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THE REACTION OF SODIUM PHENOXIDE WITH 2-CHLOROCYCLOHEXANONE-1,2-C^{14}

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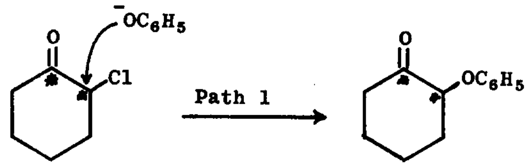
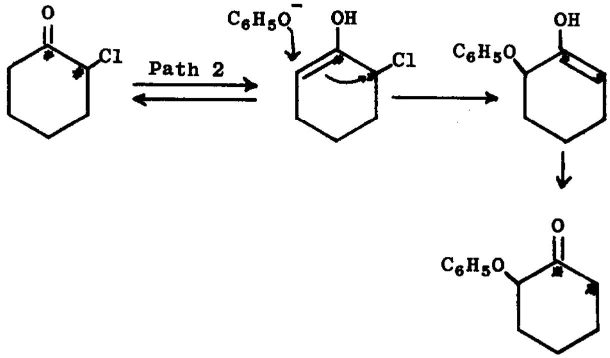
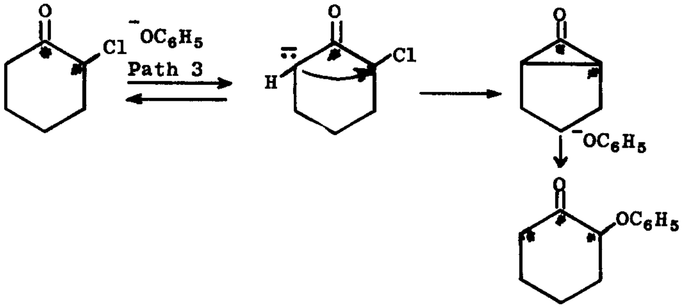
Hypothetically, the formation of 2-phenoxycyclohexanone by the reaction of sodium phenoxide with 2-chlorocyclohexanone (1,2) may occur by: 1. the Sn 2 attack of phenoxide at the α-carbon (path 1); 2. the Sn 2' attack of phenoxide at the 2-carbon in the enol, 6-chloro-1-cyclohexenol (path 2); or 3. the attack of phenoxide at either the α- or α'- carbon of a symmetrical cyclopropanone intermediate (path 3) (3). Evidence regarding the operation of paths 2 and 3 was offered by Gates and co-workers (4) in the oxide ring closure reactions of the *cis* and *trans* 1,7-dibromodihydrothebainones. Further evidence on a related system has been offered by House and Thompson (5) in the reaction of sodium methoxide with 9-chloro-*trans*-1-decalone supporting the operation of path 3 (or a zwitterionic intermediate (3)).

A decision between the various possibilities is offered by the use of 2-chlorocyclohexanone-1,2-C^{14}. Path 1 would lead only to 2-phenoxycyclohexanone with an equal distribution of label at C-1 and C-2. Path 2 alone would produce


$^{-}OC_6H_5$
O
Cl
Path 1
O
OC_6H_5


O
Cl
Path 2
$C_6H_5O^{-}$
OH
Cl
C_6H_5O
OH
O
C_6H_5O


O
Cl
$^{-}OC_6H_5$
Path 3
O
H
Cl
O
$^{-}OC_6H_5$
O
OC_6H_5

product with the label equally distributed at C-1 and C-6. Finally, Path 3 would result in 50% of the initial activity at C-1 and 25% at C-2 and C-6 respectively. Subject to the unlikely occurrence of equal amounts of reaction by paths 1 and 2 (a result equivalent to path 3), the experiment offers the possibility of an unequivocal choice of pathways.

An improved synthesis for 2-chlorocyclohexanone-1,4-C^{14} was sought since the available synthesis (6) consists of eleven steps in a yield of 5% (based on starting labeled sodium cyanide). The following sequence permitted the synthesis in five steps in 15% yield.

Tetramethylene dibromide was treated with sodium cyanide to form adiponitrile (96% yield) (7). This was hydrolyzed to adipic acid in 95% yield (7) and converted to diethyl adipate in 95% yield (8). Cyclization to adipoin proceeded in yields of 46-53% (9). Conversion of adipoin to 2-chlorocyclohexanone was carried out by slow addition of adipoin in toluene to a warm toluene solution containing equimolar amounts of thionyl chloride and quinoline. Yields were typically 35% of theoretical.

The reaction of freshly prepared 2-chlorocyclohexa- (1.55 ± 0.01 mc./mole) with sodium phenoxide was carried out as described by Ebel (10). The yield of recovered 2-phenoxycyclohexanone was 67% with additional material unrecovered in the mother liquors. A search of the crude reaction products showed no cyclohexenone and a trace of adipoin plus a high boiling product.

The 2-phenoxycyclohexanone (1.55 ± 0.01 mc./mole) was oxidized with potassium permanganate in acetone to phenyl hydrogen adipate (1.55 mc./mole) in 41-44% yield. Treatment of the half ester with excess phenylmagnesium bromide and then acetic anhydride gave 1,1,6,6-tetraphenyl-1,5-hexadiene (1.55 ± 0.01 mc./mole) in 29% yield. Oxidation of the diene with potassium permanganate gave benzophenone which was isolated as the 2,4-dinitrophenylhydrazone in 60% yield (specific activity from duplicate experiments 0.55 ± 0.01 and 0.57 ± 0.01 mc./mole). The physical properties of each intermediate agreed with the literature values.

Given starting material, equally labeled at positions 1 and 2, of 1.55 mc./mole, the calculated value for the benzophenone would be 0.58 ± 0.01 mc./mole assuming only path 3 was in operation. Since there is no significant difference with the duplicate experimental results, we conclude that only a symmetrical intermediate (be it a cyclopropanone or zwitterion) is consistent with the results.

Further support for the above contention was found in the observation that 2-chloro-6,6-dimethylcyclohexanone failed to react with sodium phenoxide after considerably longer reaction times than those used for the 2-chlorocyclohexanone.

ACKNOWLEDGMENT

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REFERENCES

1. M. Mousseron and R. Jacquier, Compt. rend., 229, 374 (1949).

2. T. I. Temnikova and N. A. Oshueva, Zh. Obshch. Kim., 28, 3224 (1958).

3. Since the radiochemical consequences of a cyclopropanone or a zwitterion intermediate are identical, no differentiation between these possibilities will be made in this discussion.

4. M. Gates and M. S. Shepard, J. Am. Chem. Soc., 84, 4125 (1962), and M. Gates and G. M. K. Hughes, Chem. and Ind., 1506 (1956).

5. H. O. House and H. W. Thompson, J. Org. Chem., 28, 164 (1963).

6. A. Murray and D. L. Williams, "Organic Syntheses with Isotopes," Interscience Publishers, Inc., New York, 1958, pp. 659 and 823.

7. K. E. Miller, D. I. Lusk, J. F. Marks, E. Blanc, and T. R. Fernandez, J. Chem. Eng. Data, 9, 227 (1964).

8. V. M. Micovic, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, 1943, p. 264.

9. J. C. Sheehan, R. C. O'Neill, and M. A. White, J. Am. Chem. Soc., 72, 3376 (1950).

10. F. Ebel, Helv. Chim. Acta, 12, 3 (1929).