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The Reaction of 2-Cyclopropylethylamine-1-^{14}C with Nitrous Acid[1,2]

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2-Cyclopropylethylamine-1-^{14}C reacts with nitrous acid to give, in 57% yield, a mixture of 2-cyclopropylethanol, cyclopropylmethylcarbinol and cyclopentanol in relative amounts of 1.00:0.76:0.18. The isotope position distribution in these alcohols corresponds to an extensive rearrangement whose predominant feature is an irreversible shift of cyclopropyl from C-2 to C-1, which is uniquely determined by the conformation of the rearranging ion. The formation of cyclopentanol is interpreted as a 1,3-shift, an unusual participation of cyclopropyl.

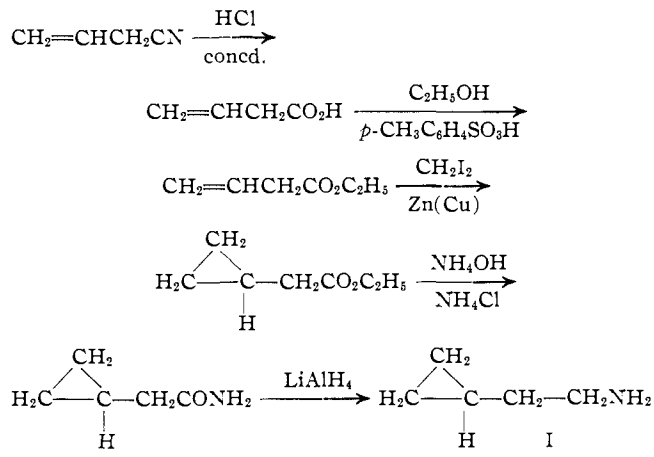
There has been a continuing interest in those reactions of cyclopropyl compounds which involve carbonium ions as reactive intermediates. Reactions which involve development of a positive charge on a cyclopropane ring carbon proceed slowly and give rearranged products.[3-5] The unusually rapid reactions and the rearrangements often observed in analogous reactions of the cyclopropylcarbinyl system have been more thoroughly investigated.[4-11]

In view of their unique character, it might be anticipated that cyclopropyl groups on a carbon atom adjacent to a reaction center could also participate in a reaction in characteristic ways. We have been led to seek for evidence for such participation in part because of considerations of structure and reactivity and also because in earlier work in this Laboratory, one such example has been discovered and explored. Cloke showed that aryl cyclopropyl ketimines rearrange on heating to aryl pyrrolines, and that the rearrangement takes place at a lower temperature in the case of the ketimmonium salts or in the presence of a small amount of pyrrolinium salt.[12,13]

Other reactions in which nitrogen adjacent to a carbon bearing a cyclopropyl group is a reactive center were found to give rearrangement reactions of the usual type, with cyclopropyl groups competing, but weakly, with alkyl and aryl groups for migration. Thus, the sulfuric acid catalyzed reaction of hydrazoic acid with cyclopropyl ketones gives mixtures of amides of cyclopropanecarboxylic acid and N-cyclopropylcarboxamides,[14] and the acid-catalyzed rearrangement of cyclopropylcarbinyl azides gives mixtures containing cyclopropyl ketones and cyclopropylamine.[15] The reaction of methyl cyclopropyl ketone with peroxytrifluoroacetic acid, a reaction in which a positive charge is generated on oxygen adjacent to a carbon bearing a cyclopropyl group, gives cyclopropyl acetate,[16] and dicyclopropyl ketone in a similar reaction gives cyclopropyl cyclopropanecarboxylate.[17]

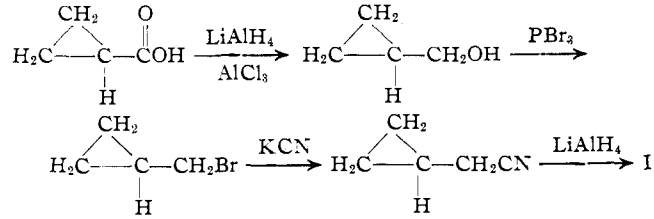
In spite of these "normal" reactions of cyclopropyl located on a carbon adjacent to a nitrogen or oxygen as a positive center we wished to examine several reactions in the 2-cyclopropylethyl system for evidence of participation of the cyclopropyl group. The reaction of 2-cyclopropylethylamine-1-^{14}C with nitrous acid is reported in this paper.

2-Cyclopropylethylamine (I) was first prepared in 0.8% over-all yield from 3-butenenitrile. In the second step the separation of ethyl crotonate, formed through



isomerization, was troublesome. The reaction of methylene iodide with ethyl 3-butenoate gave variable yields; no cyclopropyl compounds could be isolated when this reaction was attempted with the nitrile or amide.

A synthesis which proved more reliable for the preparation of C-14 labeled amine involved the reaction of phosphorus tribromide with cyclopropylcarbinol; the unsaturated and cyclobutyl isomers were separated after conversion to nitriles by preparative gas chromatography. The yield from cyclopropanecarboxylic acid was 4.5%.



The reaction of 2-cyclopropylethylamine with nitrous acid at 5° gave a 57% yield of a mixture of alcohols which was separated by gas chromatography. The alcohols obtained are listed in order of elution in Table I. They were identified by comparison of their infrared spectra and refractive indices with reference samples, which were prepared by the reduction of methyl cyclo-

(1) Based upon the Ph.D. Thesis of G. E. C.

(2) Presented at the Meeting of the Organic Chemistry Division, American Chemical Society, at Washington, D. C., in March, 1962.

(3) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).

(4) A. Streitwieser, Jr., *Chem. Rev.*, **56**, 571 (1956).

(5) D. E. Applequist and G. F. Fanta, *J. Am. Chem. Soc.*, **82**, 6393 (1960), have reported on the rearrangement of spiropentylamine which contains both elements of structure.

(6) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951).

(7) C. G. Bergstrom and S. Siegel, *ibid.*, **74**, 145 (1952).

(8) R. G. Pearson and S. H. Langer, *ibid.*, **75**, 1065 (1953); R. A. Sneen and A. L. Baron, *ibid.*, **83**, 614 (1961).

(9) H. Hart and J. M. Sandri, *ibid.*, **81**, 320 (1959).

(10) E. F. Cox, M. C. Caserio, M. S. Silver and J. D. Roberts, *ibid.*, **83**, 2719 (1961); R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver and J. D. Roberts, *ibid.*, **81**, 4390 (1959); M. C. Caserio, W. H. Graham and J. D. Roberts, *Tetrahedron*, **11**, 171 (1960).

