molecule; and a third mixture of 50 % [3-D]cyclobutene and 50 % parent molecule. Proton magnetic resonance and infrared spectra showed the samples to be of high purity (> 95%). The preparations successfully have been used for high-resolution microwave studies. The observed microwave line intensities also agreed with the percentage compositions given above.

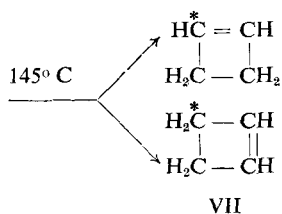
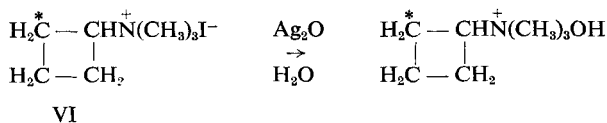
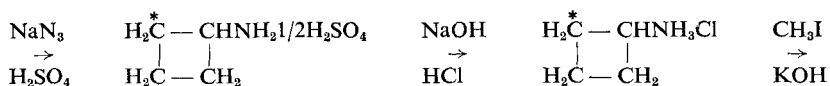
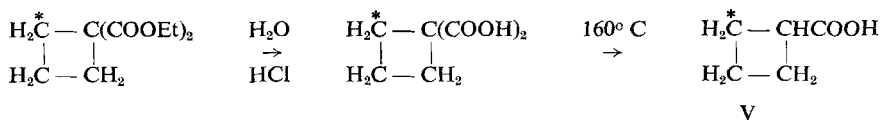
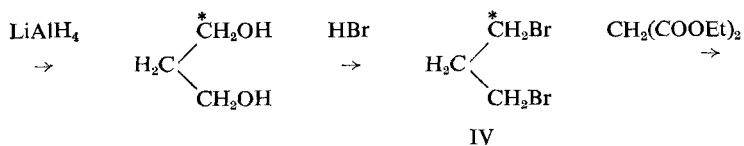
INTRODUCTION.

The purpose of this investigation was to prepare mono-isotopically substituted cyclobutenes in high yield and high purity for use in a determination of the structure of cyclobutene by means of high-resolution microwave spectroscopy*. To attain this, it is necessary to record microwave spectra of [1-¹³C], [3-¹³C], [1-D], and [3-D] isotopic species, that is, samples in which one atom of each group of nuclei, equivalent in cyclobutene, has been substituted by an isotope.

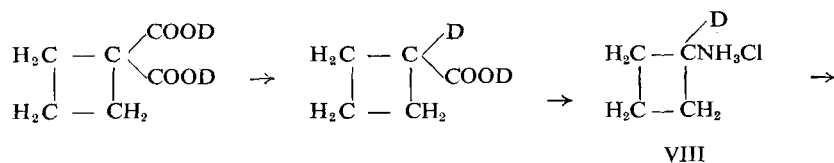
The [1-¹³C], and [3-¹³C] species were prepared as indicated schematically below :

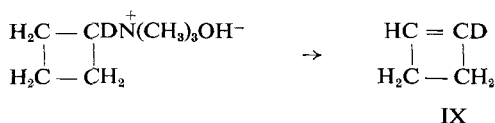


* to be published elsewhere.

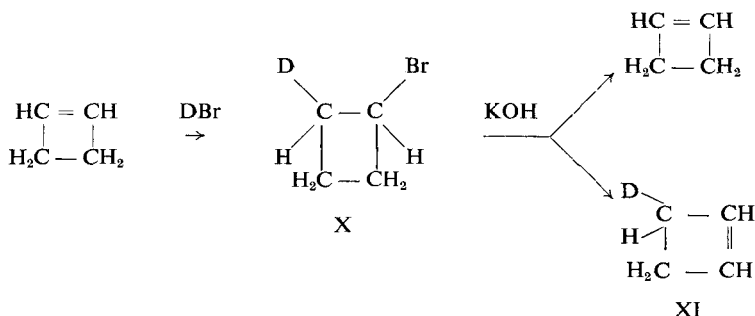


The [1-D] species was obtained in a similar manner :





Finally the [3-D] species was prepared according to the scheme :



EXPERIMENTAL.

