[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF LOUISVILLE]

PREPARATION OF TWO METHYLCYCLOHEXENOLS BY REDUCTION OF THE KETONES[1]

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In this work there has been an effort to examine several preparative methods which may be used for these compounds, particularly with regard to relative yields and purity.

A number of preparative methods are known for the preparation of 3-methyl-2-cyclohexen-1-one, two of the most promising being that of Knoevenagel as modified by Smith and Roualt (11), and that of Birch (1). Samples of this ketone prepared by the modified Knoevenagel method had refractive indices fairly close to those of samples which had been subjected to various purification procedures. Similar results ensued when this ketone was made by reduction of N-dimethyl-*m*-toluidine (1). The alternative Birch procedure, reducing *m*-tolyl methyl ether to the dihydro derivative, and then hydrolyzing to 3-methyl-2-cyclohexen-1-one, did not give a very pure sample because of the difficulty in removing the starting material.

There is literature disagreement with respect to the absorption spectra of the above ketone (1, 3). Our measurements on the sample regenerated from the semicarbazone did not show the absorption maximum at λ 280 mμ reported by Birch (1). This maximum was, however, obtained by us in some less pure samples. Inasmuch as Evans and Gillam (3) also failed to observe a maximum at this point, and Butz (2) did not find it in the case of an isomeric conjugated ketone, we conclude that it is due to an impurity, probably either a saturated or a nonconjugated ketone.

3-Methyl-2-cyclohexen-1-ol, obtained by lithium aluminum hydride reduction of the ketone, is a very unstable compound and dehydrates to a mixture of polymeric substances if distilled at too high a temperature or when attempts are made to make ester derivatives such as the 3,5-dinitrobenzoate or acetate.

4-Methyl-3-cyclohexen-1-one has been prepared by the method of Birch (1). Reduction to the alcohol was accomplished by either lithium aluminum hydride or aluminum isopropoxide. Absorption spectra measurements of some samples prepared in this manner showed dual maxima at 280 and 286 mμ, whereas the pure alcohol has very little absorption in this area. These maxima were presumed to be due to an impurity. On examining the absorption spectra of both the dihydro-*p*-tolyl methyl ether and *p*-tolyl methyl ether, it was shown that these maxima were due to the latter, which could be detected in the alcohol even in trace amounts, but which would not be noted in the spectrum of the

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ketone because it also has an absorption band in this area. The presence of *m*-tolyl methyl ether was due to insufficient washing of the ketone bisulfite addition product in the previous step, but could also be eliminated by further distillation of the alcohol. The alcohol was further purified by conversion to the solid *p*-chlorobenzoate, which was then saponified. *p*-Chlorobenzoyl chloride forms solid derivatives with this as well as several other cyclic alcohols. This appears to be a very satisfactory way of eliminating most impurities, with the possible exception of other similar alcohols.

EXPERIMENTAL PART

3-Methyl-2-cyclohexen-1-one. Various runs were made on the preparation of this compound by the method of Smith and Roualt (11). In our hands this procedure gave yields not exceeding 25%. However it was possible to bring the over-all yield of this ketone up to about 45% if the higher-boiling fractions were further decarboxylated by the rather tedious procedure described by Horning and co-workers (6).

TABLE I

REFRACTIVE INDICES OF VARIOUS SAMPLES OF 3-METHYL-2-CYCLOHEXEN-1-ONE

SAMPLE PREPARED FROM	METHOD OF PURIFICATION	n_D^{20}
Acetoacetic ester	Distillation through a Claisen flask	1.4921
Acetoacetic ester	Regeneration from semicarbazone (5)	1.4929
Acetoacetic ester	Distillation through a column	1.4928
m-Tolyl methyl ether	Distillation through a Claisen flask	>1.5000
m-Tolyl methyl ether	Regeneration from the semicarbazone	1.4931
m-Tolyl methyl ether	Use of Girard's T reagent (4)	1.4928
N-Dimethyl-*m*-toluidine	Careful washing with acid, dist. through Claisen flask	1.4919

The method of preparation described by Birch (1) from *m*-tolyl methyl ether gives equivalent yields. Using the Birch method and hydrolyzing the dihydro *m*-tolyl methyl ether with 10% hydrochloric acid solution 3-methyl-2-cyclohexen-1-one was obtained in 35% over-all yield. However, if the free ketone was not isolated, but instead the dihydro *m*-tolyl methyl ether was converted directly to the derivative of the ketone such as the semicarbazone or the dinitrophenylhydrazone, the over-all yields of these derivatives were usually 65–70%, based on the original *m*-tolyl methyl ether.

