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Lethargic Reactions. I. The Preparation of Hindered Oximes

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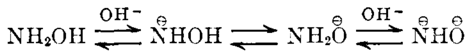
The combination of prolonged reaction times (one to six months at room temperature) and a strongly basic catalyst (potassium *tert*-amylate in *tert*-amyl alcohol) permitted the preparation of hindered oximes in nearly quantitative yields. The high yields are surprising in view of the fact that up to a few years ago the ketoximes were considered to be incapable of direct synthesis from the hindered ketones. Among the hindered ketoximes synthesized was 2,3,4,6-tetramethylacetophenone oxime, the preparation of which was claimed by Claus in 1887 and disputed by Meyer in 1896. Resolution of this dispute is attempted. Any reaction which necessitates prolonged reaction times and which cannot be forced by increasing the temperature is defined as a "lethargic reaction." The term is coined to draw attention to the potentialities of these conditions.

The oximation of hindered ketones, previously believed to be incapable of oximation,[2] was accomplished when it was discovered that a very slow reaction occurred at room temperature.[3] The reaction was so slow that several months' standing was necessary to bring about detectable oximation. At best the yields were low, and it was obvious that a more powerul reagent was needed to increase the yields to a range satisfactory for synthetic use.

The anion of hydroxylamine seemed to be the reagent of choice which possibly could react through the dianion if the medium were alkaline enough.



$$\mathrm{NH_2OH} \underset{}{\overset{\mathrm{OH^-}}{\rightleftarrows}} \overset{\ominus}{\mathrm{N}}\mathrm{HOH} \rightleftarrows \mathrm{NH_2}\overset{\ominus}{\mathrm{O}} \overset{\mathrm{OH^-}}{\rightleftarrows} \overset{\ominus}{\mathrm{N}}\mathrm{H}\overset{\ominus}{\mathrm{O}}$$

I II III IV

Combining the long reaction time with a strongly basic medium (potassium *tert*-amylate in *tert*-amyl alcohol), it was found that the oximation of hindered ketones could be brought about in almost quantitative yields as shown in Table I.

Table I

Acetophenone (or ketone)	Time, days	Crude yield of oxime, %
2,4,6-Trimethyl-	32	98
	10	53
2,3,4,6-Tetramethyl-	180	90
	10	30
Pentamethyl-	420	81
2,6-Dimethyl-4-*tert*-butyl-	180	95
Benzoylmesitylene	450	16

From the results of Table I, there can be no doubt that the combination of prolonged standing at room temperature and of the use of a strongly basic medium has succeeded in elevating the yields of hindered ketone oximes to satisfactory values. Two other methods of making hindered oximes are available: oximation at very high pressures[4] and oximation of the corresponding imino ketone,[5] but the lethargic method is recommended because of its simplicity and general applicability.

Attempts to oximate the hindered ketones in the strongly basic medium at reflux temperatures of *tert*-amyl alcohol gave appreciable amounts of ketoxime (*ca.* 50%), but the yields could not be raised beyond this figure. The relatively low yields were attributed to the incursion of a competing side reaction at the elevated temperatures, namely the decomposition of hydroxylamine to ammonia, water, and other products.[6]

The attacking species was surmised to be II (and III)[7] rather than IV (see Experimental). IV possibly could be made in a more basic medium, but no attempt was made at this time to prepare IV.

Conditions were now at hand to settle a bitter controversy that began in 1887. Claus[8] claimed that he had made the oxime of 2,3,4,6-tetramethylacetophenone and used this fact and others to criticize the steric hindrance theory of Meyer. In the words of Claus the more precisely and carefully one attempted to abide by Meyer's rule, the more the rule had to be explained and expanded. In a crushing paper Meyer[9] countered with the statement that he had attempted to duplicate Claus' work on the oxime of the above compound, that one of his colleagues had attempted to do so and that neither could repeat a single result. In Meyer's words, the results were "ganz unverstandlich." Meyer's statement seemed to have settled the matter and cast a stigma on Claus' work, for we read later in the obituary of Claus[10] that experimental errors are to be found in the work of Claus but "who among us does not err."

