

Novel Aspects in the Preparation of Phorone

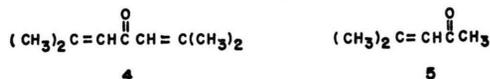
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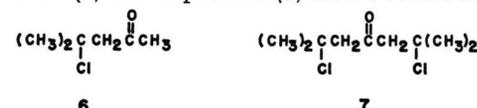
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Phorone, Mesityl Oxide, Triacetoneamine, Nitroxyls

The condensation of acetone using anhydrous hydrogen chloride results after three weeks at room temperature, in a 15% yield of phorone (4) and a 75% yield of mesityl oxide (5). In the presence of one weight percent of the Lewis acid, aluminium chloride, the yield of 4 is increased to 39%. An increase in the amount of the Lewis acid, aluminium chloride, to ten weight percent results in a 22% yield of phorone (4) and a 68% yield of mesityl oxide (5). In the presence of one hundred weight percent of aluminium chloride,



in the absence of hydrogen chloride, the condensation produces a 62% yield of mesityl oxide (5) and no phorone (4). In the course of this investigation, two intermediates, 6 and 7

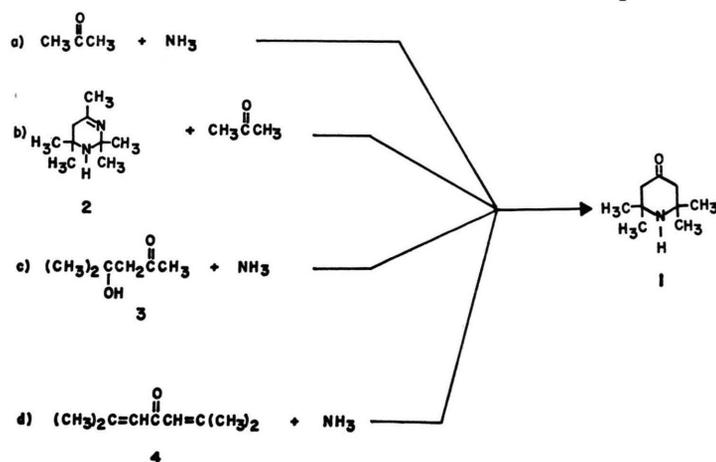


were isolated and characterized for the first time. These intermediates are the actual products formed in the condensation of acetone with hydrogen chloride, and not the "free" phorone (4) and mesityl oxide (5). The conversion of 6 and 7 to 5 and 4, respectively, occurs during the isolation stage using a saturated solution of ethanolic potassium hydroxide.

Since the discovery of the long-lived nitroxyl radical [1], 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl, and its derivatives, considerably interest has been shown in the application of these nitroxyls in various areas of biological [2, 3] and polymer [3]

science. The most commonly used nitroxyls are prepared by the catalytic oxidation of triacetoneamine (1) or its derivatives with 30% aqueous hydrogen peroxide in the presence of sodium tungstate [3, 4]. Triacetoneamine (1), in turn, can be prepared by one of four methods, (a) from acetone [5-21], (b) from acetoin (2) [13, 22-27], (c) from diacetone alcohol (3) [13], and (d) from phorone (4) [28-30].

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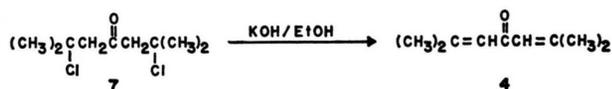


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reaction mixture with a saturated solution of ethanolic potassium hydroxide causes the disappearance of both components X and Y, and the formation of a large amount of mesityl oxide and a lesser amount of phorone, as determined by gas chromatography (see Fig. 2). Hence it is proposed that compound X



is the precursor of mesityl oxide (5), *i.e.*, its hydrochloride 6, while compound Y is the precursor of phorone (4), *i.e.*, its dihydrochloride 7. The identity