(11) S. Borčić, M. Nikoletić and D. E. Sünko, *J. Am. Chem. Soc.*, **84**, 1615 (1962).

(12) J. B. Cloke, *ibid.*, **51**, 1174 (1929).

(13) (a) J. B. Cloke, *et al.*, *ibid.*, **67**, 2155 (1945); (b) P. M. Maginnity and J. B. Cloke, *ibid.*, **73**, 49 (1951).

(14) S. C. Bunce and J. B. Cloke, *ibid.*, **76**, 2244 (1954).

(15) G. H. Potter and S. C. Bunce, Paper presented at the 134th National Meeting of the American Chemical Society, September, 1958.

(16) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(17) H. Hart and D. P. Wyman, *ibid.*, **81**, 4891 (1959).

propyl ketone, cyclopentanone and ethyl cyclopropylacetate with lithium aluminum hydride.

TABLE I

ALCOHOLS FORMED FROM 2-CYCLOPROPYLETHYLAMINE AND NITROUS ACID

Alcohol	Relative amount	n^{20}D Found	n^{20}D Literature
Methylcyclopropylcarbinol	0.76	1.4310	1.4313[8]
Cyclopentanol	0.18	1.4465[a]	1.4530
2-Cyclopropylethanol	1.00	1.4349	1.4327(25°)[17]

[a] The cyclopentanol fraction contains a small amount of 2-cyclopropylethanol.

The method of work-up of the reaction mixture was not designed to recover unsaturated hydrocarbons which are usually formed as side products in the reaction of aliphatic amines with nitrous acid. It is unlikely that any alcohol formed in excess of 1% was undetected. The presence of three additional components, in amounts less than 3% of the total, was indicated in the gas chromatography. The one product not an alcohol which was isolated in amounts sufficient for infrared spectral analysis was a nitro compound containing a cyclopropyl group, probably 2-cyclopropylnitroethane.[18] This product is believed to arise from displacement by nitrite ion on the diazonium ion. The two components of the mixture which were first eluted from the column, present only in trace amounts, may have been chlorides.

Two observations are appropriate at this point. The amount of secondary alcohol formed by hydride shift in this reaction is significantly greater than that reported for comparable reactions of aliphatic amines. For example, the reaction of *n*-butylamine gives 58% of an alcohol mixture containing 1-butanol and 2-butanol in ratio 1.00:0.54[19]; the same ratio was found for the primary and secondary acetates formed in acetic acid solution.[20] More important is the formation of cyclopentanol. The absence of any cyclobutyl derivatives indicates that the five-membered ring was not formed by a succession of 1,2-shifts. We are led by this argument and others to be presented later to interpret this as a 1,3-shift of carbon accompanying cyclopropyl ring opening, a reaction which has, as far as we are aware, no direct parallel. A 1,3-shift of methyl has sometimes been considered possible, but in only one instance does the alternative path of a succession of 1,2-shifts appear improbable.[21,22]

A study of the reaction of 2-cyclopropylethylamine-1-^{14}C with nitrous acid was undertaken, in the hope that the nature of the shift to form cyclopentanol might be elucidated, and that any possible participation of cyclopropyl in a symmetrical bridged or non-classical intermediate might be uncovered. 2-Cyclopropylethylamine-1-^{14}C, prepared by the second reaction sequence, gave a mixture of labeled alcohols in the same yield and in the same proportion as indicated in Table I.

(18) We are indebted to N. B. Colthup for this identification. Nitromethane has recently been found in the products of deamination of methylamine [A. T. Austin, *Nature*, **188**, 1086 (1960)].

(19) F. C. Whitmore and D. P. Langlois, *J. Am. Chem. Soc.*, **54**, 3441 (1932).

(20) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957).

(21) W. A. Mosher and J. C. Cox, *J. Am. Chem. Soc.*, **72**, 3701 (1950).

(22) (a) The 1,3-hydride shifts formulated by Roberts [J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954)] in rearrangement of C-14 labeled norbornyl derivatives may be 1,2-shifts in a non-classical intermediate. (b) Vinyl cyclopropane–cyclopentane isomerizations are known to take place at high temperatures [J. A. Berson and J. W. Patton, *ibid.*, **84**, 3406 (1962); W. von E. Doering, M. R. Wilcott, III, and M. Jones, Jr., *ibid.*, **84**, 1224 (1962); C. G. Overberger and A. E. Borchert, *ibid.*, **82**, 1007, 4897 (1960); and M. C. Flowers and H. M. Frey, *J. Chem. Soc.*, 3547 (1961)].

The reaction scheme used in the degradation of 2-cyclopropylethanol-X-^{14}C is illustrated in Fig. 1. The specific activities are given in μc./mmole; that of 2-cyclopropylethanol-X-^{14}C was determined as the phenylurethan derivative. The potassium permanganate oxidation of 2-cyclopropylethanol-X-^{14}C produced a mixture of cyclopropylacetic acid-X-^{14}C, cyclopropanecarboxylic acid-X-^{14}C and carbon dioxide. The ethyl esters were prepared by the Fisher esterification method, separated by means of a gas chromatograph preparative column and hydrolyzed to the corresponding acids. Cyclopropylacetic acid-X-^{14}C and cyclopropanecarboxylic acid-X-^{14}C were decarboxylated by means of the Schmidt reaction. Based on the radioactivity assay, carbon-14 was found in the ratio of 73.8–26.2 between C_1 and C_2, with no radioactivity in the cyclopropyl ring.[23]

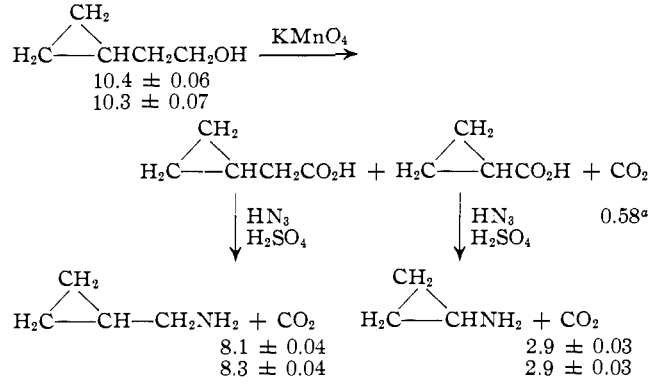


Fig. 1.—Degradation of 2-cyclopropylethanol-X-^{14}C. The specific activities are in μc./mmole. [a] Activity is low due to oxidation of impure 2-cyclopropylethanol-X-^{14}C; this result was not used in calculations.

