of barbituric acid with 5 g. of dibromoxyhydrouracil (I) was 0.8 g. of hydurilic acid (III).

Anal. Calcd. for $C_8H_6O_6N_4$: N, 22.04. Found: N, 21.78, 21.89.

It is interesting to note that carbon dioxide was evolved in small quantity during these oxidation reactions. That the pyrimidine ring in barbituric acid is partially ruptured by the oxidizing agent is also revealed by the presence of ammonium bromide which is easily identified in the aqueous filtrate after separation of the pyrimidines.

Summary

1. Malonic acid undergoes bromination with loss of carbon dioxide by interaction with dibromoxyhydrouracil giving tribromoacetic acid.

2. Barbituric acid is oxidized by interaction with dibromoxyhydrouracil giving hydurilic acid.

NEW HAVEN, CONNECTICUT RECEIVED JUNE 26, 1941

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Oxidation of Alcohols with Ketones

BY HOMER ADKINS AND RICHARD C. FRANKLIN[1]

Reactions of the type, $R_2CO + Al(OCHR'_2)_3 \rightleftharpoons Al(OCHR_2)_3 + R'_2CO$ have for many years been useful for the reduction of ketones.[2-5] More recently Oppenauer[6] utilized the reaction for the oxidation of an alcohol such as cholesterol. In order to avoid the necessity of treating aluminum with the alcohol to be oxidized, he added aluminum *t*-butoxide to the alcohol and so secured the desired alkoxide by interchange, *i. e.*, $3ROH + (t\text{-}C_4H_9O)_3Al \rightleftharpoons Al(OR)_3 + 3t\text{-}C_4H_9OH$.

The ideal oxidizing agent for this method would be a ketone which had a high oxidation potential,[7] reacted rapidly at a low temperature and was not readily condensed under the influence of aluminum alkoxides.[8] Other desirable characteristics for such a ketone would be a low molecular weight, a ready availability and a low cost.

Among the more accessible ketones are acetone, cyclohexanone, *p*-benzoquinone, benzil, methyl ethyl ketone, mesityl oxide, pinacolone, diacetone alcohol, phorone, isophorone and isobutyl methyl, diisobutyl and diisopropyl ketones. The effectiveness of these ketones has been tested against diphenylcarbinol, cholesterol, various cyclohexanols, neopentyl and other alcohols. In most instances oxidations were first made on a small scale and the rate and extent of reaction determined with a polarograph. Oxidations were then made on a preparational scale for those oxidizing agents that seemed attractive.

The studies by Cox,[9] Baker[7] and Wayne[8] in this Laboratory upon the oxidation potential and upon the susceptibility of ketones to undergo the mesityl oxide type of condensation, indicate certain general considerations to be followed in the choice of a ketone as an oxidizing agent. The oxidation potentials of *p*-benzoquinone (0.71 v.), cyclohexanone (0.195), acetone (0.162), benzophenone (0.163), and diisopropyl ketone (0.133) are such that there will be a very large difference between the concentrations at equilibrium depending upon the ketone selected as an oxidizing agent. For example, *p*-benzoquinone should oxidize diphenylcarbinol quantitatively to benzophenone if the quinone and the alcohol were mixed in equimolecular proportions. However, to attain even a 90% oxidation with diisopropyl ketone the latter would need to be used in the proportion of 80 moles to one mole of diphenylcarbinol. Nine moles of acetone or 1.4 moles of cyclohexanone should give a similar conversion.

The branched chain ketones, such as phorone, pinacolone, diisobutyl or diisopropyl ketone were very attractive as oxidizing agents for they are completely resistant to condensation and their

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(1) Wisconsin Alumni Research Foundation Fellow, 1937–1939.

(2) Meerwein and Schmidt, *Ann.*, **444**, 221 (1925).

(3) Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926).

(4) Verley, *Bull. soc. chim.*, [4] **37**, 537, 871 (1925).

(5) Lund, *Ber.*, **70**, 1520 (1937).

(6) Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(7) Baker and Adkins, THIS JOURNAL, **62**, 3305 (1940).

(8) Wayne and Adkins, *ibid.*, **62**, 3401 (1940).

(9) In the early work the false assumption was made that since acetone and cyclohexanone did not show a depolarization potential at a dropping mercury electrode, these ketones would have a lower power as oxidizing agents than unsaturated ketones such as mesityl oxide and phorone [Cox and Adkins, *ibid.*, **60**, 1157 (1938)]. There appears to be little correlation between the depolarization potential of a ketone and its power as an oxidizing agent. Another regrettable feature of this paper is that the term "reduction potential" was used for the value which we now call a "depolarization potential." An alcohol, but not a ketone, has a "reduction potential," *i. e.*, it has power as a reducing agent. Since the strength of a ketone as an oxidizing agent is inseparably linked to the strength of the corresponding alcohol as a reducing agent, it has been customary, for example, to speak of the "oxidation–reduction potential of a quinone." It seems to us simpler and more accurate to refer to the oxidizing power of a ketone or quinone as its "oxidation potential."[7]

relatively low oxidation potentials could be compensated for by using them in large molecular excess. However, they proved to be almost useless because they react so slowly, even at the maximum temperature that can be used with aluminum *t*-butoxide.

