volume. Water (100 ml.) was added, and the solution was chilled 12 hours, producing 6.1 g. (56%) of crude solid. This was recrystallized several times from a mixture of benzene and ligroin, then vacuum sublimed (75–85° (1 mm.)) to produce pure 2-chloro-2-phenylpropionamide, m.p. 100–101°.

Anal. Calcd. for $C_9H_{10}ONCl$: C, 58.84; H, 5.49. Found: C, 58.96, 59.12; H, 5.60, 5.63.

Raney Nickel and 2-Chloro-2-phenylpropionamide.—The above amide (0.57 g.) and Raney nickel (4 g.) were heated for four hours in refluxing absolute ethanol (20 ml.). Customary work-up gave 0.20 g. (43%) of crude solid, m.p. 80–86°. Recrystallization from benzene gave a sample, m.p. 88–93° undepressed on admixture with pure 2-phenylpropionamide.

STANFORD, CALFORNIA

[CONTRIBUTION NO. 2080 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Small-Ring Compounds. XIV. Radioactive Cyclobutanone from Ketene and Diazomethane-^{14}C[1]

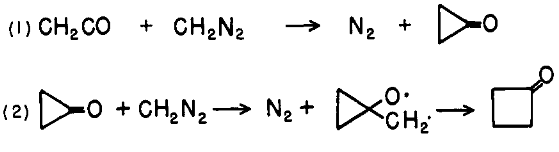
BY DOROTHY A. SEMENOW, EUGENE F. COX AND JOHN D. ROBERTS

RECEIVED JANUARY 23, 1956

It has been shown by the ^{14}C-tracer technique that cyclobutanone is formed from the reaction of ketene with diazomethane-^{14}C *via* an intermediate possessing the symmetry properties of cyclopropanone.

Introduction

The formation of cyclobutanone from ketene and diazomethane at −70° was discovered by Lipp and Köster[2] in the course of research on possible syntheses of cyclopropanone. They formulated the reaction as proceeding *via* cyclopropanone as an intermediate. In support of this mechanism, it was cited[2] that step 2 was similar to the path previously proposed for the formation of methyl ethyl ketone from acetone and diazomethane[3] and that cyclic ketones such as cyclopentanone and cyclohexanone react with diazomethane to form higher homologs.[4]

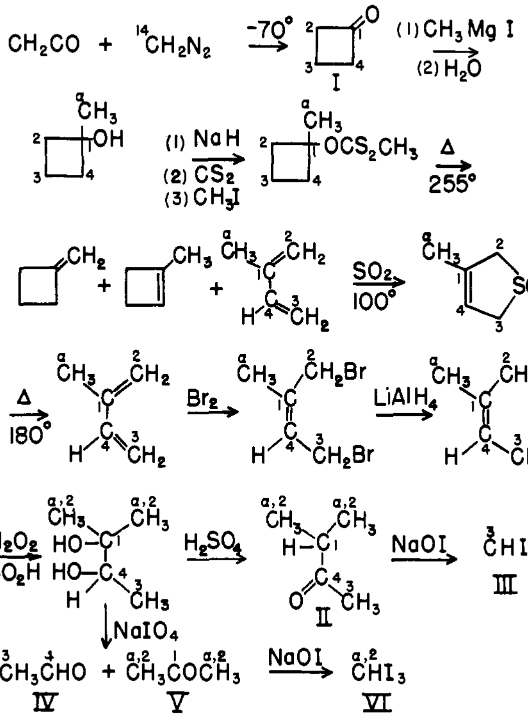


Subsequent workers[5] have questioned the cyclopropanone intermediate on the grounds that it was considered unlikely that cyclopropanone would react smoothly with diazomethane in ether at −70° while cyclobutanone is stable under these same conditions.

The present research involved the determination of the ^{14}C-distribution in cyclobutanone prepared from ketene and diazomethane-^{14}C in order to obtain direct experimental evidence bearing on the reaction mechanism.

Synthetic and Degradative Procedures

Cyclobutanone-*x*-^{14}C (I) was prepared from ketene and diazomethane-^{14}C as described previously.[2,5] The location of the ^{14}C in the cyclobutanone (I) was achieved by ^{14}C-analyses of the products of the following degradative scheme.



