

The synthesis of Dehydro-2-norbornyl and 2-Norbornyl derivatives labeled at C-3 with ^{14}C

C. C. LEE, F. L. KUNG, Bo-Sup HAHN and Adrian J. ROBSON

Department of Chemistry and Chemical Engineering, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

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SUMMARY

The synthesis from $^{14}\text{CO}_2$ of various endo- and exo-3- ^{14}C -dehydro-2-norbornyl and 2-norbornyl derivatives, suitable for use in isotopic scrambling studies, is described.

INTRODUCTION.

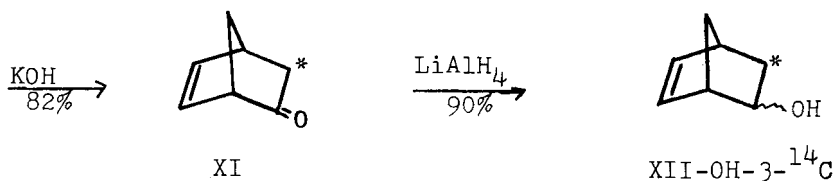
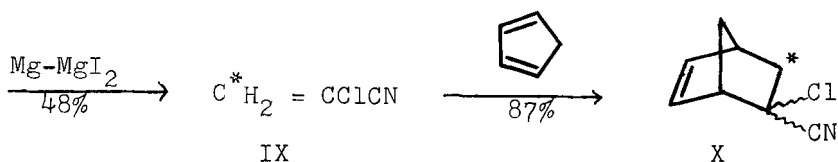
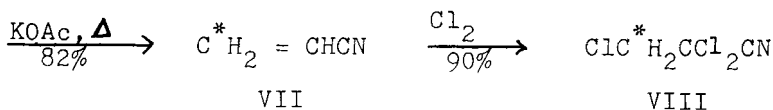
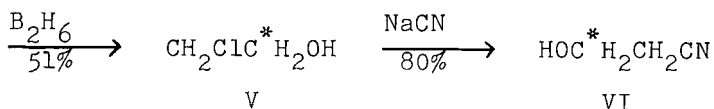
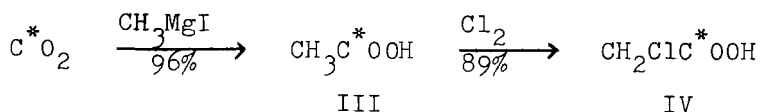
In the original work of Roberts and coworkers^(1, 2) on the solvolyses of *exo*- and *endo*-2,3- $^{14}\text{C}_2$ -2-norbornyl brosylates (*exo*- and *endo*-I-OBs-2,3- ^{14}C), because the label was located at both C-2 and C-3, a direct observation of 3,2-hydride shifts was not possible. A singly labeled substrate would have obvious advantages in this regard. Thus about 6% rearrangement of the *t*-label from C-2 to C-3 was observed in the formolysis at 25° C of *exo*-I-OBs-2-*t*⁽³⁾. Similarly, the acetolysis of *exo*- or *endo*-I-OBs-2-*t* was found to give a small amount (1-2%) of overall 3,2-shifts⁽⁴⁾, most, if not all, of which could be attributed to the subsequent ionization and rearrangement of the initially formed product, *exo*-I-OAc-*x-t*, in the reaction medium⁽⁵⁾. Such subsequent reactions of *exo*-I-OAc in the acetolysis medium apparently involved an extraordinarily large extent of 3,2-shifts relative to Wagner-Meerwein and 6,2-shifts. Of interest also is the n.m.r. study of Fraenkel and coworkers⁽⁶⁾ on the behavior of *exo*-I-OH in $\text{F}_3\text{CCOOH-H}_2\text{SO}_4$ which led to the conclusion that 3,2- and 6,2-shifts proceeded faster than Wagner-Meerwein rearrangement under these conditions. On the other hand, when the π -route to the norbornyl cation from solvolyses of 2-(Δ^3 -cyclopentenyl)-2- ^{14}C -ethyl *p*-nitrobenzenesulfonate (II-ONS-2- ^{14}C) was studied under conditions that were more likely to be kinetically controlled⁽⁷⁾, essentially no 3,2-shifts occurred, and the ^{14}C -label in the resulting *exo*-2-norbornyl product was located only at C-3, C-5 and C-7. It is, therefore, of interest to synthesize 2-norbornyl derivatives singly labeled with ^{14}C at C-3 which may, for example, be utilized in investigations that will provide further data on 3,2-shifts and for comparison with the isotopic scrambling data from π -route solvolyses.

