The Conversion of *cis*-2,6-Disubstituted Cyclohexanones into their *trans*-Isomers

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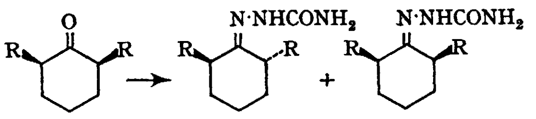
Summary The conversion of the more stable *cis*-2,6-dialkyl-cyclohexanones into their less stable *trans*-isomers can be accomplished by semicarbazone formation followed by decomposition of these derivatives with nitrous acid.

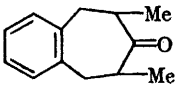
CONTINUING our investigations on allylic strain[1] in molecules, we have now found a very useful application of the principles involved, which permits the conversion of the more stable *cis*-2,6-disubstituted cyclohexanones into their less stable isomers.

Similar conversions of other 2,*x*-disubstituted cyclohexanones ($x \neq 6$) have been carried out (albeit partially) through the intermediacy of enamine formation.[2] This method is not really applicable to compounds of type (I) because enamine formation, if it can be accomplished at all, occurs in only low yield, and the subsequent hydrolysis step leads to merely a 1 : 1 mixture of *cis*- and *trans*- isomers.[3]

We have now found that when semicarbazone formation is attempted with a 2,6-*cis*-disubstituted cyclohexanone, it produces largely the semicarbazone of the *trans*- rather than the *cis*-2,6-disubstituted cyclohexanone. There seems little doubt that a preponderance of (II) is produced during semicarbazone formation due to the strong pseudo-allylic interaction [$A^{(1,3)}$-strain] that exists between the $NH{\cdot}CONH_2$ portion of the semicarbazone function and the *syn*-R group in (III). The latter is thus thermodynamically unstable with respect to (II), the reverse order to that pertaining in the parent ketones.



(I) (II) major (III) minor



(IV)

In the four cases listed in the Table, it proved comparatively easy to separate (II) from (III) by crystallization. Decomposition of (II) with nitrous acid in acetic acid then afforded a product in quantitative yield which consisted substantially of the 2,6-disubstituted ketone. The following example is representative: 2,6-dimethylcyclohexanone (6·3 g; 85·5 : 14·5 :: *cis* : *trans*) was added to a solution of semicarbazide acetate [prepared from the hydrochloride (11·2 g) and potassium acetate (10 g.)] in methanol (90 ml.) and the mixture heated under reflux for 18 hr. The crude product, obtained by concentration of the methanol solution followed by dilution with water (150 ml.), was removed by filtration, washed with water, then ether, and air-dried. Two crystallizations from methanol afforded the pure semicarbazone (II; R = Me) m.p. 192—194° (6·1 g.).

TABLE

Ketone (I) R	Semicarbazone (II) (% yield)	2,6-*trans*-disubstituted ketone (% Purity)
Me	65	98
Et	78	85
Pr	48	92
CH_2Ph	76	>90

A sample (1·83 g.) of this material in acetic acid (10 ml.) was treated at *ca* 5° over 10 min. with a solution of sodium nitrite (2·2 g.) in water (10 ml.). By a standard work-up procedure, using methylene chloride as the extractant, 2,6-dimethylcyclohexanone (1·22 g.) was obtained, which by g.l.c. assayed as 98·3 : 1·7 :: *trans* : *cis*.

In a number of other cases the method failed because we were unable to obtain the necessary semicarbazone. These include 2,6-di-isopropylcyclohexanone, 2,6-di-t-butylcyclohexanone, and 2-methyl-6-t-butylcyclohexanone. The failure here is not surprising in view of the steric hindrance involved in the initial hemi-amine acetal step of semicarbazone formation.

In the seven-membered-ring series we have so far examined only (IV).[4] In this case semicarbazone formation occurs readily but the product is a mixture of isomers which could not be separated by crystallization. However, we have found an alternative method for the preparation of *trans*-(IV) in good yield and in a high state of purity. These results together with an outline of our investigations on 2,5-dialkylcyclopentanones will be the subject of a separate publication.

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[1] F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, 1965, **87**, 4592; F. Johnson, *Chem. Rev.*, 1968, **68**, 375.

[2] F. Johnson and A. Whitehead, *Tetrahedron Letters*, 1964, 3825; H. J. Schaeffer and V. K. Jain, *J. Org. Chem.*, 1964, **29**, 2595; F. Johnson, N. A. Starkovsky, A. C. Paton, and A. A. Carlson, *J. Amer. Chem. Soc.*, 1964, **86**, 118; 1966, **88**, 149.

[3] Unpublished results by the authors.

[4] F. G. Bordwell and M. Winn, *J. Org. Chem.*, 1967, **32**, 42.

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