Results and Discussion

Inspection of the results of the ^{14}C-analyses given in Table I reveals that the several ways of adding and subtracting the various activities give agreement within the limits of error. Thus, the

TABLE I

RADIOACTIVITY ANALYSES OF DEGRADATION PRODUCTS OF CYCLOBUTANONE-*x*-^{14}C

	Meas. act.[d]	Total act., %
3-Methyl-2-butanone (II)[a]	0.1062	(100.00 ± 0.43[e])
Iodoform (III)	.02736	25.76 ± .01[e]
Acetaldehyde (IV)[b]	.06703	63.12 ± .06[e]
Acetone (V)[c]	.03896	36.69 ± .14[e]
Iodoform (VI)	.01956	18.42 ± .04[e]

[a] 3-Methyl-2-butanone as the 2,4-dinitrophenylhydrazone. [b] Acetaldehyde as dimethone. [c] Acetone as 2,4-dinitrophenylhydrazone. [d] Average activities in microcuries per millimole (μc./mmole); determined using the vibrating-reed electrometer method as described by O. K. Neville, THIS JOURNAL, **70**, 3499 (1948). [e] Standard deviation determined from three or more combustions.

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[1] Supported in part by the Petroleum Research Fund of the American Chemical Society.

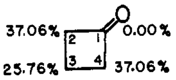
[2] P. Lipp and R. Köster, *Ber.*, **64**, 2823 (1931).

[3] H. Meerwein and W. Burneleit, *ibid.*, **61**, 1840 (1928).

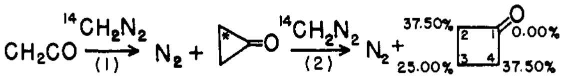
[4] E. Mosettig and A. Burger, THIS JOURNAL, **52**, 3456 (1930).

[5] S. Kaarsemaker and J. Coops, *Rec. trav. chim.*, **70**, 1033 (1951).

activities of V (C-α,1,2) and IV (C-3,4) total 99.81%, well within the limits of error for II (C-α,1,2,3,4), 100.00 ± 0.43%. The average values for the ^{14}C-distribution are shown below.

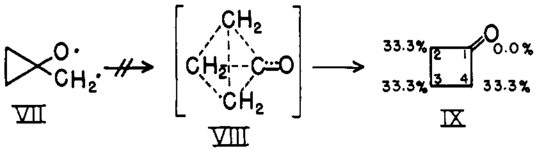


The results are consistent with initial formation of cyclopropanone from which cyclobutanone arises by introduction of a methylene group on either side of the carbonyl group with equal probability. The high reactivity toward diazomethane of the three-membered as compared to the four-membered ketonic ring may be associated with the greater angle strain in the former species.



^{14}C-Activity distribution predicted for cyclopropanone intermediate.

Definite conclusions concerning the details of the mechanisms for formation of cyclopropanone (step 1) and cyclobutanone (step 2) cannot be drawn from the results of the present investigation. However, *if* the previously postulated[2] cyclopropylcarbinyl type radical (VII) is an intermediate in Step 2, the three methylene groups do not achieve the degree of equivalence characteristic of *cationic* intermediates derived from cyclopropylcarbinyl compounds.[6]



If a highly symmetrical entity like VIII were involved, it would lead to 33.3% of the radioactivity at *each* of the methylene-positions of the cyclobutanone (IX) in contrast to the observed values of 37.1, 25.8 and 37.1% for the 2-, 3- and 4-positions, respectively.

Experimental

Cyclobutanone-*x*-^{14}C.—N-Nitroso-N-methyl-^{14}C-urea was prepared by a modification of a previously described procedure.[7] Methyl-^{14}C-urea (2.20 g., 0.030 mole, 1 mc.) and sodium nitrite (2.6 g., 0.038 mole) were dissolved in 13 ml. of water. The solution was stirred at 0° while a solution of 1.30 ml. of concentrated sulfuric acid in 14 g. of ice-water was added dropwise during 20 minutes. The dry product weighed 2.14 g. (0.021 mole), 61%, and had a measured ^{14}C activity of 30 μc./mmole. This material (1.32 g., 0.0128 mole), diluted with 31.3 g. (0.303 mole) of inactive N-nitroso-N-methylurea, was used to prepare diazomethane-^{14}C as described previously.[8] Cyclobutanone-*x*-^{14}C, approximately 2.5 μc./mmole, b.p. 39.0–40.1° (82 mm.), was prepared from the diazomethane-^{14}C and ketene (in 26% over-all yield from N-nitroso-N-methylurea-^{14}C) as described previously.[2,5]