The degradation of methylcyclopropylcarbinol-X-^{14}C, accomplished in similar fashion, is shown in Fig. 2. In this case, the benzamide of cyclopropylamine was obtained also; we do not know to what process its slight but statistically significant activity may be attributed. The carbon-14 concentrations found in the carbinol carbon positions, the methyl group and the cyclopropyl group were 77.4, 22.0 and 0.6%, respectively.

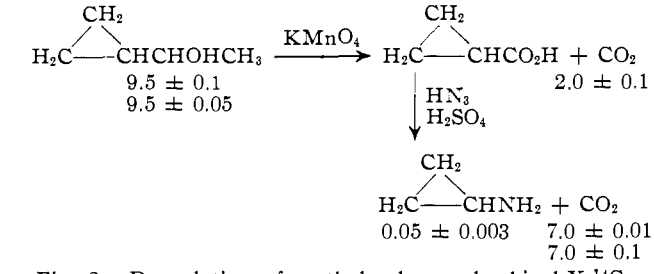


Fig. 2.—Degradation of methylcyclopropylcarbinol-X-^{14}C.

The degradation of cyclopentanol-X-^{14}C, as shown in Fig. 3, was completed only to the formation of diaminobutane (analyzed as the N,N′-dibenzoyl derivative) because the amount of isotopically labeled cyclopentanol (analyzed as the phenylurethan) was very small. The 1-position of the ring contained 37% and the remainder of the molecule 63% of the activity.

(23) An attempted preparation of the benzamide of cyclopropylamine remaining from the degradation gave an unidentified nitrogen-containing compound with radioactivity only 0.002 μc./mmole above background. The radioactivity analysis given in Fig. 1 indicates a slight surplus of carbon-14 in the products; this is attributed to a slight impurity in the diluent used to lower the specific activity of the 2-cyclopropylethanol-X-^{14}C obtained from the rearrangement product. This impurity does not affect radioassay of the carbon dioxide obtained from the decarboxylation of cyclopropylacetic acid-X-^{14}C and cyclopropanecarboxylic-X-^{14}C acid because these acids were obtained from ethyl esters which had been purified by gas chromatography.

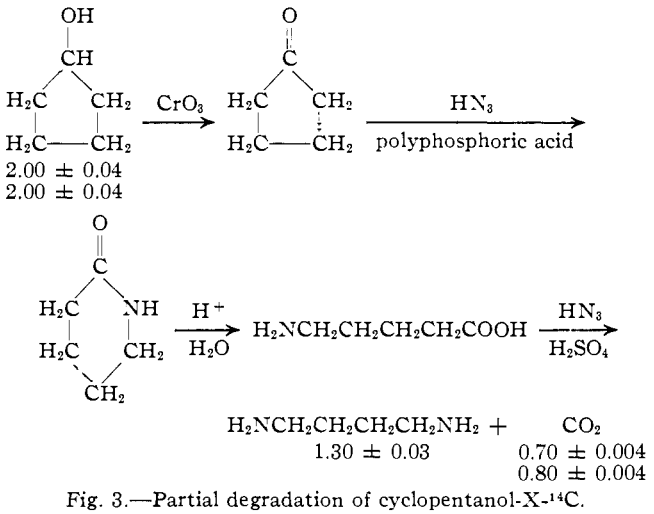


Fig. 3.—Partial degradation of cyclopentanol-X-^{14}C.

The distribution of carbon-14 in the primary alcohol led us to think at first that along with a displacement of the diazonium group by water there occurred some cyclopropyl group migration, possibly through a symmetrical ion in which a cyclopropyl group bridged the ethane carbon atoms. The distribution of carbon-14 found in the secondary alcohol was quite unexpected, and required a different interpretation.

To be sure that this unusual distribution was not an artifact, caused by rearrangement during the degradation, 1-cyclopropylethanol-2-^{14}C was prepared by the reaction of cyclopropyl cyanide and methylmagnesium-^{14}C iodide followed by lithium aluminum hydride reduction, and degraded in similar fashion. Of the initial activity of the secondary alcohol, 6.35 ± 0.05 μc./mmole, 6.25 ± 0.1 μc./mmole was present in the carbon dioxide and 0.085 ± 0.005 μc./mmole in the cyclopropanecarboxylic and resulting from the degradation. Rearrangement during permanganate oxidation thus did not exceed 1.3%.

We have thus been led to consider the intervention of an unsymmetrical intermediate species whose structure might particularly favor a 1,2-shift of cyclopropyl. Further, its structure must lead to a shift which is not readily reversed; it cannot, therefore, involve a symmetrical intermediate.

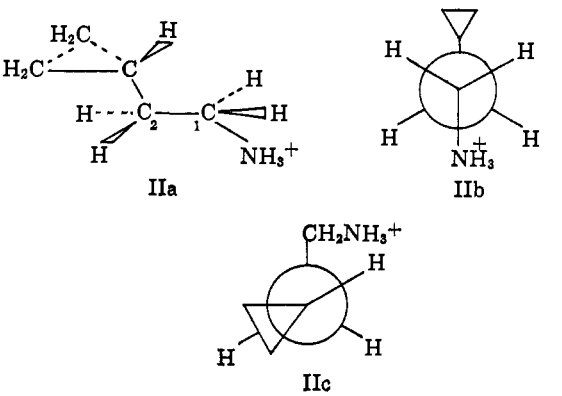
The reaction of a primary amine with nitrous acid, while related in general to reactions proceeding by a carbonium ion mechanism, has some features which are unique. In comparison with solvolysis reactions, the intermediates obtained by decomposition of alkyldiazonium ions have particularly high energy, and there is less need for assistance from neighboring groups in cation formation.[22a,24] Further, it has been shown that the rates of rearrangement in a carbonium ion formed in this way may be rapid compared with the rate of rotation about the bond between the charged carbon and its neighbor.[25]

In the sterically favored conformation of the starting cyclopropylethylammonium chloride (IIa) the cyclopropyl group should be *trans* to the amino group in rotations about C_1–C_2 (IIb), and one of the methylene groups of the cyclopropyl ring should be *trans* to C_1- (IIc).

The same conformation is assumed for the diazonium ion; both in it and in the amine salt, the stabilization that would be achieved if the cyclopropyl group were close to the positively charged center is sterically hindered.

