[Contribution from the Department of Chemistry, University of California]

Flavonones and Related Compounds. V. The Oxidation of 2′-Hydroxychalcones with Alkaline Hydrogen Peroxide

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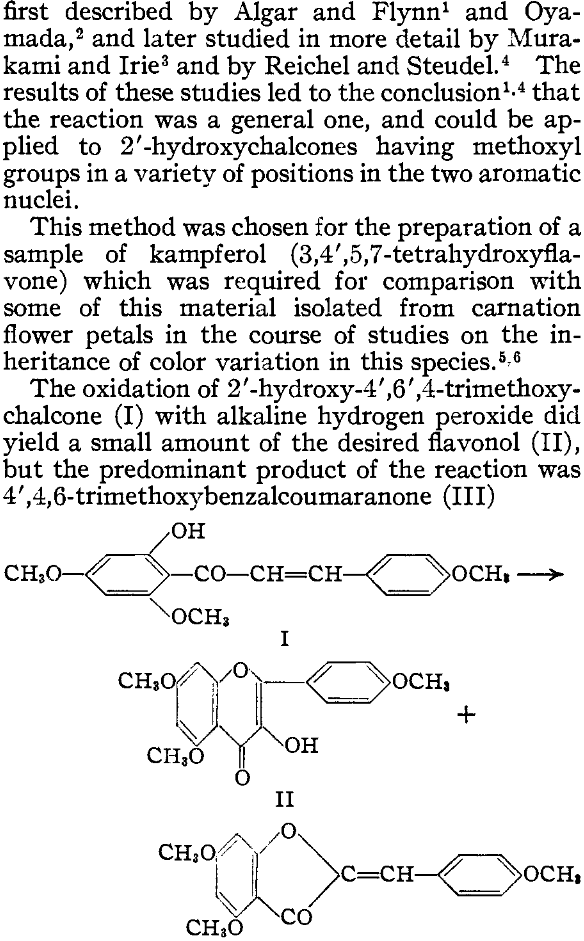
The oxidation by means of alkaline hydrogen peroxide of 2′-hydroxychalcones (and the corresponding flavanones) to 3-hydroxyflavones was first described by Algar and Flynn[1] and Oyamada,[2] and later studied in more detail by Murakami and Irie[3] and by Reichel and Steudel.[4] The results of these studies led to the conclusion[1,4] that the reaction was a general one, and could be applied to 2′-hydroxychalcones having methoxyl groups in a variety of positions in the two aromatic nuclei.

This method was chosen for the preparation of a sample of kampferol (3,4′,5,7-tetrahydroxyflavone) which was required for comparison with some of this material isolated from carnation flower petals in the course of studies on the inheritance of color variation in this species.[5,6]

The oxidation of 2′-hydroxy-4′,6′,4-trimethoxychalcone (I) with alkaline hydrogen peroxide did yield a small amount of the desired flavonol (II), but the predominant product of the reaction was 4′,4,6-trimethoxybenzalcoumaranone (III)



I

II

III

The formation of benzalcoumaranones in this reaction has not been encountered in previous studies,[1–4,7] and it is significant to note that in none of the earlier work were chalcones used which were derivatives of 2,4,6-trihydroxyacetophenone. Oxidation to the flavonol has been the only course observed when the chalcone is the benzal, anisal, veratral or piperonal derivative of 2-hydroxy-, 2-hydroxy-4-methoxy-, 2-hydroxy-3,4-dimethoxy-, or 2-hydroxy-3,4,5-trimethoxyacetophenone.[7]

It appeared likely that the presence of the 6′-methoxy group in I was responsible for the unexpected course of its reaction with alkaline hydrogen peroxide. Further studies showed that 2′-hydroxy-4′,6′-dimethoxychalcone (IV), 2′-hydroxy-4′,6′,3,4-tetramethoxychalcone (V), and 2′-hydroxy-6′-methoxy-3,4-methylenedioxychalcone (VI) yielded the corresponding benzalcoumaranones, a trace of the flavonol (quercetin-3′,4′,5,7-tetramethyl ether) accompanying the benzalcoumaranone in the case of V only.