The question remains some sixty years later: Did Claus make the oxime of 2,3,4,6-tetramethylacetophenone or did he not? Obviously, the new conditions permitted an easy synthesis of the oxime, and compari-

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[2] R. G. Kadesch, *J. Am. Chem. Soc.*, **66**, 1207 (1944).

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son of the properties of the true oxime with those of Claus' is shown. 2,3,4,6-Tetramethylacetophenone oxime: Claus: m.p. 148°, leaflets; true oxime: m.p. 136–137.5°, fine needles.

Unfortunately Claus gives very little data: no conditions, no analysis, no melting point range. Anyone of these data would have helped in making the final judgment, but we must make it on the basis of the melting point alone. And the melting points do not check well. Furthermore, if the oxime is isolated in small yield from a large amount of unchanged ketone, it has been our experience[3] that the oxime melts low and over a wide range. Claus' melting point is on the high side and yet not high enough to be the Beckmann rearrangement product (m.p. 234°). Therefore, we are forced to conclude that Claus did not have the oxime. We do maintain, however, that the potentiality for making the oxime was in the hands of Claus and that any aspersions cast on his work should not have been based on his oximation experiments.

Liberty has been taken in this paper to coin a phrase which describes this type of reaction. The "lethargic reaction" is defined as one which proceeds slowly but cannot be forced because of the incursion of side-reactions at elevated temperatures. If it were confined to oximation, the coining of the phrase would not be justified. But it is apparent from the work in this laboratory that other lethargic reactions can be found. Thus the name should draw attention to the capabilities of this technique in application to other reaction studies.

Experimental

Potassium *tert*-Amylate.—Oxide free potassium[11] (98 g., 2.5 moles) was dissolved in 1250 ml. of dry *tert*-amyl alcohol; calcd. concentration, 0.19 mole/100 ml.; found by titration with acid, 0.16 mole/100 ml. The solution was amber colored and slightly opaque from a small amount of suspended material. Aliquots were removed by means of a pipet.

2,4,6-Trimethylacetophenone Oxime.—To 125 ml. (0.2 mole) of potassium *tert*-amylate solution were added 5.5 g. (0.08 mole) of hydroxylamine hydrochloride and 10 g. (0.062 mole) of 2,4,6-trimethylacetophenone in a 250-ml. erlenmeyer flask. The flask was stoppered tightly and allowed to stand at room temperature for 32 days. No change other than the precipitation of sodium chloride was noted. The *tert*-amyl alcohol was then removed by means of a rotating evaporator. Ammonium chloride (5.3 g., 0.1 mole) in 100 ml. of water was added to the thick residue and the mixture shaken well. If the oxime came out rather oily, more water was added to dissolve the traces of *tert*-amyl alcohol. The precipitated oxime was filtered and washed thoroughly with water; 10.8 g., m.p. 98–101°, 98% yield. Sublimation at 0.03 mm. gave 9.5 g. (86%) of colorless crystals, m.p. 101.5–102.5°, reported[3] 102.5–104°. All of the hindered oximes in this paper are stable indefinitely on storage, a characteristic not true with regard to most unhindered oximes.

Variations in Oximation Studies.—Similar duplicate runs were made except that the time of oximation was reduced to 10 days. The crude yields were about 53%. Another run for 10 hr. was made at the reflux temperature of *tert*-amyl alcohol. A 57% yield of crude oxime, m.p. 96.5–99.5°, was obtained. Attempts to raise the yield of the oxime using reflux failed.