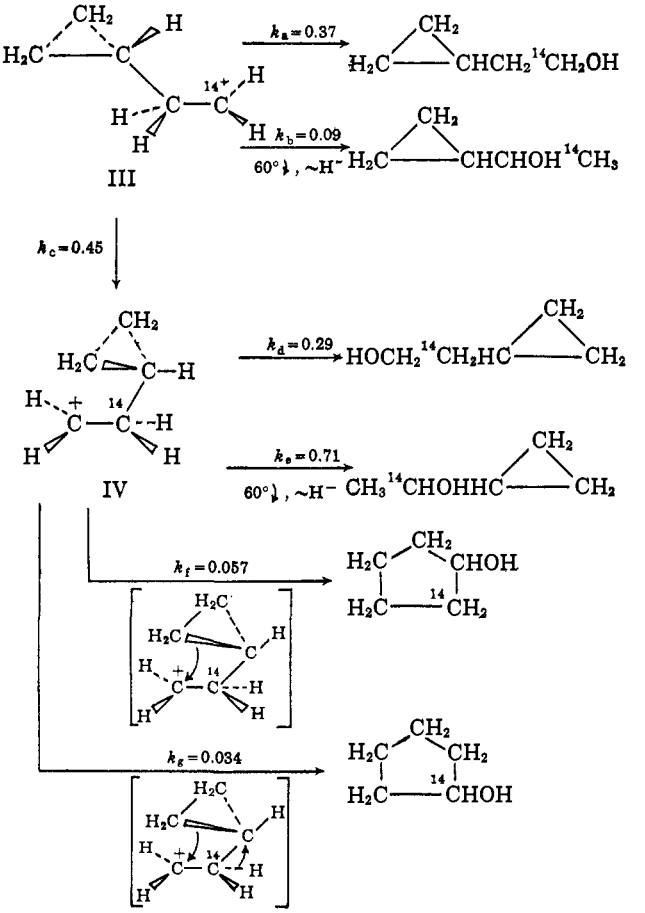
(24) J. G. Burr, Jr., and L. S. Ciereszko, *J. Am. Chem. Soc.*, **74**, 5426 (1952).

(25) B. M. Benjamin, H. J. Schaeffer and C. J. Collins, *ibid.*, **79**, 6160 (1957).



If both the loss of nitrogen from the diazonium ion to form an open, planar carbonium ion (III) and the subsequent rearrangement in the carbonium ion are rapid compared with the rate of rotation about C_2–$C_{cyclopropyl}$, then the subsequent steps of the reaction may be formulated as a series of competing and consecutive reactions whose relative rates are identified as k_a–k_g.[26]

In each case, reaction with solvent completes the step. The one process which gives no rearrangement is the reaction of III with water, for which the rate is k_a. Most of the other rates are composites of a rearrangement and reaction with water.



The numerical values shown are the solutions to simultaneous equations involving rates and the experimentally determined relative amounts of the three alcohols and of the position of carbon-14 in each.

(26) It should be stated that selection of these as the contributing reactions and the attribution of relative values to their rates may be an over-simplification, as one of the referees has pointed out. Contributions to the products which might derive from alternate conformations of II and from a rotation about the C_2–$C_{cyclopropyl}$ bond in III (presumably slower than rotation about C_1–C_2) are believed to be less and have not been included because the analysis becomes much more difficult.

Solvent attack, hydride shift (following a 60° rotation about C_1–C_2), and cyclopropyl shift are all responsible for the disappearance of III. The stabilization of IV which derives from the cyclopropyl group overlying the positive charge explains the relatively high rate k_c. Once formed, IV decomposes as does III, about one-third by solvent attack; but in rearrangement a hydride shift now predominates, rather than a cyclopropyl shift.

An additional reason for the relatively favored (k_e = 0.71) formation of carbinol-labeled methylcyclopropylcarbinol is the stability of the ion formed by hydride shift from IV. In this and not in any of the other ions postulated the conformation is such (as the ion is formed) to allow cyclopropyl participation in a "bicyclobutonium ion." The increased stability of this structure, usually associated with bond breaking to form allylcarbinyl and cyclobutyl derivatives,[10] has also been shown to facilitate reaction without giving rearrangement.[8] Very little, if any, of unsaturated or cyclobutyl alcohol is present in the reaction product.

Finally, the 1,3-shift attending the cyclopropyl ring opening can take place only from IV, with its uniquely determined conformation. If this is accompanied in part by a simultaneous hydride shift, the carbon-14 distribution in cyclopentanol is explained.[27,28]

These reactions have demonstrated unexpected ways in which a cyclopropyl group interacts with a neighboring positively charged center. A study of related reactions such as solvolyses and of reactions involving the 2-cyclopropylethylcarbanion and radical may prove to be similarly interesting.

The reaction path proposed seems not to be related directly to the other reported case of ring enlargement of cyclopropyl to a five-membered ring, the rearrangement to pyrrolines.

Acknowledgment.—The authors wish to express their appreciation for the support from the National Science Foundation, Research Grant C-12309, which made possible this research. They are indebted to Professor H. F. Herbrandson for helpful discussions.

Experimental[29]

Ethyl Cyclopropylacetate.—Esterification of 220 g. (0.6 mole) of 3-butenoic acid, b.p. 60° at 8 mm., prepared[30] from 3-butenenitrile by hydrolysis with hydrochloric acid in 69% yield, was conducted by azeotropic distillation with 1500 ml. of anhydrous ethanol, 2.0 g. of *p*-toluenesulfonic acid and 50 ml. of benzene. After distilling azeotrope and solvent through an efficient column, the ester and alcohol were concentrated to 600 ml. and poured into 1 l. of ice-water. The ester was extracted with three 200-ml. portions of ether, dried over anhydrous magnesium sulfate and distilled. Ethyl 3-butenoate boiling at 125.0–125.5°, n^{20}D 1.4114, 189 g. (65% yield), (lit.[31a] b.p. 119°, n^{20}D 1.4105), was obtained along with 15 g. of ethyl crotonate, b.p. 136–138°, n^{20}D 1.4232 (lit.[31b] b.p. 138°, n^{20}D 1.4252).

In a 500-ml. flask fitted with a magnetic stirrer and a reflux condenser protected by a drying tube filled with calcium chloride were placed 134.0 g. of Zn(Cu) couple[32] (containing 1.85 g. atoms of Zn) and 625 ml. of anhydrous ether. A crystal of iodine was added and the mixture was stirred for 0.5 hour. Addition of a mixture of 189 g. (1.66 moles) of ethyl 3-butenoate and 495 g. (1.85 moles) of methylene iodide induced a mild exothermic reaction. At the end of 15 hours of stirring and refluxing, the ether solution was decanted, the finely divided copper and unreacted couple were washed with two 30-ml. portions of ether, and the combined washes and solution were shaken with saturated ammonium chloride solution, saturated sodium bicarbonate solution and saturated salt solution. The ether solution was dried over anhydrous magnesium sulfate, filtered and distilled through a 40-cm. vacuum-jacketed column packed with Helipak. Approximately 26 g. (12%) of ethyl cyclopropylacetate, b.p. 148.2° (cor.), n^{20}D 1.4220, was obtained. The forerun contained 56.7 g. of recovered ethyl 3-butenoate.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.49; H, 9.44. Found: C, 65.11; 64.96; H, 9.62, 9.57.