Malonic [1-¹³C]acid diethylester. Known procedures^(1, 2) for the preparation of the necessary intermediate compound, malonic [1-¹³C]acid diethylester were modified resulting in a considerable increase of yield.

10.15 g (169 mmoles) of enriched CH₃¹³COOH (I) was liberated from 16.67 g (170 mmoles) of rigorously dried CH₃¹³COOK (prepared from 52 % enriched Ba¹³CO₃) by treatment with 84 % H₃PO₄ saturated with 27 g P₂O₅. After reflux for 40 min of (I) with 2.50 ml freshly distilled (CH₃CO)₂O (26 mmoles), 30.5 g (191 mmoles) of dry bromine was added under continued reflux and magnetic stirring over a period of 2 1/2 h. After further reflux and stirring for 1 h, 2 ml of water was added and H₂O, CH₃COOH and HBr was distilled-off until enriched BrCH₂¹³COOH (II) was seen to condense in the cooler. If the removal of volatile products is not carried so far, undesirable side-reactions occur in the next operation. PMR-spectra (at 60 MHz) of (II) showed that the contents of the ¹³C-compound in (II) was reduced to 40 % compared with the expected 52 %, while the acetic acid in the distillate was enriched in ¹³C to the same percentage (40 %). This suggests that exchange has occurred between (I) and (CH₃CO)₂O in the initial stage of the reaction.

Under external cooling (II) was neutralized by 33 % aqueous sodium hydroxide (phenolphthalein) and 0.5 ml of extra base was added. At 0° C a solution of 9.3 g (190 mmoles) NaCN in 25 ml of water was added (stirring). After 90 min the solution was heated to 95° C and the water was removed quantitatively *in vacuo*. 50 ml (850 mmoles) of abs. ethanol and 25 ml of benzene were added to the dry residue. After cooling to 0° C, 46 ml of conc. H₂SO₄ was added drop by drop (5 min). Under magnetic stirring the reaction mixture was refluxed for 15 h at 75° C. 25 ml of water and 35 ml of benzene

was added and the aqueous layer was extracted with 2 × 20 ml of benzene. The combined benzene extracts were washed, successively, with 15 ml of water, 15 ml of saturated aqueous Na₂CO₃ and 15 ml of water. Final drying over 10 g of MgSO₄ for 3 h and distillation at 83.5-85.5° C at *ca.* 12 mm of Hg produced 19.4 g (121 mmoles) of (COOC₂H₅) CH₂ (¹³COOC₂H₅) (III) representing a 71 % yield with respect to (I), compared to 45-53 % by the earlier procedure ⁽²⁾. The infrared spectrum and the PMR-spectrum showed that the product was pure.

1,3-dibromo-[1-¹³C]propane. By modification of a known procedure ⁽³⁾, (III) was converted directly to 1,3-dibromo-[1-¹³C]propane without isolation of the intermediate [1-¹³C]propandiole-1,3.

19.4 g (121 mmoles) of (III) dissolved in 75 ml dry diethylether was added to 200 ml of a stirred 1.25 M solution of LiAlH₄ in ether at 0° C over a period of 45 min. Reflux for 2 h. In 10 min, 10 ml of water was added drop by drop under cooling (0° C) and stirring, followed by the addition of 26.6 ml conc. H₂SO₄ (500 mmoles) for neutralisation. Ether was distilled-off at atmospheric pressure and 114 ml (1,500 mmoles) of 63 % aqueous HBr was added to produce a 48 % solution of HBr in the flask. Further 110 ml of conc. H₂SO₄ was added and after reflux for 6 h (115° C) a mixture of water, insoluble enriched Br¹³CH₂CH₂CH₂Br (IV), and other products were removed by distillation at atmospheric pressure until no more oily drops appeared in the distillate. The lower liquid layer was separated, washed with water, conc. H₂SO₄, and a 10 % aqueous solution of Na₂CO₃. After drying over 0.5 g of MgSO₄ (10 h) and distillation (b.p. 81-88° C at *ca.* 46 mm Hg) 14.2 g (70 mmoles) of (IV) was obtained (58 % with respect to (III), compared to 49 % by the earlier procedure ⁽³⁾. IR- and PMR-spectra showed (IV) to be pure.