RESULTS AND DISCUSSION.

The following series of reactions show the synthesis of a mixture of *endo*- and *exo*-3-¹⁴C-dehydro-2-norborneols (*endo*- and *exo*-XII-OH-3-¹⁴C).

The conversion of ¹⁴CO₂ to 1-¹⁴C-acetic acid (III) followed a standard procedure (7a). Chlorination of III in the presence of P, I₂ and PCl₅ at reflux temperature as described in "Isotopic Carbon" (7b) gave only about 65 % yields of IV. However, lowering the reaction temperature to that of a steam bath, as was used originally by Lyubarskii (8), raised the yield to 89%; possibly this might have been due to the minimizing of losses of volatile materials such as acid chlorides.

The direct reduction of chloroacetic acid with LiAlH₄ to ethylene chlorhydrin has been reported to give a yield of only 13 % (9), while the LiAlH₄ reduction using chloroacetyl chloride was found to give a 62 % yield (9). It



has also been reported that chloroacetic acid could be converted to chloroacetyl chloride in 95 % yield by treatment with SO_2Cl_2 ⁽¹⁰⁾. However, in our hands, the latter reaction failed to give the desired chloroacetyl chloride. When SOCl_2 was used instead of SO_2Cl_2 , the acid chloride was obtained in yields of about 65 %. Thus the combined two-step conversion of IV to V via the acid chloride and LiAlH_4 reduction would result in a yield of about 40 %. In the present work, a direct reduction of IV to V was effected by the use of diborane ^(11, 12), a 51 % yield being obtained.

The chlorohydrin V was converted to the cyanohydrin VI by a known procedure ⁽¹³⁾. The dehydration of VI to give the labeled acrylonitrile VII was effected by heating with fused KOAc ⁽¹⁴⁾, the method being modified by the inclusion of diethylene glycol as a solvent ⁽¹⁵⁾, which made it possible for a better control of the reaction.

The reaction of acrylonitrile with chlorine to give α, α, β -trichloropropionitrile, followed by dechlorination in the presence of Mg-MgI_2 to give α -chloroacrylonitrile have been described in a 1945 patent ⁽¹⁶⁾. More recently, the reaction of chlorine with acrylonitrile has been carried out in the presence of some dimethylaniline, giving an 87 % yield of the trichloropropionitrile ⁽¹⁷⁾. In the present work, VII was converted to VIII in 90 % yield by the reaction of VII with Cl_2 in the presence of pyridine. In the dechlorination of VIII to give IX by treatment with Mg-MgI_2 ⁽¹⁶⁾, the yield was raised to 48 % from the reported 40 % ⁽¹⁶⁾.

The course of reaction of Cl_2 with acrylonitrile apparently involved an initial addition of Cl_2 to the double bond, followed by a substitution of the α -hydrogen. This was demonstrated by examination of the n.m.r. spectra. At short reaction times, (e.g. 0.5 hr) the major product was α, β -dichloropropionitrile (doublet at δ 4.1 and triplet at δ 5.0 p.p.m., with relative intensities of 2 : 1). With longer contact time, α, α, β -trichloropropionitrile began to appear (singlet at δ 4.4 p.p.m.) which eventually became the major product (e.g. in 4 hr). With prolonged bubbling of Cl_2 through the reaction mixture (e.g. 10 hr), another singlet appeared at δ 4.6 p.p.m.; this presumably was due to a further substitution to give $\alpha, \alpha, \beta, \beta$ -tetrachloropropionitrile.