Cyclopropylacetamide.—A mixture of 7.0 g. (0.06 mole) of ethyl cyclopropylacetate, 20 ml. of concentrated ammonium hydroxide and 3 g. (0.06 mole) of ammonium chloride was stirred and kept warm for 28 hours. The mixture was chilled slightly with Dry Ice to initiate crystallization, allowed to stand at room temperature for 2 hours, and then cooled in an ice-bath. Approximately 1.4 g. (24%) of cyclopropylacetamide, m.p. 122.5–123.7° (reported[33] m.p. 122.5–124.0°), was obtained.

2-Cyclopropylethylamine Hydrochloride (I) from Cyclopropylacetamide.—A refluxing mixture of 0.8 g. (0.021 mole) of lithium aluminum hydride and 300 ml. of ether was allowed to pass into the cup of a Soxhlet extractor which contained 0.8 g. (0.008 mole) of cyclopropylacetamide. The reduction was continued for 2 days, after which the white addition compound was decomposed carefully with ice-water. The ether solution was filtered, the white precipitate was washed with ether several times, and the combined ether extracts were dried over sodium sulfate. The ether solution was concentrated and decolorized with Norit; dry hydrogen chloride bubbled through the solution gave a crude salt which was separated, dried in a vacuum desiccator, and recrystallized from acetonitrile. Approximately 0.4 g. (60%) of 2-cyclopropylethylamine hydrochloride, m.p. 199.0–199.3°, was obtained. The identity of this sample with that prepared from cyclopropylacetonitrile was indicated by comparison of infrared spectra obtained with sodium chloride optics (Infracord) and of infrared spectra obtained with lithium fluoride optics (Perkin Elmer model 12B) in the carbon–hydrogen region on both samples, and by an undepressed mixture melting point.

2-Cyclopropylethylamine-1-^{14}C *via* Cyclopropylcarbinol.—Cyclopropanecarboxylic acid was prepared from 3-bromochloropropane in 38% over-all yield. Individual preparations of 3-chlorobutyronitrile[34] on a 12-mole scale gave 41–59% yields; the reaction with sodium hydroxide[35] in 2-mole batches gave 61–74% of cyclopropanecarboxylic acid, b.p. 85° (20 mm.). The reduction to cyclopropylcarbinol followed Nystrom's[36] procedure; a mixture of 43.0 g. (0.25 mole) of anhydrous aluminum chloride in 250 ml. of ether and 9.5 g. (0.25 mole) of lithium aluminum hydride in 250 ml. of ether was stirred during the dropwise addition of 13.2 g. (0.15 mole) of cyclopropanecarboxylic acid. After refluxing for 2 hours, cold 3 *N* sulfuric acid was added, and the ether layer and extracts of the aqueous layer were dried over sodium sulfate and distilled through a 30-cm. column packed with glass helices. The yield of alcohol, b.p. 123.7–124.5°, n^{20}D 1.4329 (reported[37] b.p. 123.7–124°, n^{24}D 1.4308), was 7.2 g. (67%) in a typical run.

A mixture consisting chiefly of cyclopropylcarbinyl bromide together with allylcarbinyl bromide and cyclobutyl bromide was obtained by a procedure developed in this laboratory.[37] During the course of 2 hours, 144 g. (2 moles) of cyclopropylcarbinol was added dropwise at −20° with stirring to 270.7 g. (1 mole) of phosphorus tribromide, in a flask protected against moisture. The mixture was stirred for an additional 15 minutes at −20° and for 5 hours at room temperature. The liquid was decanted and the orange-colored crystalline residue was washed with three 75-ml. portions of chloroform which were then combined with the decantate. The solution was fractionated through an insulated 22-cm. column, packed with 3/16 in. glass helices. The forerun was collected up to 101° while the fraction 101–108°,

(27) The possible formation of some cyclopentanol-3-^{14}C has not been excluded experimentally. One of the referees has pointed out that it might arise by the most straightforward carbonium ion mechanism leading to cyclopentanol, a 1,3-shift in the rotational conformer of III.

(28) The hydride shift which must be involved in the formation of cyclopentanol with the observed activity cannot be a succession of random shifts about a carbonium ion, for this leads first to a maximum of 28% activity at carbon-1, and eventually to a random distribution (20% activity).

(29) Melting points are corrected [S. C. Bunce, *Anal. Chem.*, **25**, 825 (1953)]. Infrared spectra were measured with a Perkin–Elmer Infracord with sodium chloride optics; those of solids were determined in potassium bromide. Microanalyses on non-radioactive samples are by Drs. G. Weiler and F. B. Strauss, 164 Banbury Road, Oxford, Eng. Analyses for carbon were performed in connection with analysis of every sample for radioactivity and were satisfactory. Radioactivity measurements were made by means of combustion and proportional counting of carbon dioxide [R. C. Anderson, Y. Delabarre and A. A. Bothner-By, *Anal. Chem.*, **24**, 1298 (1952)]. Duplicate combustion and counting of solids gave checking results; the error is expressed as the standard counting error.

(30) E. Reitz, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 851.

(31) (a) I. Heilbron and H. Bunbary, "Dictionary of Organic Compounds," Oxford Univ. Press, New York, N. Y., 1953, Vol. IV, p. 665; (b) *ibid.*, Vol. I, p. 615; (c) *ibid.*, Vol. I, p. 646; (d) *ibid.*, Vol. IV, p. 219; (e) *ibid.*, Vol. IV, p. 270; (f) *ibid.*, Vol. I, p. 10.

(32) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **81**, 4256 (1959).

(33) W. A. West, Ph.D. Thesis, Rensselaer Polytechnic Institute, 1950.

(34) C. F. H. Allen, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 156.

(35) C. M. McCloskey and G. H. Coleman, *ibid.*, Coll. Vol. III, 1955, p. 221.

(36) R. N. Nystrom, *J. Am. Chem. Soc.*, **81**, 610 (1959).

(37) J. F. Marcelli, Ph.D. Thesis, Rensselaer Polytechnic Institute, 1957.

224 g. (83%), was collected as crude cyclopropylcarbinyl bromide.

