Summary

1. Under certain conditions lead tetraacetate effects quantitative oxidative cleavage of α-keto acids and α-keto alcohols. The reaction seems to be one of general application.

2. This reaction occurs only after formation of a vicinal hydroxyl pair and therefore has to be considered as a glycol cleavage.

3. The formation of the "pseudoglycols" takes place by addition to the keto group. Water, alcohols (*e. g.*, methyl, ethyl and benzyl alcohols) and hydrocyanic acid were found capable of such an addition.

4. In the absence of substances forming pseudoglycols by addition no reaction takes place between lead tetraacetate and α-keto acids, whereas α-keto alcohols are oxidized in good yield to their diketones.

5. The nature of the cleavage products is determined by the glycol-forming substance added.

6. In the presence of water, alcohols or hydrocyanic acid the products are as follows: (a) from 1 mole of α-keto acid and 1 mole of lead tetraacetate are obtained 1 mole of carbon dioxide and 1 mole of acid (or ester or keto nitrile). (b) From 1 mole of α-keto alcohol and 1 mole of lead tetraacetate are obtained 1 mole of acid (or its ester) and 1 mole of aldehyde (or ketone).

7. The present use of lead tetraacetate to detect vicinal hydroxyl groups in compounds of unknown constitution may be extended to the detection of the α-keto acid and α-keto alcohol groups, if one compares the reaction of the substance with lead tetraacetate in dry solvents with the behavior in the presence of compounds capable of forming pseudoglycols, as explained above.

8. The method of oxidative cleavage may be employed not only to determine α-keto acids quantitatively by the carbon dioxide evolved but also to distinguish them qualitatively from other keto acids (β, γ, · · ·, etc.).

TORONTO, CANADA RECEIVED APRIL 8, 1940

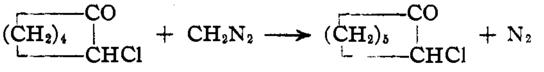
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

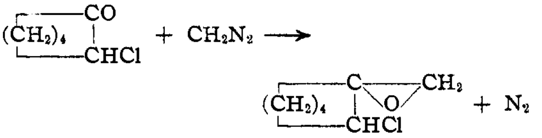
The Ring Enlargement of Two Cyclic Alpha-Chloroketones

BY THOMAS R. STEADMAN[1]

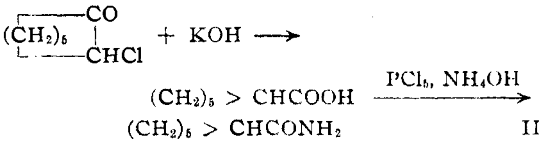
A study of the reaction of diazomethane with cyclic α-chloroketones was undertaken in these laboratories in order that further light might be shed on the process of ring enlargement of cyclic systems. Giraitis and Bullock[2] have reported briefly on work similar in character to that described in the present paper. The present investigation has been confined to experiments based on Meerwein's mode of operation,[3,4] involving the introduction of nitrosomethylurethan at a suitable rate into a solution of the ketone in methanol containing a small amount of sodium carbonate. This is quite different from the method employed by Giraitis and Bullock,[2] who used diazomethane in ethereal solution.

The principal reactions in the case of α-chlorocyclohexanone may be represented by the following equations, although the actual intermediate may not be diazomethane


I


II

It is important to note that when the ring was enlarged, the methylene group entered the ring in such a manner that the chlorine atom remained alpha to the carbonyl group. This was shown by the fact that when the chloroketone was treated with alcoholic sodium hydroxide, cyclohexane carboxylic acid was obtained and identified by conversion to the amide:


III

This degradation was first recognized by Favorskii and Boshowski.[5]

---

[1] This investigation was begun by the author at the suggestion and under the direction of the late Prof. E. P. Kohler.

[2] Giraitis and Bullock, THIS JOURNAL, **59**, 951 (1937).

[3] Meerwein, *Chem. Zentr.*, **104**, II, 1758 (1933); German Patent 579,309.

[4] Kohler, Tishler, Potter and Thompson, THIS JOURNAL, **61**, 1057 (1939).

[5] Favorskii and Boshowski, *J. Russ. Phys.-Chem. Soc.*, **50**, 582 588 (1917); *C. A.*, **18**, 1476 (1924).