These new observations afford a further insight into the course of this reaction, substantiating in part certain of the conclusions of some of the earlier investigators and invalidating others. Oyamada[2] assumed that the reaction proceeded through the flavanone in each case, but the ease with which flavanones are opened in alkali to the salts of the corresponding 2′-hydroxychalcones renders this interpretation difficult to test,[4] and it is probable that the chalcone (as the salt) is the reactive species whether the chalcone or the flavanone is used as the starting material. Algar and Flynn concluded that an ethylene peroxide or a glycol was the intermediate since an oxido intermediate would be expected to lead to a flavone or a benzalcoumaranone.[1] It is apparent that this reasoning is somewhat contradictory, since an oxide and a glycol are at equivalent oxidation levels and at a different level from an ethylene peroxide. Murakami and Irie[3] attempted to show that the first step in the reaction is the formation of the oxido compound but were unable to prepare the latter from 2′-hydroxychalcone. They did succeed in showing that under mild conditions of treatment with alkaline hydrogen peroxide, 3-hydroxyflavanone was formed, and Reichel and Steudel[4] demonstrated that this compound is readily oxidized in alkaline solution to flavonol.

In the course of the present work numerous attempts were made to prepare the oxides of 2′-hydroxy-, 2′-acetoxy- and 2′-benzoyloxychalcone, but these attempts were unsuccessful. In the case of the acyl derivatives the extraordinarily facile removal of the acyl groups was the first reaction that occurred even under mildly alkaline conditions. Baker and Robinson[8] have also attempted without success to prepare 2′-hydroxychalcone oxide.

Reichel and Steudel[4] have offered an electronic interpretation of the reaction, using 2′-hydroxychalcone as the example, in which the successive steps were considered to be the addition of the hydroperoxide ion to the chalcone (ion), the rearrangement of the addition product to yield the

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(1) Algar and Flynn, *Proc. Roy. Irish Acad.*, **B42**, 1 (1934).

(2) Oyamada, *Bull. Chem. Soc. Japan*, **10**, 182 (1934).

(3) Murakami and Irie, *Proc. Imp. Acad. Tokyo*, **11**, 229 (1935).

(4) Reichel and Steudel, *Ann.*, **553**, 83 (194).

(5) Mehlquist and Geissman, *Ann. Missouri Bot. Gardens*, **36**, 39 (1947).

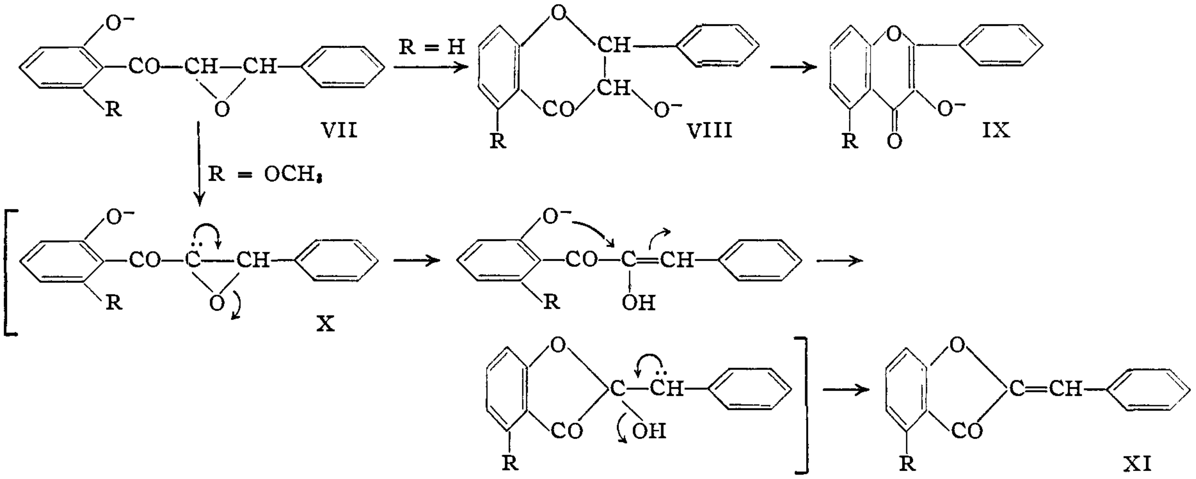
(6) Geissman and Mehlquist, *Genetics*, **32**, 410 (1947).