1-Methylcyclobutanol-*x*-^{14}C.—To the stirred Grignard reagent from 22.0 g. (0.15 mole) of methyl iodide and 3.8 g. (0.16 mole) of magnesium in 60 ml. of dry ether was added 7.9 g. (0.11 mole) of cyclobutanone-*x*-^{14}C (approximately 0.56 μc./mmole) in 30 ml. of dry ether over 30 minutes. The mixture was maintained at reflux for 1.5 hours, then cooled to −70°, and 8 ml. of water added cautiously. The ethereal layer was decanted from the hydrated magnesium salts, and the salts were thoroughly washed with ten 10-ml. portions of ether. The ethereal portions were combined and dried over magnesium sulfate. The 1-methylcyclobutanol-*x*-^{14}C, after fractionation through a 23-cm. column fitted with a tantalum wire coil, weighed 5.5 g. (60%), b.p. 114.5–115.0° (740 mm.).

O-1-Methylcyclobutyl-*x*-^{14}C S-Methyl Xanthate.—The procedure was as described previously.[9] From 5.5 g. (0.064 mole) of 1-methylcyclobutanol-*x*-^{14}C, 2.3 g. (0.095 mole) of sodium hydride, 6.9 g. (0.091 mole) of carbon disulfide and 12.9 g. (0.091 mole) of methyl iodide was obtained, after distillation through a 23-cm. column fitted with a tantalum wire coil, 8.8 g., 78%, of O-1-methylcyclobutyl-*x*-^{14}C S-methyl xanthate, b.p. 67.0–69.5° (1.3 mm.).

Methylenecyclobutane-*x*-^{14}C, 1-Methylcyclobutene-*x*-^{14}C and Isoprene-*x*-^{14}C.—The apparatus consisted of a 50-ml. flask containing 25 ml. of biphenyl surmounted by an air condenser. A rubber policeman was connected to one opening of a T-tube at the top of a condenser and the other opening was connected in series to an empty trap, a fritted-disk gas-washing bottle containing 40% sodium hydroxide, a drying tube, a Dry Ice condenser with receiver and finally a Dry Ice trap. All connections were of Tygon tubing. The biphenyl was heated to reflux and 8.5 g. (0.048 mole) of O-1-methylcyclobutyl-*x*-^{14}C S-methyl xanthate was injected through the rubber policeman with a hypodermic syringe as rapidly as foaming permitted. After completion of the addition, the system was flushed with dry nitrogen while the apparatus was warmed with a heat lamp. The yield of hydrocarbon was 2.8 g. (86%). The infrared spectrum of the product indicated the following composition: methylenecyclobutane (18%), 1-methylcyclobutene (25%) and isoprene (57%).

3-Methyl-2,5-dihydrothiophene-1,1-dioxide-*x*^{14}C (Isoprene Cyclic Sulfone).—The hydrocarbon mixture (2.8 g., 0.036 mole) resulting from the preceding reaction was heated with 2.1 g. (0.031 mole) of non-radioactive isoprene, 0.18 mole of sulfur dioxide and 0.08 g. (0.0008 mole) of hydroquinone for 12 hours at 100–102° in a sealed tube. After removal of the excess sulfur dioxide, the product was dissolved in the minimum of water at 50–60°, treated with Norite and filtered. The yield of white, glistening plates of cyclic sulfone was 2.6 g. (38%), m.p. 63.2–63.8°. When this procedure was applied to unlabeled material yields averaging 83% were obtained. Omission of hydroquinone led to considerable polymerization, and two experiments (with hydroquinone) at room temperature gave only a tough, yellow polymer which, when macerated and extracted with hot water, gave only 24–31% of isoprene cyclic sulfone.

Isoprene-*x*-^{14}C.—An 8 × 300-mm. fractionating column packed with a platinum spiral and equipped with a heating jacket and a 50-ml. boiler was fitted at the top with an inlet for dry nitrogen and an outlet which led successively to an empty trap, a fritted disk gas-washing bottle containing 20% sodium hydroxide, a drying tube, a Dry Ice condenser with receiver and, finally, a Dry Ice trap. Isoprene-*x*-^{14}C cyclic sulfone (2.6 g., 0.019 mole) diluted with 3.2 g. (0.024 mole) of non-radioactive sulfone was placed in the boiler and the flow of nitrogen started. The jacket was maintained at 170–180°. The boiler was heated with a bath at 110° and the temperature was raised to 180° over 45 minutes. A heat lamp was used to facilitate removal of the last of the isoprene-*x*-^{14}C from the system. The collected isoprene-*x*-^{14}C (2.68 g., 92%) of approximately 0.1 μC./mmole had an infrared spectrum identical to that of authentic material.