The possibility that β-chloroketones might also undergo the Favorskii degradation is considered unlikely. No evidence bearing directly on the point could be found in the literature, but such an eventuality would require that both the α- and the β-chloroketones should pass through a common intermediate, the α,β unsaturated ketone. This is an hypothesis difficult to accept. It is much more likely that the reaction is analogous to the benzilic acid rearrangement.

Attempts to secure a semicarbazone from the chloroketone proved futile, but it is common for α-halogen atoms to reduce the carbonyl activity of ketones in this respect.

The structure of 2-chloro-1-methylenecyclohexane oxide as formulated in Equation II above was proved by hydrogenation of the substance, thus forming cyclohexylcarbinol, which was readily identified as the phenylurethan.

From a typical experiment involving α-chlorocyclohexanone and diazomethane, there was obtained a 52% yield of pure α-chlorocycloheptanone and a 16% yield of pure 2-chloro-1-methylenecyclohexane oxide. It was estimated that the intermediate fractions from the distillation contained further yields of about 7.5% of the ketone and 8% of the oxide. Taking these materials into consideration, together with a distillation residue of 3%, it was possible to account for 86.5% of the ketone used. This compares favorably with the material balance reported by Kohler and his associates[4] for the reaction of cycloöctanone with diazomethane. The three to one ratio of ketone to oxide corresponds roughly with the similar ratio observed in the case of the unsubstituted cyclic ketone. However, it should be noted that the results of this experiment contrast sharply with the report by Giraitis and Bullock[2] that a quantitative yield of α-chlorocycloheptanone was obtained from α-chlorocyclohexanone and diazomethane in ethereal solution.

From the reaction of diazomethane with α-chlorocycloheptanone, three substances were isolated. One of them was recovered starting material, as indicated by its physical properties and an analysis. A second substance was tentatively identified as 2-chloro-1-methylenecycloheptane oxide. The third compound, α-chlorocycloöctanone, upon treatment with alcoholic alkali, gave cycloheptane carboxylic acid, which was identified as the amide.

After long standing in a stoppered flask under an atmosphere of air, the α-chlorocycloöctanone which had been obtained by careful fractional distillation under diminished pressure was found to contain a small amount of a white, crystalline compound. This was filtered off, washed free of α-chlorocycloöctanone with ether and then recrystallized from dilute hydrochloric acid. The recrystallized material proved to be suberic acid, as shown by an analysis and a mixed melting point determination with an authentic sample of suberic acid. Presumably suberic anhydride was formed by oxidation of the chloroketone and this transformed to the acid on recrystallization.

Despite the fact that a 10% excess of nitrosomethylurethan was used in the reaction with α-chlorocycloheptanone, 36.8% of the starting material was recovered in a good state of purity. The pure α-chlorocycloöctanone and the pure isomeric oxide were obtained in roughly equal amounts (the yields of ketone and oxide being 13 and 11.7%, respectively). The impure intermediate fractions were estimated to contain more of the starting material (15.4%) and further yields of α-chlorocycloöctanone (2.4%) and oxide (4.4%). These, together with distillation residues amounting to 10.8%, accounted for 94.5% of the starting material.

The work of Kohler and his associates[4] on the reaction of diazomethane with cycloöctanone and cyclononanone showed that these reactions were subject to steric hindrance due probably to both the lessened reactivity of the carbonyl group and the difficulty of introducing another methylene group into an already crowded ring system. Owing to the possibility of the interaction of several factors in the reactions studied in the present investigation, the interpretation of the experimental results is not easy. The fairly good yields of products obtained in the reaction of diazomethane with α-chlorocyclohexanone are comparable with those obtained under similar conditions in the case of cyclohexanone, demonstrating that α-chloro substitution has exercised no pronounced effect on the reactivity of the carbonyl group in this direction.