Is the Dianion ($^{\ominus}NHO^{\ominus}$) the Active Reagent or the Monoanion ($^{\ominus}NHOH$ or $NH_2O^{\ominus}$)?—Two runs were made at the same time. One run had the reagent ratios: ketone 0.02 mole, hydroxylamine hydrochloride 0.03, and potassium *tert*-amylate 0.06. The second run had the ratios: ketone 0.02, hydroxylamine hydrochloride 0.03, and potassium *tert*-amylate 0.124. After 43 days, each run was worked up in the usual manner. The crude yields (88%) of acetomesitylene oxime were identical. It is to be noted that the first run had no excess base since 0.03 mole is needed to neutralize the hydrogen chloride combined with the hydroxylamine; the second run had sufficient base to convert the anion at least partially to the dianion.

2,3,4,6-Tetramethylacetophenone Oxime.—We are indebted to Hutcheson[12] for the preparation and characterization of 2,3,4,6-tetramethylacetophenone (acetoisodurene). The ketone ($n^{22}D$ 1.5251, 0.07 mole) was oximated as described for acetomesitylene except that the reaction mixture was allowed to stand for 6 months. Following the usual isolation procedure, a powder was obtained in 90% yield based on oxime formation, m.p. 132–138°. The powder was recrystallized from aqueous isopropyl alcohol to give small needles, 75% based on starting material, m.p. 136–137.5° (previous sintering).

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.71; H, 8.53; N, 7.31.

The oxime was rearranged in quantitative yield to N-acetylisoduridine by refluxing with aqueous hydrochloric acid (von Auwer's method[13] for hindered oximes), m.p. 223–224°, reported[14] m.p. 217.5°.

Anal. Calcd. for $C_{12}H_{17}NO$: N, 7.32. Found: N, 7.26.

An oximation carried out for 10 days instead of 6 months gave a 30% yield of methylisoduryl ketoxime and a 60% yield of recovered ketone.

Oximation for 4 months using sodium ethoxide in ethanol rather than potassium *tert*-amylate in *tert*-amyl alcohol gave a 5% yield (based on original ketone) of an unknown substance, m.p. 108.5–109°.

Anal. (for the suspected oxime of the dypnone of acetoisodurene). Calcd. for $C_{24}H_{29}NO$: C, 82.9; H, 8.4; N, 4.03. Found: C, 81.7; H, 9.13; N, 4.18.

Since the analyses were poor and the characterization scanty, we do not claim to know the structure of the substance, m.p. 109°.

Pentamethylacetophenone Oxime.—The corresponding ketone (m.p. 84–85°, 0.03 mole) was converted to the oxime in 96% crude yield, m.p. 175–179°. The time of oximation was 14 months, probably a much longer time than necessary. The crude oxime was recrystallized from methylcyclohexane and resublimed to give a colorless solid in 81% over-all yield, m.p. 182–183°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33. Found: C, 76.05; H, 9.32.

The oxime was rearranged by von Auwer's method[13] to pentamethylacetanilide, m.p. 216.5–217°, reported[15] m.p. 213°.

2,6-Dimethyl-4-*tert*-butylacetophenone Oxime.—In 6 months the ketone (0.15 mole) was converted to the oxime in 95% crude yield which after recrystallization from methylcylcohexane with Norit gave colorless leaflets in 72% yield, m.p. 158–160°, reported[16] m.p. 157.5–161.5°.

Benzoylmesitylene Oxime.—In 15 months the ketone (0.044 mole) was converted to the oxime in 16% over-all yield, plates from methylcyclohexane, m.p. 147.5–148.5°, reported[5,16] m.p. 142–144°.

Failures.—Anthraquinone in the *tert*-amylate solution containing hydroxylamine gave a dark green precipitate. After 2 months' standing, the mixture was treated in the usual manner and yielded 48% anthraquinone, yellow needles from amyl acetate, m.p. 286.5–287.5°. The poor recovery of starting material together with no oxime formation and the appearance of the intermediate suggested the formation of an anthraquinhydrone system.

2,3,5,6-Tetrachloroacetophenone was cleaved under the oximation conditions to 1,2,4,5-tetrachlorobenzene, m.p. 141–142°, in 70% crude yield. This competing reaction was not unexpected.[17]

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