(7) Bargellini and Oliverio, *Ber.*, **75B**, 2083 (1942).

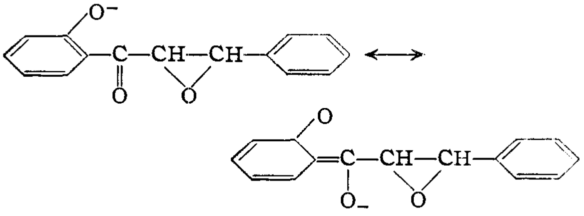
(8) Baker and Robinson, *J. Chem. Soc.*, 1798 (1932).

glycol (*o*-hydroxyphenyl-α,β-dihydroxyphenethyl ketone) and the displacement of the β-hydroxy group by the attack of the 2′-, anionic, oxygen atom to close the ring to 3-hydroxyflavanone.

A simpler and more satisfactory picture of the course of the reaction, and one which includes a consideration of the new observations described here, is that the first intermediate is indeed the oxide (VII). This reacts further to yield the flavanone (VIII) probably by a direct nucleophilic attack by the anionic oxygen atom upon the β-carbon atom, followed by oxidation to the flavonol (IX). When a substituent is present in the 6′-position of the chalcone, this course is not (exclusively) followed. It is probable that when R is a group which can offer substantial inhibition to the resonance in the system involving the anionic oxygen atom and the ortho carbonyl group, the result is an increase in the effective acidity of the α-hydrogen atom. Attack of a base upon this hydrogen atom gives rise to X, in which the oxide ring is opened by the attack of the electron pair on the adjacent (α-) carbon atom, leading through the changes formulated below to the benzalcoumaranone (XI)



This mechanism does not exclude the possibility that a mixture of the two possible products will be formed, since it does not suggest, and there is no reason to expect, that when R = OCH_3, the course VII → VIII → IX is excluded. The effect of the 6′-substituent is seen to be one of favoring the course leading to the benzalcoumaranone, since when resonance in VII of the system



is possible the series VII → X → XI would be less likely.

An alternative explanation for the effect of a 6′-substituent in directing ring closure to the benzalcoumaranone is that a direct steric effect favors the formation of a 5-membered rather than a 6-membered ring. Arnold and Rondestvedt[9] have shown that a 6-membered ring offers more steric hindrance to the position ortho to its point of juncture with another ring than does a 5-membered ring. In the present case, the more favorable bond angles in XI would allow less hindrance between R and the carbonyl group peri to it than in the case of IX, and might offer a plausible reason for a faster reaction in the ring closure to the benzalcoumaranone.

Results obtained in related studies indicate, however, that this explanation is not an adequate one. There appears to be a close analogy between the alkaline hydrogen peroxide oxidation of 2′-hydroxychalcones and the ring closure of 2′-hydroxy-α,β-dibromodihydrochalcones with alkali.[10-12] In the latter reaction, too, the number and position of the alkoxyl groups in the two aromatic rings influences the course of the reaction and determines whether a flavone or a benzalcoumaranone is formed. When the original chalcone is derived from 2,4,6-trihydroxyacetophenone, benzalcoumaranone formation is favored; but it is important to note that in this reaction the direction of ring closure is influenced also by the nature of the substituents in the benzal ring, and to some degree by the conditions of the reaction. Consequently, it appears that here simple steric effects are not the most important directing influences. It is with these observations in mind that the suggestion is made that benzalcoumaranone and flavonol formation are the result of two different kinds of attack upon a common intermediate, and that the course of the reaction is determined pri-

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[9] Arnold and Rondestvedt, This Journal, **68**, 2176 (1946).

[10] Kostanecki, *et al.*, *Ber.*, **31**, 696, 705, 1758, 2951 (1898); **32**, 315, 318, 1030, 2260 (1899).

[11] Warriar, Khanolkar, Hutchins and Wheeler, *Current Sci.*, **5**, 475 (1937); Nadkarni, Warriar and Wheeler, *J. Chem. Soc.*, 1798 (1937); Hutchins and Wheeler, *ibid.*, 91 (1939).

[12] Auwers and Anschütz, *Ber.*, **54**, 1543 (1931).

marily by the effects of substituents upon the reactivity of the α- and β-carbon atoms in the chalcone derivative.