However, the lower yields of products resulting from the reaction of diazomethane with α-chlorocycloheptanone, when contrasted with the behavior of cycloheptanone under similar circumstances, lend support to the idea put forward by Stoll and Stoll-Comte[6] to explain by steric con-

---

(6) Stoll and Stoll-Comte, *Helv. Chim. Acta*, **13**, 1185 (1930).

siderations the difficulties encountered in synthesizing cycloalkanones with eight to thirteen ring members. The replacement of a hydrogen with a relatively larger chlorine atom in these ketones should tend to make more difficult the formation of rings of such size. This has been borne out by the finding that the reaction of α-chlorocycloheptanone with diazomethane gave rise to smaller yields of products and a lower ratio of ketone to oxide than resulted from the reaction of α-chlorocyclohexanone with diazomethane under similar conditions. The decrease in the yield of products may be ascribed to the lower degree of reactivity of the carbonyl group of α-chlorocycloheptanone as compared with that of α-chlorocyclohexanone. The decrease in the ratio of ketone to oxide is probably due to the steric hindrance offered to the introduction of a methylene group into the ring. An extension of the evidence offered herein would be highly desirable.

Experimental Part

α-Chlorocyclohexanone.—The chlorination of cyclohexanone in acetic acid solution according to directions by Bartlett and Rosenwald[7] resulted in 50–60% yields of α-chlorocyclohexanone, m. p. 22–23°.

α-Chlorocyclohexanone and Diazomethane.—In a 500-cc. three-necked, round-bottomed flask equipped with a thermometer, a dropping funnel, an outlet for nitrogen, and an efficient mechanical stirrer operated through a mercury seal, there was placed 133 g. (1 mole) of freshly distilled α-chlorocyclohexanone, 100 cc. of absolute methanol, and 1–2 g. of finely powdered anhydrous sodium carbonate. Over a period of about seven hours, 146 g. (1.1 moles) of nitrosomethylurethan was added dropwise to the well-stirred reaction mixture, which was cooled as necessary to maintain a temperature between 20 and 30°. When the evolution of nitrogen had ceased, the solution was filtered into a modified Claisen flask and the methanol, together with some methylethyl carbonate, removed by distillation at atmospheric pressure. By careful and repeated fractional distillations of the residue through an efficient column packed with three feet (91 cm.) of glass helices, it was possible to obtain 76.2 g. (52%) of α-chlorocycloheptanone, b. p. 87–88° (10 mm.), and 22.7 g. (16%) of 2-chloro-1-methylenecyclohexane oxide, b. p. 62–63° (10 mm.), m. p. −10 to −8°. The other fractions obtained in the final distillation (10 mm.) were: (1) 59–62°, 3.3 g.; (2) 63–64°, 3.6 g.; (3) 64–70°, 3.4 g.; (4) 70–80°, 3.0 g.; (5) 80–86°, 7.1 g.; (6) 86–87°, 2.4 g.; and a residue of 4.7 g. The ketone was a colorless, mobile liquid with a pungent odor, d^{20}_4 1.140 (Favorskii and Boshowski[5] reported d^{20}_4 1.133), $n^{20}\mathrm{D}$ 1.4870.

Anal. Calcd. for $C_7H_{11}OCl$: Cl, 24.2. Found: Cl, 24.3.

By refluxing 15 g. (0.1 mole) of α-chlorocycloheptanone with alcoholic potassium hydroxide, approximately 4 g. (36% yield) of cyclohexane carboxylic acid was secured in a somewhat impure state. For purposes of identification, the liquid acid was treated with an excess of phosphorus pentachloride and the resulting acid chloride poured into concentrated ammonium hydroxide. After one treatment with active charcoal and two recrystallizations from water, white leaflets of cyclohexane carboxamide, m. p. 183–184° (uncor.), were obtained; reported,[8] 184°.

The oxide was also a colorless, mobile liquid with an odor much like that of the isomeric ketone, d^{20}_4 1.120, $n^{20}\mathrm{D}$ 1.4763.

Anal. Calcd. for $C_7H_{11}OCl$: Cl, 24.2. Found: Cl, 24.1.

Hydrogenation of the oxide to cyclohexylcarbinol in 95% ethanol, using Raney nickel as catalyst, required much time. An equivalent amount of potassium hydroxide was used in the reaction mixture to absorb the hydrogen chloride formed. From 7.3 g. of oxide was obtained 3.15 g. of liquid, b. p. 81–86° (15 mm.), which was conclusively identified as cyclohexylcarbinol by conversion to a phenylurethan, m. p. 81.5–82.0° (cor.), mixed melting point with an authentic sample 81–82° (cor.). Since the phenylurethan of cycloheptanol has a melting point of 84–85°, it was thought advisable to perform a mixed melting point with an authentic sample of this phenylurethan: found, m. p. 78–80°.