A solution of 110.7 g. (3.36 moles) of sodium cyanide-^{14}CN[38] in 150 ml. of water was stirred while 224.0 g. (1.66 moles) of crude cyclopropylcarbinyl bromide dissolved in 200 ml. of ethanol was added dropwise over a period of 1 hour. The mixture was stirred and refluxed for 4 hours. The crude cyclopropylacetonitrile-1-^{14}C was steam distilled and approximately 3.0 l. of distillate was collected. The distillate was saturated with potassium carbonate and extracted with five 100-ml. portions of ether. The ether extracts were combined and washed with four 10-ml. portions of 3:1 sulfuric acid in order to remove isonitrile. The ethereal solution was then neutralized with sodium bicarbonate solution, dried with anhydrous sodium sulfate, and the ether removed.

Separation of the mixture of three isomeric nitriles was attempted (non-radioactive experiments) by fractional distillation through a 40-plate column (packed with Podbielniak Helipak) at high reflux ratio, but the best fraction, b.p. 147°, still was found by vapor chromatography to contain two components.

A preparative column[39] for a Perkin–Elmer model 154-B vapor fractometer was therefore constructed to effect this separation. The column, having a 0.5-in. diameter and a 9-ft. flow path, was packed with 20% Carbowax 1540 (Union Carbide Corporation) on C-22 Firebrick, 42–60 mesh.[40] The maximum capacity of this column, for a moderately efficient separation of the isomers at 100°, with a flow rate of 110 cc./min. of helium, was a 0.5-ml. sample. The vapors were collected in an ice-water cooled spiral trap. A 20% yield of pure cyclopropylacetonitrile-1-^{14}C was obtained. The vapor chromatograph of the isolated cyclopropylacetonitrile-1-^{14}C, using an analytical column, indicated that the sample contained only one component. Crude cyclobutyl cyanide-^{14}C and 4-pentenenitrile-^{14}C were also isolated and characterized by their infrared spectra.[41]

The spectrum of cyclopropylacetonitrile had absorptions characteristic for the three-membered ring at 3.2, 3.3 and 9.7 μ. Absorption at 6.06 μ characteristic of unsaturation was found in the spectrum of 4-pentenenitrile and absorption at 10.7 μ, characteristic of the four-membered ring, was found in that of cyclobutyl cyanide. A band at 4.4 μ, characteristic of the cyanide group, was found in each spectrum. The absence of absorptions at 6.06 and at 10.7 μ in the spectrum of cyclopropylacetonitrile was additional evidence of its purity.

A mixture of 11.4 g. (0.3 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether was stirred at room temperature while 24.3 g. (0.3 mole) of cyclopropylacetonitrile-1-^{14}C, obtained by gas chromatography, dissolved in 100 ml. of anhydrous ether was added dropwise at room temperature over a period of 1.5 hours. The white precipitate was stirred with refluxing for 2 hours. The remaining lithium aluminum hydride and precipitate were decomposed by the careful addition of ice-water, and after stirring for 2 hours, the solution was filtered and dried over sodium hydroxide flakes, then concentrated to approximately 200 ml. and treated with Norit. After filtration, dry hydrogen chloride was bubbled through the solution, and the precipitated salt was collected and dried in a vacuum desiccator. The salt was recrystallized from acetonitrile with Norit, and 13.8 g. of 2-cyclopropylethylamine-1-^{14}C hydrochloride, m.p. 200.0–200.3° (38.5% yield), was obtained in 3.3% radioactive yield. The benzamide, m.p. 55.9–57.0°, was prepared according to Shriner, Fuson and Curtin.[42a]

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.25, 76.46; H, 7.77, 7.83; N, 7.25, 7.50.

Reaction of 2-Cyclopropylethylamine-1-^{14}C with Nitrous Acid.—To a stirred solution of 10.3 g. (0.086 mole) of 2-cyclopropylethylamine hydrochloride in 180 ml. of water and 20 ml. of 1 *N* hydrochloric acid at 5°, a solution of 20.7 g. (0.3 mole) of sodium nitrite in 100 ml. of water was added dropwise. The solution was then heated to boiling and the mixture distilled until about 50 ml. of distillate was collected. The distillate was saturated with potassium carbonate and continuously extracted with ether for 81 hours, and the extract was dried over anhydrous magnesium sulfate and distilled. One fraction was collected, b.p. 65–142°, 4.2 g. (57% yield).

Separation of the products was first accomplished by vapor-phase chromatography on a 1-meter, 0.25-in. column packed with 20% Carbowax 4000 (Union Carbide Corporation) on C-22 firebrick, 42–60 mesh. A 0.01-ml. sample was the maximum capacity for a moderately efficient separation at 100°, with a flow rate of 60 cc./min. helium. The vapors were collected in an ice-cooled 2-mm. U-trap. The amounts of each fraction were estimated by comparison with the area under the curves of chromatographs of weighed amounts of authentic samples, and have been indicated in Table I. Cyclopentanol was difficult to separate from 2-cyclopropylethanol; the other separations were not difficult. A liquid which was more slowly eluted was present in very small proportion; an amount just sufficient for an infrared spectrum indicated a primary nitro group (6.45 μ), and a cyclopropyl group (3.25, 3.35 and 9.7 μ). Larger quantities (0.3–0.4 ml.) were separated with the preparative column packed with Carbowax 4000 on C-22 firebrick.

Degradation of 2-Cyclopropylethanol-X-^{14}C.—In a 500-ml. flask equipped with a side-arm and magnetic stirrer were placed 4.9 g. (0.057 mole) of 2-cyclopropylethanol-X-^{14}C and 12 g. (0.076 mole) of potassium permanganate in 200 ml. of water. The flask was attached to a vacuum system by means of a condenser. A stream of high purity nitrogen was passed through the flask and then through a coil trap cooled in liquid nitrogen. At the end of this period the flask was disconnected, the vacuum rack was evacuated and the carbon dioxide was transferred to one of the reservoir bulbs, 2.24 l. at 7 mm. (1 mmole), and then analyzed for radioactivity.

The aqueous reaction mixture was acidified and filtered. The clear filtrate was concentrated and extracted with five 50-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and distilled. The residue, approximately 1.5 g., containing a mixture of cyclopropylacetic acid-X-^{14}C and cyclopropanecarboxylic acid-X-^{14}C, was combined with 50 ml. of absolute ethanol, 10 ml. of benzene and 1 ml. of concentrated sulfuric acid. The mixture was refluxed for 5 days with the removal of the ternary azeotrope, then concentrated to approximately 10 ml., poured into 25 g. of ice–water mixture, made basic with excess potassium carbonate and extracted with ten 5-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate and distilled. The residue, a mixture of ethyl cyclopropylacetate-X-^{14}C and ethyl cyclopropanecarboxylate-X-^{14}C, was separated by means of gas chromatography on the column described for the separation of the isomeric nitriles. Approximately 0.5 g. of each ester was obtained.