Only five of the oxidizing agents tested seem to have real merit, *i. e.*, acetone, methyl ethyl ketone, cyclohexanone, benzil and *p*-benzoquinone. Some of the advantages and disadvantages in the use of each of these oxidizing agents are as follows. The first three mentioned readily undergo the mesityl oxide type of condensation. Both benzil and its reduction products, benzoin and diphenyl ethylene glycol, have physical properties which may make it difficult to isolate the desired oxidation product. Benzil reacts rather slowly and it has a relatively high molecular weight. *p*-Benzoquinone and its reduction product, hydroquinone, may also interfere with the separation of the products of reaction, but the tendency of the quinone to condense with other compounds is an even greater handicap in its use as an oxidizing agent. However, the rapidity with which *p*-benzoquinone reacts and its very high oxidation potential make it useful. Cyclohexanone is attractive because of its relatively high oxidation potential, and the rapidity with which it reacts. Acetone and methyl ethyl ketone are attractive because of their accessibility and the relative ease of isolation of the desired ketone after the completion of the oxidation.

In general, it may be said that methyl ethyl ketone aud cyclohexanone are the best oxidizing agents for high molecular weight alcohols, such as the sterols. Benzil is likely to be a good reagent for the preparation of ketones or aldehydes which may be distilled out of the reaction mixture below 100°. *p*-Benzoquinone and benzil are good oxidizing agents for the preparation of ketones boiling at 100 to 200°, especially those which are likely to undergo condensation.

No precise general statements can be made with respect to the optimum temperature and duration of reaction or the concentration of reactants. In general, one mole of alkoxide per mole of alcohol to be oxidized has been used, although equally good results were obtained where the amount of the alkoxide was cut in half. The volume and dryness of the solvent and reactants determine in part the amount of alkoxide that must be used. There must be enough alkoxide present to remove all the water present in the reaction mixture in addition to about 0.5 mole of alkoxide per mole of alcohol to be oxidized. Dilution of the reaction mixture minimizes condensation. For example, the extent of condensation of cyclohexanone was reduced from 26 to 13% by diluting the reaction mixture from 0.8 to 0.05 molar with respect to the alcohol to be oxidized. Benzene, toluene and dioxane appear to be about equally satisfactory as diluents.

A high ratio of 40 to 80 moles of ketone for one mole of a sterol appears to be desirable, while with other alcohols a lower ratio may be equally satisfactory. For example, about 20 moles of acetone or methyl ethyl ketone, 3 to 10 moles of cyclohexanone or 1 to 3 moles of *p*-benzoquinone or benzil per mole of alcohol to be oxidized have given the optimum yields.

Oxidations with *p*-benzoquinone may go to completion after an hour or so at room temperature or with cyclohexanone after a week. However, in general, it is preferable to carry out the oxidations at 55–60°.

Experimental Part

Only a few of the many experiments upon which the foregoing summary is based are given below. Most of the reactions were carried out under a reflux condenser with mechanical agitation in a three-necked flask. The preparation of aluminum *t*-butoxide[10] and the method used in making polarographic analyses has been described.[7]

Aluminum alkoxides were decomposed in the reaction mixtures, by slowly adding with stirring to the hot solution, a little more than three moles of water per mole of alkoxide. The solid aluminum hydroxide was separated by centrifuging and was then washed three to five times with a suitable solvent such as ether. The solvents were then distilled through a fractionating column. This method gave a 90–95% recovery of the reactants. In certain cases the aluminum hydroxide was removed from the reactants by washing with sulfuric acid.

Diphenylcarbinol (15 g.), benzil (17.2 g.), and aluminum *t*-butoxide (15 g.) were refluxed in toluene (100 ml.) for fourteen and one-half hours. After hydrolysis and removal of the aluminum hydroxide, the mixture upon fractional distillation gave 14.2 g., b. p. 115–117° (2 mm.), from which 12.4 g., m. p. 47.5–49°, of benzophenone was obtained by recrystallization from alcohol. The residue from the distillation of benzophenone was taken up in hot alcohol and 13 g. of benzoin, m. p. 133–134°, was obtained. These two products represent 83 and 76%, respectively, of the theoretical yield.

Diphenylcarbinol (10 g.), *p*-benzoquinone (6 g.), and the alkoxide (13 g.) in benzene (100 ml.) were heated at 55–57° for four and one-half hours. Polarographic analyses made upon the reaction mixture showed that the alcohol had

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[10] Wayne and Adkins, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XXI, 1941.

been converted to benzophenone to the extent of 97%. Distillation gave 9.1 g. of product which analyzed (polarograph) 88% benzophenone. Benzophenone, m. p. 46–47°, was obtained from the crude product by recrystallization from alcohol.