1,4-Dibromo-2-methyl-2-butene-*x*-^{14}C (Isoprene 1,4-Dibromide).—The procedure was as described previously.[10] From 2.68 g. (0.039 mole) of isoprene-*x*-^{14}C and 6.25 g. (0.039 mole) of bromine was obtained, after distillation through a 23-cm. column packed with a tantalum wire coil, 7.07 g. (80%) of isoprene-*x*-^{14}C 1,4-dibromide, b.p. 61.0–64.0° (1.9 mm.).

2-Methyl-2-butene-*x*-^{14}C (Trimethylethylene-*x*-^{14}C).—The reduction of the dibromide was carried out essentially

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[6] J. D. Roberts and R. H. Mazur, THIS JOURNAL, **73**, 3542 (1951).

[7] R. D. Heard, J. R. Jamieson and S. Solomon, *ibid.*, **73**, 4985 (1951).

[8] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 461.

[9] J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949).

[10] A. F. Shepard and J. R. Johnson, *ibid.*, **54**, 4385 (1932).

as described previously.[11] The apparatus consisted of a 100-ml. three-necked flask with stirrer, dropping funnel, and gas-exit tube connected through a drying tube to a Dry Ice condenser with receiver, and finally to a Dry Ice-cooled trap. Diethylcarbitol (dried over sodium) (20 ml.) and 0.97 g. (0.025 mole) of lithium aluminum hydride were stirred and heated to 70°, and a solution of 7.07 g. (0.031 mole) of isoprene-*x*-^{14}C dibromide in 6 ml. of dry diethylcarbitol was added over a period of 65 minutes, the reaction being quite vigorous. After an additional 20 minutes, 10 ml. of water was added cautiously, the evolved hydrogen driving the last traces of trimethylethylene-*x*-^{14}C into the receiver. The product (1.99 g., 92%) had an infrared spectrum identical to the spectrum of authentic trimethylethylene, b.p. 37.6–38.5° (738 mm.), prepared by heating *t*-amyl chloride with water.

2-Methyl-2,3-butanediol-*x*-^{14}-C.—The procedure was as described previously.[12] From the treatment of 1.99 g. (0.028 mole) of 2-methyl-2-butene-*x*-^{14}C with performic acid followed by saponification was obtained, after distillation through a 23-cm. column packed with a tantalum wire coil, 1.21 g. (42%) of 2-methyl-2,3-butanediol-*x*-^{14}C, b.p. 89.5–89.7° (22.2 mm.).

Degradation of 2-Methyl-2,3-butanediol-*x*-^{14}C to II, III, IV, V and VI.—The procedures were as described previously.[12] The 2,4-dinitrophenylhydrazone of 3-methyl-2-butanone-*x*-^{14}C (II) after three recrystallizations from methanol–water had m.p. 122.9–123.5°. The iodoform-^{14}C samples (III and VI) after three recrystallizations from methanol–water had m.p. 118.2–119.5 dec. The dimethone derivative of acetaldehyde-*x*-^{14}C (IV) after 3 recrystallizations from cyclohexane had m.p. 142.9–143.5°. Ether extraction of the crude dinitrophenylhydrazone of acetone-^{14}C (V) was necessary to separate the unreacted 2,4-dinitrophenylhydrazine (insoluble in ether). The dinitrophenylhydrazone of V was then recrystallized three times from methanol–water to give material of m.p. 124.4–125.1°.

PASADENA, CALIFORNIA

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[11] L. W. Trevoy and W. G. Brown, THIS JOURNAL, **71**, 1675 (1949).

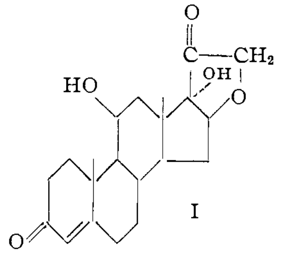
[12] J. D. Roberts, R. E. McMahon and J. S. Hine, *ibid.*, **72**, 4237 (1950).