1-carboxy-[2-¹³C]cyclobutane. 14.2 g (70 mmoles) of (IV) was converted to 10.1 g (50.5 mmoles) of an approximately equimolar mixture of the cyclic diesters, 1,1-dicarbethoxy-[2-¹³C]cyclobutane and the normal species (b.p. 102-3° C at 12 mm Hg) ⁽⁴⁾. Control by IR- and PMR-spectra was satisfactory. Again following ⁽⁴⁾, the diesters were hydrolyzed to 6.54 g (45.4 mmoles) of an enriched mixture of 1,1-dicarboxycyclobutanes which was converted to 4.44 g (44 mmoles) of an enriched mixture of 1-carboxy-cyclobutanes (V). The PMR- and IR-spectra showed no impurities.

[2-¹³C]cyclobutyltrimethylammonium iodide. 4.44 g (44 mmoles) of (V) was converted to the corresponding 1-amino-cyclobutenes according to ⁽⁵⁾. Yield 3.98 g (37.0 mmoles) of the dry hydrochlorides. The usual spectroscopic purity tests were satisfactory. Subsequent conversion of this quantity to a mixture of *ca.* 8 g of cyclobutyltrimethylammonium iodide and *ca.* 4 g of KI + KCl was carried out following ⁽⁶⁾. The mixture (VI) was not purified by recrystallization before the next (and final) step of the procedure.

[1-¹³C] and [3-¹³C]cyclobutene. Treatment of (VI) by an excess of Ag₂O + H₂O ⁽⁷⁾ precipitated AgI + AgCl. After filtering (G3) the aqueous

solution (40 ml) was added drop by drop into a hot (145° C) evacuated, two-necked, 100 ml flask in which the pressure was kept at a minimum (1-5 mmHg) by continuously pumping through a trap. The latter contained 100 ml of a 1N solution of H₂SO₄ in diethylene glycol monobutyl ether intended to dissolve water and enriched cyclobutene while binding trimethylamine chemically. This purpose was attained by slowly heating the trap to +5° C after the end of the pyrolysis (stopcockclosed). After cooling to -40° C volatile cyclobutenes (VII) (b.p. 2° C at atm. pressure) with a trace of ethylene were distilled-off. The condensed gasses were cooled to -100° C and ethylene removed fractionally. The remanence proved to be pure, enriched cyclobutene as revealed by an infrared spectrum of the gas (no ethylene left). The PMR-spectrum of a 20 % solution of (VII) in CCl₄ showed the expected ¹³C-splitting of both the vinylic and the allylic proton resonance lines. The intensities of the ¹³C satellite lines showed that the [1-¹³C], and the [3-¹³C]cyclobutene species were present in almost equal concentrations (ca. 20 %). The yield of the pure enriched cyclobutene was 23 mmoles compared to 169 mmoles of enriched CH₃¹³COOH as starting material.