of both compounds 6 and 7 was verified by preparing 6 and 7 from 5 and 4, respectively. Thus, saturation of mesityl oxide (5) and phorone (4) with gaseous hydrogen chloride, followed by a workup with 10% aqueous sodium hydroxide gave the desired compounds, 6 and 7, respectively. Elemental analysis of the yellow products, which rapidly turned to a deep violet in color, was in agreement with the values calculated for chlorides 6 and 7. Analysis of the infrared spectra of the products indicated the disappearance of the carbon-carbon double bond absorptions present in phorone (4) (at $\nu = 1630\text{ cm}^{-1}$) and in mesityl oxide (5) (at $\nu = 1610\text{ cm}^{-1}$), and a shift in the carbonyl absorption of phorone (4) from 1670 cm^{-1} to the 1730 cm^{-1} of 7, and of mesityl oxide (5) from 1690 cm^{-1} to the 1740 cm^{-1} of 6, indicating the loss of conjugation with the double bond in compounds 6 and 7, as compared to 5 and 4, respectively. In addition, the appearance of the carbon-chlorine bond absorption at $550\text{--}560\text{ cm}^{-1}$ was observed. Further, the structure of the products was verified by comparison of the NMR spectra of the chlorides 6 and 7 with those of mesityl oxide (5) and phorone (4), respectively. The spectrum of mesityl oxide (5) was characterized by the vinylic absorption at $\delta = 6.02\text{ ppm}$ (1 H), the singlet of the acyl methyl and methyl *cis* to the acyl group at $\delta = 2.1\text{ ppm}$ (6 H), and the singlet of the methyl *trans* to the acyl group at $\delta = 1.9\text{ ppm}$ (3 H). The spectrum of the corresponding chloride 6 was considerably different, *i.e.*, characterized by the absence of the vinylic absorption, the presence of the singlet acyl methyl absorption at $\delta = 2.15\text{ ppm}$

(3 H), the singlet geminal dimethyl absorption at $\delta = 1.7\text{ ppm}$ (6 H), and the singlet methylene absorption at $\delta = 2.9\text{ ppm}$ (2 H). Similar spectral differences were noted in the case of phorone (4) and the dichloride 7. The spectrum of phorone (4) was characterized by the vinylic absorption at $\delta = 5.95\text{ ppm}$ (2 H) and the pair of singlets of the environmentally different geminal dimethyl groups at $\delta = 1.82\text{ ppm}$ (6 H) and $\delta = 2.05\text{ ppm}$ (6 H). The spectrum of the dichloride 7 was characterized by the absence of the vinylic absorption, the presence of the singlet methylene absorption at $\delta = 2.95\text{ ppm}$ (4 H), and the singlet absorption of the now equivalent geminal dimethyl groups at $\delta = 1.7\text{ ppm}$ (12 H). If the halogen atoms in the chlorides 6 and 7 were *o* to the carbonyl, the NMR spectra would be considerably different. Gas chromatographic analysis of 6 and 7 indicated that the retention times of these compounds are identical with those of the unknown components X and Y, respectively. Treatment of compounds 6 and 7 with a saturated solution of ethanolic potassium hydroxide converted them to mesityl oxide (5) and phorone (4), respectively, as was shown in the preceding schemes. It is postulated that mesityl oxide (5) and phorone (4) are simultaneously formed from acetone in the presence of hydrogen chloride, and not as a result of the condensation of acetone with mesityl oxide, since an attempted condensation of a 1:1 (mole:mole) mixture of mesityl oxide and acetone, saturated with gaseous hydrogen chloride, did not result in any detectable amount of phorone, even after three weeks at room temperature (see experimental section). As can be seen from Table I, the increase in the amount of phorone (4) present corresponds to a decrease in the amount of mesityl oxide (5), indicating that over the extended period of time, a reaction is occurring between 4 and 5, whereby the longer reaction times favor the formation of 4. After three weeks at room temperature the condensation of acetone in the presence of gaseous hydrogen chloride gave a 15% yield of phorone (4) and a 76% yield of mesityl oxide (5).

The yield of phorone (4) can be improved by the addition of small amounts of the Lewis acid, anhydrous aluminium chloride. Thus introduction of one weight percent of aluminium chloride, increased the yield of phorone (4) to 39%, while the yield of mesityl oxide (5) decreased to 52% (Table I).