The semicarbazone was recrystallized from ethanol-water solution or from benzene-methanol until a melting point of 200° was reached. However, melting point is not always a good criterion of purity of this compound, inasmuch as one sample, m.p. 199–200° was shown to contain a considerable quantity of the semicarbazido-semicarbazone, m.p. 213.5°, which was found to be insoluble in the 1/1 benzene-methanol solution.

It is of interest to note that the samples which have undergone more extensive purification all have refractive indices of 1.4930 ±2 at 20°. In contrast, the sample prepared from *m*-tolyl methyl ether could not be readily purified by disillation alone, five passes through a 600 × 6 mm. spiral packed column being insufficient to eliminate all of the *m*-tolyl methyl ether. Refractive indices are shown in Table I.

Other physical properties of the ketone are: b.p. 96°/25 mm., 78.5–79°/12 mm.; λ_{max} 226 mμ, log ϵ 4.25; λ_{max} 325 mμ, log ϵ 1.45; λ_{max} 335 mμ, log ϵ 1.46 (isooctane solvent).

This ketone was also prepared in the form of its 2,4-dinitrophenylhydrazone, by bromination of 3-methylcyclohexanone, followed by dehydrobromination with 2,4-dinitrophenylhydrazine in acetic acid, a method previously used by one of us (8) for preparing the 2-methyl isomer. The derivative obtained was in this instance rather impure, however, and required chromatography for adequate purification.

3-Methyl-2-cyclohexen-1-ol. This compound was prepared by reducing 22.5 g. of the ketone, utilizing the method developed by Nystrom and Brown (7), for similar reductions. It was absolutely essential to avoid overheating in the distillation step. The major fraction (15.5 g.) came over at 56°/1 mm. On redistillation, it was divided into several sub-fractions, all having the same boiling point, but ranging in refractive index from 1.4813 to 1.4831 at 20°. The middle one of these had the following properties: d_4^{23} 0.9463, n_D^{20} 1.4822.

Anal. Calc'd for $C_7H_{12}O$: C, 74.95; H, 10.72.
Found: C, 74.64; H, 10.76.

The alcohol was readily converted to the α-naphthylurethan, m.p. 118–119°, prepared according to the method of Shriner and Fuson (9).

Anal. Calc'd for $C_{18}H_{19}NO_2$: N, 5.10. Found: N, 5.18.

Various attempts to prepare the acetate, 3,5-dinitrobenzoate, and the phenylurethan met with failure, dehydration being the result. Various high-boiling fractions were produced, all of which had a high carbon analysis, usually 85–87%. Similar results were obtained if the alcohol was distilled at pressures produced by a water-pump, indicating that dehydration and polymerization had occurred.

4-Methyl-3-cyclohexen-1-one. This compound was prepared in a 40% yield by reduction of 35 to 50-g. lots of *p*-tolyl methyl ether in the manner described by Birch (1). To obtain the maximum yield it was essential to carry out the reaction in as short a time as possible, yet avoiding the foaming caused by too rapid addition of sodium. The ammonia should be evaporated rapidly, ice-water added cautiously to the residue, and the reaction product immediately extracted with ether. The dihydro-*p*-tolyl methyl ether is then partially separated from the unchanged *p*-tolyl methyl ether by distillation at atmospheric pressure through a Snyder column. Formation of the bisulfite is accomplished by shaking for three or four days with a large excess of saturated bisulfite solution, adding a little more bisulfite from time to time in order to keep the solution saturated. Thorough washing of the bisulfite compound with methanol and ether is essential. The ketone regenerated from this addition compound was fractionally distilled to constant refractive index using a 600 × 6 mm. column packed with a nichrome wire spiral and equipped with a total reflux-partial takeoff distilling head. Absorption spectra and refractive index were measured immediately after the second distillation. B.p. 170–173°/755 mm., 76°/25 mm.; n_D^{20} 1.4652; d_4^{20} 0.9551; λ_{max} 287 mμ, log ε 1.23 (in isooctane).

The ketone was readily converted to the *semicarbazone*, m.p. 187–188°, and the *2,4-dinitrophenylhydrazone*, m.p. 121–122°, described by Birch (1).