Ethyl cyclopropanecarboxylate-X-^{14}C (0.5 g., 0.0044 mole) was hydrolyzed directly in the trap in which it was collected by adding 0.5 g. (0.013 mole) of sodium hydroxide in 2 ml. of water and refluxing until the mixture was completely miscible. The solution was then acidified and extracted with five 2-ml. portions of ether, and the combined ether extracts were dried over magnesium sulfate and distilled. The residue was cyclopropanecarboxylic acid-X-^{14}C, 0.2 g. (53%).

In a 50-ml. flask equipped with an addition tube and a magnetic stirrer were placed 0.2 g. (0.0023 mole) of cyclopropanecarboxylic acid-X-^{14}C and 1.0 ml. of concentrated sulfuric acid. The flask was attached to a vacuum system by means of a Dry Ice–acetone condenser. Over a period of several minutes 0.12 g. (0.0028 mole) of hydrazoic acid in 1.5 ml. of chloroform was added dropwise while the mixture was stirred and heated at 50°. The system was continuously flushed for 4 hours with high purity nitrogen. The evolved carbon dioxide was collected in a coil trap cooled in liquid nitrogen, was transferred to one of the reservoir bulbs, and analyzed for radioactivity.

The acid solution was neutralized with dilute sodium hydroxide. A white precipitate, m.p. 192.6–193.4°, was obtained while attempting to prepare the benzamide derivative[42a] of cyclopropylamine-X-^{14}C (m.p.[43] 98.5°). The radioactivity of the unknown material was 40 c.p.m. for a 0.746-mg. sample; analysis in combustion for carbon-14 counting gave 76.81% carbon.

The hydrolysis of ethyl cyclopropylacetate-X-^{14}C and the isolation of cyclopropylacetic acid-X-^{14}C were conducted by the methods used for the hydrolysis of ethyl cyclopropanecarboxylate-X-^{14}C and isolation of cyclopropanecarboxylic acid-X-^{14}C. Approximately 0.2 g. (50% yield) of cyclopropylacetic acid-X-^{14}C was obtained, which was then decarboxylated by similar procedures.

Degradation of Methylcyclopropylcarbinol-X-^{14}C.—In a 500-ml. flask equipped with a side-arm and magnetic stirrer were placed 3.5 g. (0.041 mole) of methylcyclopropylcarbinol-X-^{14}C and 9.5 g. (0.06 mole) of potassium permanganate in 200 ml. of water. The procedure followed in this oxidation and assay of the products was like that described for 2-cyclopropylethanol-X-^{14}C. Approximately 1.7 g. (33% yield) of crude cyclopropanecarboxylic acid-X-^{14}C was obtained.

(38) Obtained from New England Nuclear Co. All syntheses and degradations with carbon-14 compounds were first conducted with inactive material.

(39) N. Brenner and V. J. Coates, Paper presented at the Fittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, March, 1957.

(40) We are indebted to M. Hadsell of the General Electric Research Laboratory, Schenectady, N. Y., for suggestions about the packings used for separation of the nitriles and of the isomeric alcohols produced in the re-arrangement reaction.

(41) J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, N. Y., 1958, pp. 30, 36, 264.

(42) (a) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 226; (b) *ibid.*, p. 211.

(43) R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. C. Silver and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 4390 (1959).

The degradation of 1.7 g. (0.02 mole) of cyclopropanecarboxylic acid-X-^{14}C by similar procedures gave carbon dioxide and the benzamide of cyclopropylamine-X-^{14}C, m.p. 96–98° (lit.[43] 98.5°), prepared as described by Shriner, Fuson and Curtin.[42a]

Partial Degradation of Cyclopentanol-X-^{14}C.—In a 100-ml. flask equipped with a condenser, dropping funnel and magnetic stirrer was placed 2.7 g. (0.03 mole) of cyclopentanol-X-^{14}C. A solution of 4.8 g. of potassium dichromate, 6.1 g. of concentrated sulfuric acid and 32 ml. of water was added dropwise during 90 minutes in order that the temperature would not rise above 60°.[44] The acid solution was stirred for 1 hour, extracted with five 20-ml. portions of ether, and the combined ether extracts were dried over anhydrous magnesium sulfate and distilled. Crude cyclopentanone-X-^{14}C (b.p. 128–131°; lit.[31c] 130°), 2.3 g. (90% yield), was obtained.

In a 100-ml. flask equipped with a mechanical stirrer and condenser were placed 2.3 g. (0.028 mole) of cyclopentanone-X-^{14}C and 54 g. of polyphosphoric acid. Approximately 2 g. (0.03 mole) of sodium azide was added in small portions over a period of 1 hour. The temperature was slowly increased to 50° and maintained at this temperature for 9 hours. The reaction mixture was neutralized with 50% sodium hydroxide solution and extracted with ten 25-ml. portions of chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and distilled. Crude 5-aminovalerolactam-X^{14}C, 1.5 g. (50% yield) [b.p. 140° (15 mm.) (lit.[31d] 137°(14 mm.), for inactive material], was obtained.

In a 100-ml. flask containing 1.5 g. (0.015 mole) of 5-aminovalerolactam-X-^{14}C were added 1.5 ml. of concentrated hydrochloric acid and 5 ml. of water. The mixture was heated and magnetically stirred for 3 hours. The volume of solution was increased to 15 ml. with water and the solution was treated successively in the following manner: 0.75 g. of litharge powder, 0.4 g. of litharge powder, 0.075 g. of lead hydroxide, 0.75 g. of silver oxide and finally hydrogen sulfide. The solution was filtered and concentrated to approximately 2 ml. and placed in a desiccator overnight.