[1-D]cyclobutene. 9.7 g (67 mmoles) of 1,1-dicarboxy-cyclobutane, purchased from Aldrich Chemical Co., was refluxed two times with 13.5 ml (675 mmoles) of D₂O for 2 h. The PMR-spectrum of the recovered acid did not show any carboxylic proton peak (less than 5 %). The deuterated acid was converted to 6.1 g (60.4 mmoles) of 1-carboxy-[1-D]cyclobutane, while 6.28 g (57.9 mmoles) of the dry hydrochlorid of 1-amino-[1-D]cyclobutane (VIII) was obtained in the next step. Finally 32.6 mmoles of pure enriched [1-D]cyclobutene (IX) was obtained by pyrolysis as above. Until this step it was impossible to reveal any contents of the corresponding hydrogen compounds of the intermediates by means of the PMR- and IR-spectra, whereas the PMR-, and MW-spectra of (IX) showed the presence of ca. 25 % of the unsubstituted species. This suggests that the Hofmann elimination in the present case follows the path of an α-elimination as well as the path of a β-elimination, while in general, only β-elimination or so-called α', β-elimination (α' being a hydrogen atom of the N(CH₃)₃ group) occurs in a Hofmann elimination reaction^(8, 9, 10). To ensure that the occurrence of the undeuterated species in (IX) was not a result of an exchange reaction undeuterated cyclobutyltrimethylammonium iodide was treated with Ag₂O + D₂O and pyrolysed as discribed. The PMR- and IR-spectra of the obtained cyclobutene did not show any contents of deuterated species.

1-Bromo-[2-D]cyclobutane. A known method⁽¹¹⁾ for liquid-phase addition of HBr to carbon-carbon double bonds was slightly modified to prepare 1-bromo-[2-D]cyclobutane (X).

19.85 mmoles of normal cyclobutene, prepared from 1,1-dicarboxy-cyclobutane by a series of reactions as described above, and 20.6 mmoles of DBr, prepared according to⁽¹²⁾, were distilled successively and underhigh vacuum into a 50 ml quartz flask cooled with liquid nitrogen. A quartz beaker

filled with isopropyl alcohol (-78°C) was placed around the quartz flask and the reaction mixture was irradiated by a quartz mercury arc lamp for 15 min. At the end of this period the temperature of the bath was -65°C at which temperature volatile components were removed fractionally. The distillation was repeated at -40°C . Control of the remaining 2.37 g (17.4 mmoles) of (X) by PMR-spectra was satisfactory.

[3-D]cyclobutene. 5.6 g (100 mmoles) of KOH in 10 ml of 95 % ethanol was added to the quantity of (X) obtained in the preceding step. The mixture was refluxed for 3 h at 115°C during which a volatile product (XI), not retained by the water condenser, was collected in a Dry Ice-cooled trap. The IR-, PMR- and MW-spectra of (XI) showed that it was a pure, approximately equimolar mixture of [3-D]cyclobutene and normal cyclobutene. This further shows that the addition reaction and the elimination reaction are of the same type i.e. both either *cis* or *trans* reactions. No α -elimination of HBr from (X) seems to take place. The yield of (XI) was 4.8 mmoles.

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REFERENCES

1. CHRISTIE, C. F. — U. S. Patent 2, 459, 144, Jan. 18, 1949.
2. GIANETTO, R. and BOUTHILLIER, L. P. — *Can J. Biochem. and Physiol.*, **32** : 154 (1954).
3. BAK, B. and CLAUSON-KAAS, N. — *Acta Chem. Scand.*, **12** : 995 (1958).
4. CASON, J. and ALLEN, C. F. — *J. Org. Chem.*, **14** : 1036 (1949).
5. HEISIG, G. B. — *J. Am. Chem. Soc.*, **63** : 1698-99 (1941).
6. WILLSTÄTTER, R. *et al.* — *Ber.*, **38** : 1992 (1905), and *Ann.*, **317** : 220 (1901).
7. ROBERTS, J. D. and SAUER, C. W. — *J. Am. Chem. Soc.*, **71** : 3925 (1949).
8. COPE, A. C. and TRUMBULL, E. R. — *Organic Reactions*, Vol. XI, J. Wiley and Sons, Inc., New York, 1960, p. 317.
9. COPE, A. C. and MEHTA, A. S. — *J. Am. Chem. Soc.*, **85** : 1949 (1963).
10. KIRMSE, W. — *Angew. Chem.*, **77** : 1 (1965).
11. VAUGHAN, W. E. *et al.* — *J. Org. Chem.*, **7** : 477 (1942).
12. CLUSIUS, K. and WOLF, G. — *Z. Naturforsch.*, **2a** : 495 (1947).