Table I. Condensation of acetone in the presence of gaseous hydrogen chloride. Formation of phorone (4) and mesityl oxide (5) as a function of the reaction time.

Time elapsed [d]	Reaction in absence of catalyst			Reaction with 1% AlCl ₃ ^a			Reaction with 10% AlCl ₃ ^a		
	Acetone ^b [%]	5 ^b [%]	4 ^b [%]	Acetone ^b [%]	5 ^b [%]	4 ^b [%]	Acetone ^b [%]	5 ^b [%]	4 ^b [%]
4	11	80	9	17	75	8	14	65	11
7	11	78	11	13	75	12	13	73	11
9	10	76	14	6	71	23	12	76	12
12	9	79	12	7	70	22	17	70	14
16	9	76	15	7	63	29	15	70	15
19	10	74	16	6	61	33	13	70	17
21	10	73(76) ^c	17(15) ^c	7	55(52) ^c	38(39) ^c	10	70(68) ^c	20(22) ^c

^a Weight percent, ^b determined by gas chromatography (accuracy of method is $\pm 5\%$), ^c distillation.

However, three weeks were still necessary for obtaining a maximum yield of 4. In the presence of ten weight percent of aluminium chloride, the amount of phorone (4) decreased to 22%, whereas the yield of mesityl oxide (5) increased to 68%. In spite of a decrease in the yield of 4, it is nevertheless higher in this case than that obtained from the reaction in the absence of aluminium chloride.

The condensation of acetone in the presence of an equal weight of aluminium chloride resulted in a very viscous reaction mixture, thus making the introduction of gaseous hydrogen chloride problematic. This reaction was complete after only twenty hours at room temperature to give a 62% yield of mesityl oxide (5) and no phorone (4).

In conclusion, it was shown that a simple modification of the century-old procedure [31] for the condensation of acetone with anhydrous hydrogen chloride results in an improvement in the yield of phorone (4), thus making it, because of simplicity, a competitive process with other methods as far as yield and cost are concerned. Whereas additions of small amounts, *e.g.*, one weight percent, of the Lewis acid aluminium chloride, favor the formation of phorone (4), larger amounts, *e.g.* \geq ten weight percent, or no aluminium chloride favor the formation of mesityl oxide (5). The greater the amount of aluminium chloride used, the greater is the amount of 5 relative to 4 that is formed. Finally, some insight was gained into the reaction path of the condensation of acetone with gaseous hydrogen chloride by detecting first, and then independently synthesizing, the precursor chlorides 6 and 7 which are the actual products of the condensation.

The desired "free" phorone (4) and mesityl oxide (5) are, in fact, only formed during the dehydrohalogenation reaction of intermediate chlorides 6

and 7, respectively, using ethanolic potassium hydroxide.

Experimental

Materials: All reagents were of the best quality commercially available.

Analytical procedures: All melting points and boiling points are uncorrected. Microanalyses were performed on a F&M Scientific Corporation Carbon, Hydrogen, Nitrogen Analyzer, Model 185. A Varian 2000 dual column, temperature programmable gas chromatograph with a thermal conductivity detector was used. The following overall conditions were maintained: injector temperature 220 °C; detector temperature, 250 °C; bridge current, 150 ma; sample size 5 μ l with the appropriate attenuations. The column used was 20% Carbowax 20 M on 60/80 mesh acid, washed Chromasorb W, 6 ft by 1/4 in. Analyses were performed isothermally at 160 °C, with a flow rate of 40 ml of He/min. All identifications of products were made by a comparison of retention times and peak enhancement ("spiking") with authentic samples. Peak areas were measured by the height times width at half-height method. Infrared analyses were performed on a Perkin Elmer, Model 337 spectrometer. All NMR spectra were obtained on a Varian T-60 spectrometer, using TMS as the standard.