Diphenylcarbinol (10 g.), cyclohexanone (16 g.) and the alkoxide (13 g.) in toluene (60 ml.) were allowed to stand at 20–25° for a week. Polarographic determinations upon the reaction mixtures showed that the alcohol had been converted to benzophenone to the extent of about 90%. Benzophenone (8 g.) was also obtained when the same reactants were held at 56° for three hours. 2-Cyclohexylidene-cyclohexanone was isolated in a yield of about 20% from the reaction carried out at 20–25°.

Diphenylcarbinol (10 g.), isobutyrophenone (40.3 g.) and the alkoxide (13.4 g.) were refluxed in toluene (105 ml.) for forty-two hours. A polarographic analysis indicated that 81% of the alcohol was oxidized. The amount of benzophenone recovered was 68% of the theoretical. Benzaldehyde (18 g.) in 100 ml. of benzene was added during one and one-half hours to a solution at 55–56° of 10 g. of diphenylcarbinol and 13 g. of alkoxide in 100 ml. of benzene. After reaction for one hour, 10 g. of a sample, 91% pure, of benzophenone was obtained.

2-Ethylcyclohexanol (15 g.), *p*-benzoquinone (65 g.) and aluminum *t*-butoxide (14.8 g.) in a liter of toluene were allowed to stand at 20–25° for eight days. After the removal of aluminum hydroxide, the toluene solution was washed with a 5% solution of sodium hydroxide and with water. After distillation and fractionation through a modified Widmer column 11.4 g. of 2-ethylcyclohexanone, b. p. 178–182° (738 mm.), $n^{25}{}_{\mathrm{D}}$ 1.4500, identified as its semicarbazone, m. p. 160–161° (from benzene), was obtained.[11] The sample of ketone was shown to contain no more than 3% of 2-ethylcyclohexanol.

Cholesterol (7.5 g.) in 100 ml. of methyl ethyl ketone with 7 g. of aluminum *t*-butoxide in 50 ml. of benzene was refluxed for eight hours. The crude product (8.4 g.) after recrystallization from equal parts of acetone and methanol gave 6.2 g. of cholestenone, m. p. 78–79°, or an 84% yield.

Cholesterol was oxidized with acetone as by Oppenauer,[6,12] and with cyclohexanone as by Butenandt[13] and others. The results obtained were similar to those previously reported.

Summary

Some of the factors governing the choice of a ketone and experimental conditions for the oxidation of an alcohol with a ketone in the presence of aluminum *t*-butoxide have been considered.

(11) Bartlett and Berry, THIS JOURNAL, **56**, 2683 (1934).

(12) Cason and Fieser, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XXI, 1941.

(13) Butenandt, Schmidt-Thome and Weisz, *Ber.*, **72**, 423 (1939).

MADISON, WISCONSIN RECEIVED JUNE 9, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Activated Complex Theory Applied to Fast Reactions. The Reaction of Aldchlorimines with Bases[1]

BY W. E. JORDAN,[2] H. E. DYAS AND D. G. HILL

There are two theories currently in use to explain the mechanism by which chemical reactions attain their measured rates. One, generally known as the collision theory, was first applied to reactions in solution by Moelwyn-Hughes.[3] It treats reactions in solution by the methods of gas reactions, and uses the fundamental equation $k' = PZe^{-E/RT}$ in which k' is the rate constant, Z is the collision number calculated as if the reactants were gas molecules, P is a probability factor, and E the Arrhenius activation energy. Moelwyn-Hughes has shown that for many reactions, the P factor has the order of magnitude of unity and that the treatment has considerable application. The cases where P is far from unity, however, are also numerous, and the explanation of this fact is somewhat unsatisfactory. Particularly is this true for reactions in which P is greater than unity, in which case the practice seems to be to assign it to some ill-defined "internal degrees of freedom," borrowing the term from the theory of unimolecular gas reactions.

The activated complex theory as developed by Eyring, Wynne-Jones and Eyring, and Evans and Polanyi[4] has been applied particularly to very "fast" reactions. The equation derived from statistics is $k' = \frac{kT}{h} e^{-\Delta F^*/RT}$. This was shown by Stearn and Eyring[5] to explain several very rapid reactions and to ascribe the very large rate to a gain in entropy in the formation of the

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(1) This paper is in part taken from a thesis submitted by H. E. Dyas to the Graduate School of Arts and Sciences of Duke University, Durham, North Carolina, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1941.

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(3) Moelwyn-Hughes, "The Rate of Chemical Reactions in Solution," Clarendon Press, Oxford, England, 1933.

(4) H. Eyring, *J. Chem. Phys.*, **3**, 107 (1935); Wynne-Jones and Eyring, *ibid.*, **3**, 492 (1935); Evans and Polanyi, *Trans. Faraday Soc.*, **21**, 875 (1935); see also Faraday Soc., Discussion on Reaction Kinetics, Sept., 1937.

(5) Stearn and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).