In a 50-ml. flask equipped with an addition tube and a magnetic stirrer was placed 1.5 g. (0.014 mole) of 5-aminovaleric acid-X-^{14}C and 2.8 ml. of concentrated sulfuric acid. Over a period of 10 minutes 0.65 g. (0.015 mole) of hydrazoic acid in 7.5 ml. of chloroform was added dropwise while the flask was heated at 50°. The evolved carbon dioxide was collected and the N,N′-dibenzamide derivative of 1,4-diaminobutane-X-^{14}C, 1.3 g. (33%), m.p. 175–176° (lit.[31e] 177°), was prepared.[42a]

1-Cyclopropylethanone-2-^{14}C.—In a 300-ml., three-necked flask equipped with a mechanical stirrer, condenser and dropping funnel were placed 4.8 g. (0.2 g. atom) of magnesium turnings which had been previously dried, 50 ml. of anhydrous ether and a crystal of iodine. A few drops of an ethereal solution of methyl-^{14}C iodide[38] (17.3 g., 0.12 mole, 0.25 mc.) in 50 ml. of anhydrous ether were added. After the reaction had been initiated the methyl-^{14}C iodide solution was added dropwise while the flask was cooled in an ice-bath over a period of 0.5 hour. When the exothermic reaction terminated, the mixture was stirred and refluxed for 2 hours. Approximately 8 g. (0.12 mole) of cyclopropyl cyanide in 50 ml. of ether was added dropwise over a period of 0.5 hour. The mixture was then stirred and refluxed for 18 hours, then 90 ml. of 3 *N* hydrochloric acid was added with stirring. After stirring for 1.5 hours, the ether layer was separated and the aqueous phase was extracted with three 25-ml. portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate overnight and distilled. Approximately 3.8 g. (38%) of 1-cyclopropylethanone-2-^{14}C, b.p. 112–113° (lit.[31f] b.p. 114°), was obtained.

1-Cyclopropylethanol-2-^{14}C.—A mixture of 7.6 g. (0.2 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether was stirred at room temperature while 20 g. (0.23 mole) of 1-cyclopropylethanone-2-^{14}C dissolved in 75 ml. of anhydrous ether was added dropwise over a period of 45 minutes. The white precipitate was stirred and refluxed for 2 hours. The remaining lithium aluminum hydride and precipitate were decomposed by the careful addition of 30 ml. of ice-water and, after stirring for an additional 3 hours, the solution was filtered, dried over sodium hydroxide flakes, and distilled. Approximately 15.3 g. (77% yield, 2.1% radioactive yield), b.p. 122.5° (lit.[8] 120.5–121.0°), of 1-cyclopropylethanol-2-^{14}C was obtained. The phenylurethan derivative was prepared,[42b] m.p. 67.9–68.2°, and analyzed for radioactivity.

Degradation of 1-cyclopropylethanol-2-^{14}C was conducted as described for the isotopically labeled cyclopropylmethylcarbinol from the rearrangement reaction, and carbon dioxide from the permanganate oxidation and from the Schmidt degradation of cyclopropanecarboxylic acid was isolated and counted.

(44) J. E. Nickels and W. Heintzelman, *J. Org. Chem.*, **15**, 1142 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND.]

Preparation of (−)-*cis*-2,4-Dimethylcyclohexanone from (+)-Pulegone

BY JOSEPH WOLINSKY AND DAVID CHAN

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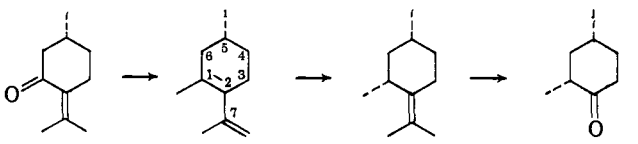
A novel and convenient preparation of (−)-*cis*-2,4-dimethylcyclohexanone from (+)-pulegone is described. The action of methylmagnesium iodide with (+)-pulegone affords 2-isopropenyl-1,5-dimethyl-1-cyclohexene (methylisopulegene) contaminated by 5% of 1-isopropylidene-2-methylene-4-methylcyclohexane. Although methylisopulegene does not absorb ultraviolet light above 210 mμ, it is smoothly reduced by use of sodium in liquid ammonia to give *cis*-1-isopropylidene-2,4-dimethylcyclohexane. Ozonolysis of the latter olefin affords (−)-*cis*-2,4-dimethylcyclohexanone.

Lawes[1] has shown that the thermal degradation of cycloheximide[2] (known also as actidione[3] and naramycin A[4]), an antibiotic which finds application in agriculture and is reported to possess anti-tumor activity,[5] affords (+)-*trans*-2,4-dimethylcyclohexanone (I), whereas alkaline degradation[3] yields (−)-*cis*-2,4-dimethylcyclohexanone (II). Djerassi[6] has related the absolute configuration of the asymmetric center at C-4 in ketone II to R-glyceraldehyde. In this report we wish to describe a novel and convenient method, outlined in Chart I, for the preparation of (−)-*cis*-II from (+)-pulegone. This conversion independently confirms the absolute configuration at C-4 in ketone II and cycloheximide.

CHART I



III IV II

Our interest in non-planar dienes[7,8] originally directed our attention to "methylpulegene,"[9–11] a diene produced by the reaction of pulegone with methylmagnesium iodide. Grignard[12] suggested the diene was a mixture of 2-isopropenyl-1,5-dimethyl-1-cyclohexene

(1) B. C. Lawes, *J. Am. Chem. Soc.*, **84**, 239 (1962).

(2) B. E. Leach, J. H. Ford and A. J. Whiffen, *ibid.*, **69**, 474 (1947).

(3) E. C. Kornfeld, R. G. Jones and T. V. Parke, *ibid.*, **71**, 150 (1949).

(4) T. Okuda, M. Suzucki, Y. Egawa and K. Ashino, *Chem. Pharm. Bull.*, **7**, 27 (1959).

(5) H. C. Reilly, C. C. Stock, S. M. Buckley and D. A. Clark, *Cancer Research*, **13**, 684 (1953).

(6) E. J. Eisenbraun, J. Osiecki and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 1261 (1958).

(7) E. E. van Tamelen, S. Levin, G. Brenner, J. Wolinsky and P. Aldrich, *ibid.*, **81**, 1666 (1959).

(8) H. H. Inhoffen, G. Quinkert, H. Hess and H. Erdmann, *Ber.*, **89**, 2273 (1956); H. H. Inhoffen, K. Brückner, K. Irmscher and G. Quinkert, *ibid.*, **88**, 1424 (1955).

(9) V. Grignard, *Chem. Zentr.*, **72**, 624 (1901).

(10) K. Auwers and F. Eisenlohr, *Ber.*, **43**, 830 (1910).

(11) H. Rupe and F. Emmerich, *ibid.*, **41**, 1750 (1908).

(12) V. Grignard and J. Savard, *Compt. rend.*, **181**, 589 (1925); for divergent views see J. Simonsen and L. N. Owen, "The Terpenes," The University Press, Cambridge, 1947, Vol. I, 2nd Edition, p. 379.