

ISOTOPIC SCRAMBLING IN THE REPORTED SYNTHESIS OF DEHYDRO-2-NORBORNYL AND 2-NORBORNYL DERIVATIVES LABELED AT C-3 WITH ^{14}C .

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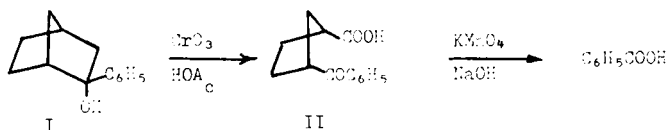
SUMMARY

The recently reported synthesis of C-3 labeled dehydro-2-norbornyl and 2-norbornyl derivatives (1) was found to be in error. Only about 70% of the ^{14}C -label was located at C-3, the other 30% being found at C-2. One of the steps in the original synthesis, involving the conversion of ethylene chlorohydrin to ethylene cyanohydrin, was shown to be responsible for this isotopic scrambling.

The recently reported synthesis of a mixture of endo- and exo-3- ^{14}C -dehydro-2-norborneols⁽¹⁾ has been found to be in error in that the ^{14}C -label was not solely located at C-3. After hydrogenation and then oxidation to 2-norbornanone, the original degradation was carried out by treatment with $\text{C}_6\text{H}_5\text{MgBr}$ to give 2-phenyl-endo-2-norborneol followed by oxidation with KMnO_4 -KOH to give $\text{C}_6\text{H}_5\text{COOH}$, the activity in this latter acid being a measure of the ^{14}C -content at C-2.⁽²⁾ The oxidation to $\text{C}_6\text{H}_5\text{COOH}$ involved the refluxing of the reaction mixture for 5 days⁽²⁾ and this gave variable yields.

Possibly, the presence of impurities coupled with the use of materials of relatively low specific activity in order to conserve the labeled compound could have led to the initial belief that the ^{14}C -activity at C-2 was low. Subsequent studies showed that the ^{14}C -content of the $\text{C}_6\text{H}_5\text{COOH}$ from the alkaline KMnO_4 oxidation was not negligible.

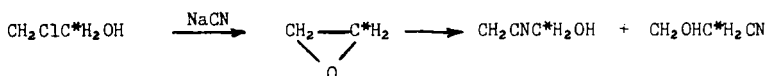
A modification of the degradation, as shown below, gave more consistent yields and improved control, even though it involved an additional step.



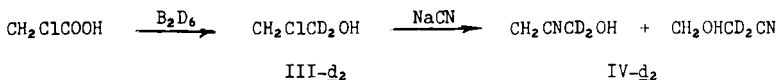
The oxidation of 2-phenyl-endo-2-norborneol (I) to 3-benzoylcyclopentane-1-carboxylic acid (presumably cis) (II) was effected by the method of Fieser and Szmuszkovicz.⁽³⁾ One gram of I dissolved in 40 ml. of HOAc was stirred with 0.2 g. of CrO_3 for 5 min. to allow the reaction to be initiated. The temperature was then held at 30°C ., an additional 3.0 g. of CrO_3 was introduced in portions, and the mixture was stirred for 2 hr. Water (100 ml.) was then added and the material was extracted with ether. The extract was washed with water to remove HOAc and the desired keto acid II was recovered by extraction with dilution NaOH. The NaOH solution was acidified with HCl and then extracted with ether. After drying and removal of the ether, the residual keto acid II remained as an oil. This residue was oxidized by refluxing for 24 hr. with 6.0 g. of KMnO_4 , 15 ml. of 10% NaOH and 50 ml. of H_2O , giving rise to 0.50 g. of $\text{C}_6\text{H}_5\text{COOH}$. The overall yield of the benzoic acid based on I was 77%. The authenticity of the keto acid II was established by converting a small sample of this compound to its semicarbazone, m.p. $180 - 181^\circ\text{C}$. Anal. Calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_3\text{N}_3$: C, 61.07; H, 6.24; N, 15.26. Found: C, 61.17; H, 6.38; N, 15.11. The ^{14}C -activity in the $\text{C}_6\text{H}_5\text{COOH}$

derived from the labeled alcohol I was about 30% of that of I. Degradation of the labeled norborneol in the usual manner⁽²⁾ via cis-cyclopentane-1,3-dicarboxylic acid gave inactive cis-cyclopentane-1,3-diamine. These results indicated that in the labeled dehydro-2-norbornyl or 2-norbornyl skeleton, 70% of the ¹⁴C was located at C-3 and 30% at C-2, not 100% at C-3 as was originally anticipated.

Consideration of the series of reactions utilized in the original synthesis of the labeled dehydro-2-norbornyl derivatives⁽¹⁾ suggested that the scrambling of the ¹⁴C between C-3 and C-2 might have arisen in the reaction between NaCN and ethylene chlorohydrin (III) to give ethylene cyanohydrin (IV). Since this reaction involved a primary chloride and was carried out in absolute methanol,⁽⁴⁾ it was erroneously believed to be an S_N2 reaction that would not cause any rearrangement. However, it is now apparent that even under these conditions, at least part of the reaction could have proceeded via ethylene oxide, hence scrambling the ¹⁴C-label over the two carbon atoms:



The isotopic scrambling in the conversion of III to IV has now been confirmed by mass spectrometry using deuterated materials as indicated below:



Utilizing the same experimental procedures employed in the reported synthesis,⁽¹⁾ deuterated III-d₂ was prepared from reaction of chloroacetic acid with B₂D₆ (from NaBD₄ and BF₃ in tetrahydrofuran). The mass spectrum obtained at 15 e.v. showed that all of the deuterium was located at the carbon atom bearing the hydroxyl group, since the D-content calculated from the CD₂OH⁺ ion (m/e 33) was the same as that of the molecular ion.