The Diels-Alder reaction of IX with cyclopentadiene to give X ⁽¹⁸⁾, the conversion of X to 3-¹⁴C-dehydronorcamphor (XI) ⁽¹⁹⁾, and the reduction of XI to a mixture of about 90 % *endo*- and 10 % *exo*-3-¹⁴C-dehydro-2-norborneols (*endo*- and *exo*-XII-OH-3-¹⁴C) ⁽²⁰⁾, were effected by known procedures. The overall yield from ¹⁴CO₂ to the mixed dehydronorborneols was nearly 8 %. These mixed alcohols (*endo*- and *exo*-XII-OH-3-¹⁴C) may be converted to pure *endo*- or *exo*-XII-OBs-3-¹⁴C ⁽²⁰⁾ which may be utilized for solvolytic studies to supplement previous data ⁽²¹⁾, and to clarify further the effects of temperature on the extents of isotopic scrambling and the possibility of competitive reactions under solvolytic conditions ⁽²⁰⁻²²⁾. Hydrogenation of the mixed *endo*- and *exo*-XII-OH-3-¹⁴C would give the mixed 3-¹⁴C-2-norborneols, *endo*- and *exo*-I-OH-3-¹⁴C, which may be converted ^(4, 5, 23) to

the pure *endo*- or *exo*-I-OBs-3-¹⁴C, and to pure *exo*-I-OAc-3-¹⁴C or *exo*-I-OH-3-¹⁴C, suitable for use in isotopic scrambling studies.

EXPERIMENTAL.

1-¹⁴C-Chloroacetic Acid (IV).

In a two-necked 50-ml. flask fitted with a gas inlet tube and a reflux condenser protected by a CaCl₂ tube were placed 15.0 g of CH₃¹⁴COOH (0.25 mole, from ¹⁴CO₂ + CH₃MgI, refluxed with Ac₂O and redistilled to remove any water), 0.2 g of I₂, 0.4 g of red phosphorus and 0.8 g of PCl₅. The material was heated in an oil bath at 95-100° C and a slow stream of dry Cl₂ gas was passed through the reaction mixture. The reaction was stopped when a small sample withdrawn from the flask crystallized on cooling (4-5 hr.). The product was recovered by vacuum distillation, b.p. 78-80° C at 4 mm, yielding 21.0 g (89 %) of IV which crystallized on cooling. It melted alone and on admixture with authentic chloroacetic acid at 60-61° C.

1-¹⁴C-2-Chloroethanol (V).

1-¹⁴C-Chloroacetic acid (9.45 g, 0.10 mole) was reduced with B₂H₆ in anhydrous tetrahydrofuran according to the general procedure described by Ioffe and coworkers⁽¹²⁾. The reaction mixture was stirred at room temperature for 12 hr and the resulting material was decomposed by 75 ml of methanol. After the solvent was removed, the residue was hydrolyzed by heating in 100 ml of water at 70° C for 15 min. The hydrolyzate was continuously extracted with ether for 24 hr and the product was recovered from the dried extract by fractionation, yielding 4.1 g (51 %) of V, b.p. 58° C at 50 mm. Its n.m.r. spectrum was identical with that of authentic 2-chloroethanol.

β-¹⁴C-Acrylonitrile (VII).

The reaction vessel was a 50 ml round-bottom flask fitted with a 6-inch steam-heated reflux condenser, the top of which was connected to an ordinary water-cooled condenser set up for distillation. In the reaction vessel were placed 15.0 g (0.21 mole) of 1-¹⁴C-2-cyanoethanol (VI, prepared in 80 % yield from V + NaCN⁽¹³⁾), 6.0 g of fused KOAc, 0.2 g of hydroquinone and 15 ml of diethylene glycol. The reaction mixture was gradually heated in a Wood's metal bath until the bath temperature was maintained at 230° C. With the steam-heated reflux condenser preventing the distillation of the solvent, the distillate containing water and VII began to appear when the bath temperature reached 180° C and the heating was stopped when no more distillate appeared at 230° C. The organic layer of the distillate was separated, dried over CaCl₂ and fractionated to give 9.2 g (82 %) of VII, b.p. 78° C (lit.⁽¹⁵⁾ b.p. 78° C). Its n.m.r. spectrum was identical with that of authentic acrylonitrile.

β -¹⁴C- α , β -Trichloropropionitrile (VIII).