α-Chlorocycloheptanone and Diazomethane.—Using the method outlined for α-chlorocyclohexanone, 143 g. (0.98 mole) of α-chlorocycloheptanone was treated with a 10% excess of nitrosomethylurethan. Three careful fractional distillations of the reaction mixture under diminished pressure permitted the separation of three products. The lowest boiling fraction was identified tentatively as 2-chloro-1-methylenecycloheptane oxide, 18.4 g. (11.7% yield), b. p. 84–86° (10 mm.), $n^{20}\mathrm{D}$ 1.4848.

Anal.[9] Calcd. for $C_8H_{13}OCl$: Cl, 22.07. Found: Cl, 22.18.

The middle fraction was considered to be starting material, α-chlorocycloheptanone, 55 g. (38% recovered), b. p. 88–90° (10 mm.), $n^{20}\mathrm{D}$ 1.4861.

Anal.[9] Calcd. for $C_7H_{13}OCl$: Cl, 24.22. Found: Cl, 24.18.

The highest boiling fraction proved to be α-chlorocyclooctanone, and was obtained in 13.0% yield (20.2 g.), b. p. 104–106° (10 mm.), $n^{20}\mathrm{D}$ 1.4930, $n^{15}\mathrm{D}$ 1.4952 (reported[10]: $n^{14.5}\mathrm{D}$ 1.4938). The other fractions obtained from the final distillation (10 mm.) were: (1) 80–84°, 1.2 g.; (2) 86–87°, 2.6 g.; (3) 87–88°, 3.6 g.; (4) 90–91°, 7.4 g.; (5) 91–94°, 10.9 g.; (6) 94–101°, 2.3 g.; (7) 101–103°, 2.3 g.; (8) 103–104°, 2.3 g.; and distillation residues totalling 16.7 g.

Extension of the Favorskii degradation to α-chlorocyclooctanone confirmed the tentative identification. Treatment of the ketone with an excess of alcoholic sodium hydroxide gave cycloheptane carboxylic acid, which was readily identified by conversion to the amide, m. p. 192–193° (uncor.); reported,[11] m. p. 193–194°.

After standing for approximately six months in a stoppered flask under an atmosphere of air, the α-chlorocyclo-

---

[7] Bartlett and Rosenwald, THIS JOURNAL, **56**, 1990–1994 (1934).

[8] Aschan, *Ann.*, **271**, 264 (1892).

[9] Analysis by Mr. H. S. Wight.

[10] Godchot and Mousseron, *Bull. soc. chim.*, (4) **51**, 782 (1932).

[11] Zelinsky, *Ber.*, **35**, 2691 (1902).

octanone was found to contain a precipitate of a white, crystalline compound which was filtered off and washed free of α-chlorocycloöctanone with ether. Two recrystallizations of the substance from 5% hydrochloric acid resulted in a substance, m. p. 140.5–141°, which contained neither chlorine nor nitrogen. A mixed melting point determination with an authentic sample of suberic acid showed no depression of the melting point.

Anal.[9] Calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.11. Found: C, 55.28; H, 8.05.

Summary

Two alicyclic α-chloroketones have been found to undergo ring enlargement on treatment with diazomethane. From the yields of ketonic materials obtained, evidence has been adduced for the Stoll and Stoll-Comte[6] hypothesis regarding steric effects in certain alicyclic ring systems.

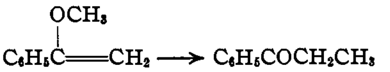
CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 23, 1940

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Condensation of α-Methoxystyrene with Halogen Compounds

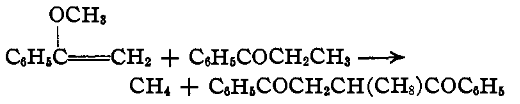
BY C. W. MORTENSON AND M. A. SPIELMAN

In addition to the normal rearrangement (1),[1]