Experimental[13]

Oxidation of 2′-Hydroxy-4′,6′,4-trimethoxychalcone.—To an ice-cold solution of 2.06 g. of 2′-hydroxy-4′,6′,4-trimethoxychalcone in a mixture of 14 ml. of 16% aqueous sodium hydroxide and 40 ml. of methanol was added 5.3 ml. of 15% hydrogen peroxide (analyzed before use). The mixture was kept at 5° overnight and the yellow solid which separated was collected, washed with methanol (A, see below) and recrystallized from acetone. The pure product formed canary yellow needles, m. p. 166.5–167.5°. It gave a deep crimson color with concentrated sulfuric acid, and no color with ferric chloride nor with magnesium–hydrochloric acid in alcoholic solution.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.23; H, 5.12; OCH_3, 29.81. Found: C, 68.99; H, 5.11; OCH_3, 29.42.

The compound showed no depression of melting point when mixed with a sample of 4′,4,6-trimethoxybenzalcoumaranone prepared by treatment of 2-hydroxy-4,6-dimethoxyphenyl-α,β-dibromo-β-anisylethyl ketone with alcoholic alkali.

From the methanol washings (A) of the crude benzalcoumaranone was obtained 0.29 of crude, crystalline material which upon repeated recrystallization from methanol yielded 0.05 g. of 5,7,4′-trimethoxyflavonol, m. p. 150–153° (reported,[14] 150–151°). This compound gave in concentrated sulfuric acid a yellow solution with a green fluorescence, and a pink solution when treated with magnesium and concentrated hydrochloric acid in alcoholic solution. Demethylation with hydriodic acid and acetylation of the product yielded kampferol tetraacetate,[14] m. p. 182–184°.

Oxidation of 2′-Hydroxy-4′,6′,3,4-tetramethoxychalcone.—To a cold solution of 0.70 g. of 2′-hydroxy-4′,6′,-3,4-tetramethoxychalcone in a mixture of 30 ml. of methanol and 6 ml. of 16% aqueous sodium hydroxide was added 3 ml. of 15% hydrogen peroxide. The yellow solid which separated upon standing overnight at 5° was collected. The crude material melted at about 165° and recrystallization effected only a partial purification. After a short treatment with sodium acetate–acetic anhydride, followed by decomposition of the excess acetic anhydride with ice water and recrystallization of the product from dilute alcohol, afforded tiny, canary-yellow needles of the benzalcoumaranone, m. p. 173–174°, reported[15] 175°). The compound gave the characteristic deep crimson-magenta color in concentrated sulfuric acid.

The alkaline filtrate was diluted with water, acidified and extracted with ether. After washing the ether solution with sodium bicarbonate solution the solvent was removed, yielding 0.12 g. of a crude solid. Crystallization from alcohol yielded 0.07 g. of 5,7,3′,4′-tetramethoxyflavonol, m. p. 193–194° (reported,[16] 197–198°). Its alcoholic solution gave a bluish-red coloration with magnesium and hydrochloric acid and a brownish-green color with ferric chloride.

Oxidation of 2′-Hydroxy-4′,6′-dimethoxychalcone.—A cold solution of 0.48 g. of 2′-hydroxy-4′,6′-dimethoxychalcone, 20 ml. of methanol, 5 ml. of 16% aqueous sodium hydroxide and 2.5 ml. of 15% hydrogen peroxide was kept at 5° overnight. The yellow precipitate weighed 0.30 g., and after recrystallization from alcohol melted at 152–153°. The melting point of 2-benzal-4,6-dimethoxycoumaranone-3 has been reported as 150–151°.[17] With concentrated sulfuric acid the compound gave a deep yellow-orange color.

From the alkaline filtrate was isolated only a small amount of 2-hydroxy-4,6-dimethoxybenzoic acid (neut. equiv. calcd., 198.1; neut. equiv. found, 197.4).

Oxidation of 2′-Hydroxychalcone. Method of Oyamada.—The oxidation of 1.0 g. of 2′-hydroxychalcone was carried out as described by Oyamada.[2] The yield of flavonol was 0.57 g.