The reaction vessel was a 25 cm \times 3 cm dia. test tube which was fitted with a gas inlet with sintered glass bubbler and a gas outlet. A solution of 40.0 g (0.75 mole) of β -¹⁴C-acrylonitrile (VII) in 10 ml of pyridine was placed in the vessel and maintained at 10-20° C in a water bath. Chlorine gas was bubbled through the reaction mixture until the gain in weight was 79 g (3-4 hr) which corresponded theoretically to the conversion of 40.0 g of VII to VIII. Fractionation of the resulting mixture gave 100.7 g (90 %) of VIII, b.p. 47-50° C at 12 mm (lit. ⁽¹⁷⁾ b.p. 80-82° C at 60 mm). Its n.m.r. spectrum showed a singlet at δ 4.4 p.p.m.

 β -¹⁴C- α -Chloroacrylonitrile (XI).

To 29 g (1.2 mole) of Mg turning in 300 ml of dried *n*-butyl ether in a 500-ml three-necked flask equipped with a sealed mechanical stirrer, a dropping funnel and a condenser set up for distillation, 51 g (0.2 mole) of iodine was added in small portions with stirring. After the addition of iodine was completed, the mixture was stirred at room temperature for about 1 hr until all the iodine color disappeared. A small amount of hydroquinone (0.5 g) was introduced, and the flask was then immersed in an oil bath maintained at 150-155° C. With rapid stirring, 96.0 g (0.60 mole) of VIII was added dropwise at a rate such that the material distilled (product + solvent) appeared at approximately twice the rate of addition of VIII. After the addition of VIII was completed, 50 ml of *n*-butyl ether was introduced into the viscous residue and the material was again distilled. The addition of solvent followed by distillation was repeated two more times, giving rise to a total of about 400 ml of distillate. The distillate was shaken with Hg to remove the iodine color. It was then fractionated in the presence of a small amount of freshly added hydroquinone to give 25.3 g (48 %) of IX, b.p. 85-88° C (lit. ⁽¹⁶⁾ b.p. 85-88° C). Its n.m.r. spectrum consisted of a quartet at δ 5.95-6.07 p.p.m. and was identical with that of an authentic sample of α -chloroacrylonitrile.

3-¹⁴C-Dehydro-2-norbornyl and 3-¹⁴C-2-Norbornyl Derivatives.

The Diels-Alder reaction between IX and cyclopentadiene was effected in benzene solution at 40° C as described by Krieger ⁽¹⁸⁾. An 87 % yield of X (mixture of *endo* and *exo*) was obtained, m.p. 45-47° C (lit. ⁽¹⁸⁾ m.p. 45-47° C). A solution of X in DMSO was hydrolyzed by concentrated KOH as described by Freeman and coworkers ⁽¹⁹⁾ to give an 82 % yield of 3-¹⁴C-dehydronorcamphor (XI), m.p. 21-23° C (lit. ⁽¹⁹⁾ m.p. 22-23° C), which showed identical infrared and n.m.r. spectra as an authentic sample.

The LiAlH₄ reduction of XI gave a 90 % yield of a 9 : 1 mixture of *endo*- and *exo*-3-¹⁴C-dehydro-2-norborneols (*endo*- and *exo*-XII-OH-3-¹⁴C) ⁽²⁰⁾. These mixed alcohols could be converted to the mixed brosylates, *endo*-

and *exo*-XII-OBs-3-¹⁴C, which on selective solvolysis gave pure *endo*-XII-OBs-3-¹⁴C^(2, 20). Reaction of *endo*-XII-OBs-3-¹⁴C with anhydrous tetramethylammonium acetate in dry acetone⁽²⁰⁾ or with tetrabutylammonium acetate in benzene⁽²³⁾ gave pure *exo*-XII-OAc-3-¹⁴C, which could in turn be converted to *exo*-XII-OH-3-¹⁴C and *exo*-XII-OBs-3-¹⁴C. After hydrogenation and by a series of analogous processes^(4, 5, 23), *endo*-I-OBs-3-¹⁴C, *exo*-I-OAc-3-¹⁴C, *exo*-I-OH-3-¹⁴C and *exo*-I-OBs-3-¹⁴C could be obtained.

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