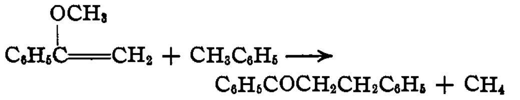
$$C_6H_5\overset{\displaystyle OCH_3}{\overset{|}{C}}{=}CH_2 \longrightarrow C_6H_5COCH_2CH_3 \qquad (1)$$

α-methoxystyrene and a few similar enol ethers undergo a peculiar side reaction (2) in which the unchanged ether condenses with the rearrangement product to eliminate methane and form a γ-diketone. Later[2] it was discovered that at



$$C_6H_5\overset{\displaystyle OCH_3}{\overset{|}{C}}{=}CH_2 + C_6H_5COCH_2CH_3 \longrightarrow CH_4 + C_6H_5COCH_2CH(CH_3)COC_6H_5 \qquad (2)$$

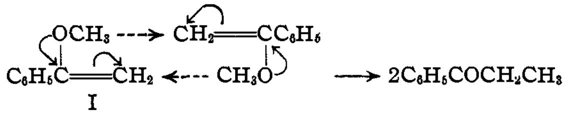
250° α-methoxystyrene also condenses with hydrocarbons such as toluene and cyclohexane (3).



$$C_6H_5\overset{\displaystyle OCH_3}{\overset{|}{C}}{=}CH_2 + CH_3C_6H_5 \longrightarrow C_6H_5COCH_2CH_2C_6H_5 + CH_4 \qquad (3)$$

This reaction, so far as we know, has no analogy except, perhaps, in the recently discovered photolytic condensation of phosgene or oxalyl chloride with cyclohexane.[3] Only ethers capable of undergoing the rearrangement[4] also take part in the condensation, and it is evident that there is some common factor in the two reactions.

The hypothesis here advanced to account for the behavior of α-methoxystyrene is that both the rearrangement and the condensation involve the polarized hetero-enoid system in I. Collision, under the proper circumstances, of two such

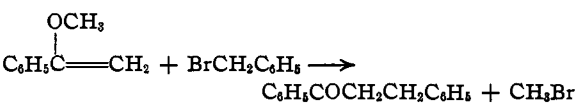


I

molecules leads to the so-called rearrangement which, in the light of such an interpretation, becomes an intermolecular alkylation. The mechanism explains why the reaction is of the second order and why the alkyl group on the oxygen atom of one molecule may, at the end of the reaction, turn up on the carbon atom of another.[1]

Collision of the polarized molecule I with a reactive but different molecular species leads to the condensation reaction. Attack should be at the anionoid center on the methylene carbon atom,[5] and in that event a reaction should take place with alkyl halides which are cationoid in their reactivity and definitely more polarized than hydrocarbons. A few typical halogen compounds of varying degrees of reactivity have been studied.

α-Methoxystyrene when heated with an eightfold excess of benzyl bromide yields β-phenylpropiophenone in 51% of the theoretical yield.



$$C_6H_5\overset{\displaystyle OCH_3}{\overset{|}{C}}{=}CH_2 + BrCH_2C_6H_5 \longrightarrow C_6H_5COCH_2CH_2C_6H_5 + CH_3Br$$

When equimolecular amounts of the halide are used, the yield is 35%, which is well above the 8% yield obtained from toluene under comparable conditions. *n*-Butyl bromide, containing a moderately active halogen atom, condenses in 28% yield, whereas bromobenzene does not react at all.

---

[1] Lauer and Spielman, THIS JOURNAL, **55**, 4923 (1933).

[2] Spielman and Mortenson, *ibid.*, **61**, 666 (1939).

[3] Kharasch and Brown, *ibid.*, **62**, 454 (1940).

[4] The second order, intermolecular rearrangement of enol ethers (MacDougall, Lauer and Spielman, *ibid.*, **55**, 4089 (1933)) possesses only a formal similarity to the familiar first order, intramolecular rearrangement of allyl ethers (Kincaid and Tarbell, *ibid.*, **61**, 3085 (1939); Hurd and Schmerling, *ibid.*, **59**, 107 (1937)).

[5] The anionoid reactivity of α-methoxystyrene is shown by the avidity with which it adds water, alcohol, acids, etc. For terminology refer to Robinson, "Outline of an Electrochemical Theory of the Course of Organic Reactions," The Institute of Chemistry of Great Britain and Ireland, London, 1932.