COMMUNICATIONS TO THE EDITOR

STEROIDAL CYCLIC KETALS. XXI.[1] THE PREPARATION OF 16β,21-EPOXIDO-STEROIDS

Sir:

We wish to report the synthesis of a steroid which has been tentatively assigned the structure 11β,17α-dihydroxy-3,20-dioxo-4-pregnen-16β,21-epoxide (I).



I

This represents, in essence, the first synthesis of a steroid possessing the pentacyclic skeleton of a perhydro-furocyclopentenophenanthrene, the basic structure of the pseudosapogenins.[2] Moreover, this ring system with a β-tetrahydrofuranone moiety as in I has been employed in a hypothetical structure of diginin[3,4] and its aglycone, diginigenin.[4]

Acetylation of 3,20-bis-ethylenedioxy-5,16-pregnadiene-11β,21-diol (II)[5] in pyridine afforded its 21-acetate III, m.p. 167–168°,[6] $[\alpha]_D$ −32°[6] (*Anal.* Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.72; H, 8.38) which on hydroxylation with osmium tetroxide was converted into 21-acetoxy-3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α-triol (IV). The latter, m.p. 189–192°, $[\alpha]_D$ −19° (*Anal.* Calcd. for $C_{27}H_{40}O_9$: C, 63.76; H, 7.93. Found: C, 63.59; H, 8.21), was also obtained by selective acetylation of 3,20-bis-ethylenedioxy-5-pregnene-11β,16α,17α,21-tetrol (V).[1] Mesylation afforded 21-acetoxy-3,20-bis-ethylenedioxy-16α-methanesulfonyloxy-5-pregnene-11β,17α-diol (VI), m.p. 169–171° (*Anal.* Calcd. for $C_{28}H_{42}O_{11}S$: S, 5.60. Found: S, 6.38).

Compound VI in 5% alcoholic potassium hydroxide was refluxed for 4 hours, and a 1:4 displacement reaction[7] (the derived anion at C-21 displaced by way of the β-face the 16α-mesyloxy group) occurred to afford in 79% yield 3,20-bis-ethylenedioxy-11β,17α-dihydroxy-5 pregnene-16β,21-epoxide (VII), m.p. 232–234°, $[\alpha]_D$ −81°, ν_{max}^{KBr} 3620, 1682, 1160 and 1105 cm.$^{-1}$ (*Anal.* Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.14; H, 7.82). Compound VII was also obtained by reduction with lithium aluminum hydride[8] of 3,20-bis-ethylenedioxy-17α-hydroxy-11-oxo-5-pregnene-16β,21-epoxide (VIII), m.p. 230.5–232.5°, $[\alpha]_D$ −76°, ν_{max}^{KBr} 3620, 1722, 1680, 1090 and 1060 cm.$^{-1}$ (*Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.61; H, 8.00), similarly prepared by a displacement reaction.

Acid hydrolysis (8% v./v. sulfuric acid in methanol, 16 hours reflux) of VII gave 11β,17α-dihydroxy-3,20-dioxo-4-pregnen-16β,21-epoxide (I), m.p. 235–237°, $\lambda_{max.}^{abs.\ alc.}$ 241 mμ (ϵ 15,900), $[\alpha]_D$ +8°, ν_{max}^{KBr} 3790, 3508 (hydroxyl, doublet), 1780 (20-carbonyl), 1662 (3-carbonyl), 1631 (Δ^4) and 1066 cm.$^{-1}$ (strong C–O) (*Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.72;

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[1] Paper XX, W. S. Allen and S. Bernstein, THIS JOURNAL, **78**, 1909 (1956).

[2] R. E. Marker, *et al.*, *ibid.*, **64**, 1655 (1942).

[3] W. Karrer, E. C. Barell Festschrift, Basel, 1936, p. 238, isolated diginin from the leaves of *Digitalis purpurea*.

[4] C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **23**, 975 (1940); **25**, 1611 (1942); C. W. Shoppee, *ibid.*, **27**, 246, 426 (1944).

[5] W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

[6] M.p.'s are uncorrected. Rotations are for chloroform solution at 24–25°.

[7] S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 9; and S. Peat, "Advances in Carbohydrate Chemistry," Vol. 2, Academic Press, Inc., Publ., New York, N. Y., 1946, p. 56.

[8] When this reduction was attempted with sodium borohydride in tetrahydrofuran and 5% sodium hydroxide (overnight reflux) the product was principally starting material.