4-Methyl-3-cyclohexen-1-ol. The 4-methyl-3-cyclohexen-1-one was reduced to the corresponding alcohol by either lithium aluminum hydride or aluminum isopropoxide. The former gave yields of 54% and higher using the method of Nystrom and Brown for heptaldehyde (7). The isopropoxide reduction following the method of Wilds (13) gave yields not exceeding 35% and was more time consuming. The alcohol was fractionally distilled *in vacuo* through the spiral packed column. In one sample prepared in this way, there were observed two minor maxima in the absorption spectra, at λ 280 mμ and 286 mμ. These were subsequently shown to be due to *p*-tolyl methyl ether (λ_{max} 230 mμ, log ε 4.60; λ_{max} 280 mμ, log ε 3.25; λ_{max} 286 mμ, log ε 3.20) which was present in an amount no larger than 0.5% as estimated from the spectra. The maximum at λ 230 mμ is not suitable for estimation of this impurity, because the value of the specific extinction of the alcohol itself has a tendency to rise at the lower wave lengths, probably on account of its double bond. This inpurity could be eliminated by further fractionation through the column, or its appearance could be completely eliminated by a more adequate washing of the bisulfite addition product in the preparation of the ketone. However all samples prepared in this manner had a slightly low carbon analysis.

Further purification was obtained by converting to the *p*-chlorobenzoate by refluxing with *p*-chlorobenzoyl chloride for 20 minutes, adding dilute sodium hydroxide, and refluxing ten minutes longer. After several extractions with petroleum ether, the solvent was evaporated to about half-volume and cooled in a Dry Ice-bath, whereupon the *p*-chlorobenzoate separated out. It was filtered in a cooled filter and further recrystallized in the same manner from either petroleum ether or acetone, m.p. 59–60°.

Anal. Calc'd for $C_{14}H_{15}ClO_2$: C, 67.08; H, 6.03.
Found: C, 67.20; H, 6.36.

To regenerate the alcohol, 4.5 g. of ester was boiled 12 hours with 30% NaOH solution, after which much solid began to separate. The solution was then diluted with an equal amount of water and refluxed another 12 hours, finally extracted with ether, dried, and fractionated; b.p. 83°/18 mm. n_D^{20} 1.4748, yield 1.0 g. (47%). A considerable portion of unsaponified ester was still present.

Anal. Calc'd for $C_7H_{12}O$: C, 74.95; H, 10.75.
Found: C, 75.00; H, 10.72.

The alcohol was converted to the *3,5-dinitrobenzoate* by the method of Shriner and Fuson (9), m.p. 110° after recrystallization from methanol-water.

Anal. Calc'd for $C_{14}H_{14}N_2O_4$: C, 54.89; H, 4.61.
Found: C, 54.99; H, 4.38.

Acetate of 4-methyl-3-cyclohexen-1-ol. The alcohol (1 g.) was refluxed for four hours with 2 g. of acetic anhydride. The solution was poured over ice, extracted with ether, washed with sodium bicarbonate solution, dried, and distilled. The yield of product was 93%, b.p. 182°/755 mm., d_4^{20} 0.9603; n_D^{20} 1.4638. The acetate was also prepared using acetyl chloride and pyridine.

Wolff-Kishner reduction of 4-methyl-3-cyclohexen-1-one semicarbazone. The reduction of 13 g. of this semicarbazone by the method described by Todd (12) for a similar compound gave only 0.5 g. of a product with a boiling point of 105–111° (1-methylcyclohexene, b.p. 111–112°) with most of the product being a high-boiling viscous oil. The methylcyclohexene fraction was converted to the *nitrosochloride*, m.p. 89–90°. A mixture melting point with an authentic sample (m.p. 92–93°) showed no depression. The nitrosochloride was converted to the *nitrolpiperidine*, m.p. 153° [literature 146–147° (1) and 152° (10)].

SUMMARY

1. 3-Methyl-2-cyclohexen-1-one has been prepared by standard methods. Refractive indices of the various preparations are shown.

2. 3-Methyl-2-cyclohexen-1-one and 4-methyl-3-cyclohexen-1-one have been reduced to the corresponding alcohols.

3. Ultraviolet absorption spectra of the 4-methyl-3-cyclohexen-1-ol have been shown to reveal the presence of minute quantities of the starting material, *p*-tolyl methyl ether, in instances where it was incompletely removed.

4. Purification of 4-methyl-3-cyclohexen-1-ol has been accomplished by conversion to the *p*-chlorobenzoate, utilizing a low temperature crystallization procedure.

5. 3-Methyl-2-cyclohexen-1-ol was shown to be comparatively unstable to heat or mild dehydrating agents, either of which will produce dehydration polymerization.

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