Method of Murakami and Irie.—Two grams of 2′-hydroxychalcone, oxidized according to the procedure of Murakami and Irie,[3] yielded 1.0 g. of 3-hydroxyflavanone along with a small amount of flavonol. The flavanone melted at 177–180° (reported,[3] 174–177°).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.97; H, 5.04. Found: C, 74.53; H, 5.03.

Oxidation of 2′-Hydroxy-4′-methoxychalcone.—To a cold suspension of 1.0 g. of 2′-hydroxy-4′-methoxychalcone in 7 ml. of 15% aqueous sodium hydroxide was added 3 ml. of 13% hydrogen peroxide. After standing at 5° overnight, the mixture was filtered, yielding 0.84 g. of the sodium salt of 7-methoxyflavonol. The flavonol was obtained by treatment of the sodium salt with acid; it melted at 174.5–175.5° after recrystallization from alcohol. Kostanecki and Stoppani reported a m. p. of 180° for this compound.[18] It gave a yellow, blue-green fluorescing solution in concentrated sulfuric acid and an olive-green color with ferric chloride.

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.39; H, 4.50. Found: C, 71.60; H, 4.47.

It formed a colorless **acetate**, m. p. 176–177°.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.67; H, 4.51. Found: C, 69.25; H, 4.53.

2′-Hydroxy-6′-methoxy-3,4-methylenedioxychalcone

Two grams of 2-hydroxy-6-methoxyacetophenone was moistened with 2 ml. of methanol, and 5 ml. of 60% aqueous potassium hydroxide was added. To the pasty, greenish solid resulting was added 2.0 g. of piperonal, and the mixture shaken vigorously. The mixture grew warm, a deep red-brown color developed and a thick, oily phase separated. After fifteen minutes, during which time the mixture was shaken frequently, enough methanol was added to produce a clear solution (*ca.* 5 ml.) and the solution was poured into iced, dilute hydrochloric acid. The red-orange gum which separated crystallized when ether was added. After recrystallization from chloroform–petroleum ether the product (3.4 g.) formed brilliant orange needles, m. p. 137–138°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.43; H, 4.70. Found: C, 68.49; H, 5.15.

Oxidation of 2′-Hydroxy-6′-methoxy-3,4-methylenedioxychalcone: 4-Methoxy-3′,4′-methylenedioxybenzalcoumaranone.—To a suspension of 1.0 g. of the chalcone in 5 ml. of methanol was added 5 ml. of 20% aqueous sodium hydroxide, followed by 2.0 ml. of 30% hydrogen peroxide. The mixture was shaken; after about fifteen seconds it grew warm and suddenly set almost to a paste with the appearance of a yellow solid. After standing for an hour at 0° the semi-solid mixture was stirred with water and ether, and filtered. The solid weighed 0.50 g. It was not a salt; it gave a brilliant magenta color with concentrated sulfuric acid and no color with magnesium–alcoholic hydrochloric acid. It was soluble in pyridine, chloroform and hot, glacial acetic acid, and crystallized from the latter solvent as small, bright yellow needles, m. p. 222–223.5°, resolidifying upon cooling.

Anal. Calcd. for $C_{17}H_{12}O_5$: C, 68.89; H, 4.09. Found: C, 68.79; H, 4.48.

The alkaline filtrate contained no material having the properties of a flavonol.

Summary

1. The oxidation of 2′-hydroxychalcones with alkaline hydrogen peroxide yields flavonols when the chalcones are unsubstituted in the 6′-position.

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(13) Melting points are uncorrected.

(14) Kostanecki, Trampe and Tambor, *Ber.*, **37**, 2096 (1904).

(15) Perkin, *J. Chem. Soc.*, 951 (1920).

(16) Kostanecki, Lampe and Tambor, *Ber.*, **37**, 1404 (1904).

(17) Feuerstein and Kostanecki, *ibid.*, **31**, 1758 (1898).

(18) Kostanecki and Stopanni, *ibid.*, **37**, 1184 (1904).

When a methoxyl group is present in the 6′-position the predominant product is a benzalcoumaranone.

2. A mechanism is suggested to account for these results, and an analogy is drawn between this reaction and the ring closure of 2′-hydroxychalcone dibromides with alkali.

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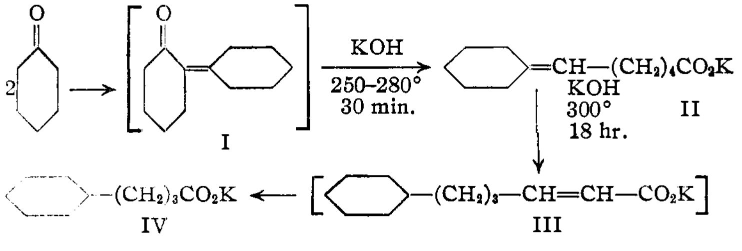
The Action of Alkali on Cyclohexanones

BY THEODORE L. CAIRNS, ROBERT M. JOYCE AND RICHARD S. SCHREIBER

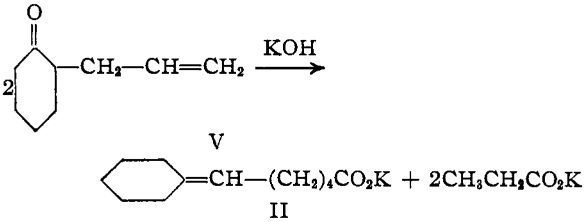
The cleavage of certain ketones by alkali with the formation of acids is well known for aromatic,[1] aralkyl,[2] and activated ketones such as β-keto acids. Relatively little work has been done with simple aliphatic ketones. This paper reports the results of an investigation of the nature of the products formed when cyclohexanone and one of its 2-substituted derivatives are treated with molten alkali. Other workers have shown that acids of unknown structure along with large amounts of neutral condensation products resulted when cyclohexanone was heated with potassium hydroxide at 180–190° for twenty-four hours.[3]

Three distinct types of reactions between cyclohexanone and potassium hydroxide have now been found, depending on the temperature used. The results can best be explained on the basis of the series of changes involving (1) formation of cyclohexylidenecyclohexanone (I), (2) cleavage of the ketone ring to a cyclohexylidenecaproic acid (II) and (3) migration of the double bond and degradation of the intermediate α,β-unsaturated acid to cyclohexanebutyric acid (IV). These transformations are shown in the accompanying equations and are discussed below.

At temperatures up to 220° the addition of cyclohexanone to molten potassium hydroxide resulted in the formation of a white crystalline solid which yielded only neutral products when treated with water. In the temperature range 250–280° a similar white precipitate formed momentarily but was very rapidly converted by an exothermic reaction to a yellow oil (II). When cooled, this yellow oil solidified and, after solution in water and acidification, a 12-carbon unsaturated acid was obtained. The position of the double bond in the acid from II was not established but no doubt exists concerning the carbon skeleton since this product yielded cyclohexanecaproic acid when hydrogenated. Prolonged treatment of II with molten alkali resulted eventually in a *saturated* 10-carbon acid identified as cyclohexanebutyric acid (IV). This transformation may involve the migration of the double bond of II into the α,β-position (III) followed by a retrograde aldol reaction to give cyclohexanebutyraldehyde which in turn would be converted by the alkali to IV. Support for the mechanism as pictured above is found in the fact that cyclohexylidenecyclohexanone yielded II when heated with molten potassium hydroxide.



In the case of 2-allylcyclohexanone (V) an unusual cleavage took place with the formation of the potassium salts of propionic acid and the acid II, derived from cyclohexanone, in accordance with the equation



The fact that propionic acid, and not acrylic acid, was isolated indicates that this change may involve the migration of the double bond in the allyl side chain into conjugation with the carbonyl group and hydrolytic removal of this residue with the formation first of propionaldehyde and then of propionic acid.

Experimental[4]

Action of Potassium Hydroxide on Cyclohexanone (280°—thirty minutes).—Two hundred twenty-five (225) grams of solid potassium hydroxide was fused in a heavy-walled glass tube in an atmosphere of nitrogen. To this was added, with vigorous agitation, 43.6 g. of cyclohexanone over a period of thirty minutes while the temperature was maintained between 260 and 280°. The mixture was cooled and dissolved in water to form a clear solution with

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(1) Bachmann, THIS JOURNAL, **57**, 737 (1935).

(2) Lock and Bock, *Ber.*, **70B**, 916 (1937).

(3) Wallach and Behnke, *Ann.*, **369**, 99 (1909).

(4) We are indebted to Dr. J. W. Stillman of these laboratories, under whose supervision the microanalyses reported here were carried out.