Condensation of acetone by anhydrous hydrogen chloride

General procedure: Acetone (300.0 g, 5.4 mol) was cooled by an ice/salt bath and saturated with anhydrous hydrogen chloride gas. During the saturation, the solution turned to a deep orange in color. Following completed introduction, the reaction mixture was left to stand for three weeks at room temperature. After 20 h of standing, the solution became a deep violet in color. To the reaction mixture was added diethyl ether (300 ml), and the mixture was washed with aqueous 10% NaOH, whereby the ether layer turned from violet to yellow in color. Alkaline washings of the ether layer were continued until the aqueous layer

became basic to litmus. The ethereal solution was then washed with distilled water (5 × 50 ml), and dried over anhydrous MgSO₄. The solvent was removed on a rotating evaporator at 10–15 °C (10–15 torr). The remaining yellow oil rapidly changed at room temperature to a deep violet in color. Gas chromatographic analysis indicated that a small amount of mesityl oxide (5) was present together with larger amounts of mesityl oxide hydrochloride (7) and phorone dihydrochloride (6). Free phorone (4) was not detected.

Diethyl ether (300 ml) was added to the violet colored concentrate, whereby the coloration changed to yellow. The ethereal solution was treated with a saturated solution of KOH in absolute ethanol until no more NaCl precipitated. The ethereal solution was washed with distilled water (10 × 50 ml), and dried over anhydrous MgSO₄. The drying agent was removed by filtration and the filtrate concentrated on a rotating evaporator at 5–10 °C (10–15 torr) to a yellow liquid. Distillation afforded mesityl oxide (5; 201 g, 76%; b.p. 120–130 °C, lit. [36] b.p. 130 °C; n_D^{25} 1.4425, lit. [36] n_D^{25} 1.4419) and phorone (4; 37 g, 15%; b.p. 190–196 °C, lit. [36] b.p. 198–199 °C; n_D^{25} 1.4986, lit. [36] n_D^{25} 1.4978).

The purity of both 4 and 5, as determined by gas chromatography, was 98% ± 2%.

Condensation of acetone by anhydrous hydrogen chloride and one weight percent aluminium chloride

A solution of acetone (100.0 g, 1.7 mol) and aluminium chloride (1.00 g, 0.008 mol) was cooled by an ice/salt bath and saturated with gaseous hydrogen chloride. During the introduction of hydrogen chloride, the color of the solution turned to a deep orange. Following the saturation, the reaction mixture was left to stand for 3 weeks at room temperature. After standing 20 h the solution became a deep violet in color. Following the workup as described in the General Procedure, there was obtained mesityl oxide (5; 43 g, 52%; b.p. 125 to 130 °C, lit. [36] b.p. 130 °C; n_D^{25} 1.4428, lit. [36] n_D^{25} 1.4419) and phorone (4; 31 g, 39%; b.p. 190–197 °C, lit. [36] b.p. 198–199 °C; n_D^{25} 1.4980, lit. [36] n_D^{25} 1.4978).

The purity of both 4 and 5, as determined by gas chromatography, was 99% ± 1%.

Condensation of acetone by anhydrous hydrogen chloride and ten weight aluminium chloride

A solution of acetone (100.0 g, 1.7 g) and aluminium chloride (10.0 g, 0.08 mol) was cooled by an ice/salt bath and saturated with gaseous hydrogen chloride. During the introduction, the color of the solution turned to a deep orange. Following the saturation, the reaction mixture was left to stand for 3 weeks at room temperature. After 20 h of standing, the solution became a deep violet in color. Following the workup, there was obtained mesityl oxide (5; 57 g, 68%; b.p. 120–130 °C, lit. [36] b.p. 130 °C; n_D^{25} 1.4426, lit. [36] n_D^{25} (1.4419) and

phorone (4; 17 g, 22%; b.p. 190–198 °C, lit. [36] b.p. 198–199 °C; n_D^{25} 1.4983, lit. [36] n_D^{25} 1.4978).

The purity of both 4 and 5 as determined by gas chromatography, was 98% ± 2%.

Reaction of mesityl oxide (5) with anhydrous hydrogen chloride. Preparation of chloride 6

Mesityl oxide (5; 20.0 g, 0.20 mol) was cooled by an ice/salt bath and saturated with gaseous hydrogen chloride. Following saturation, the deep violet colored solution was left to stand at room temperature for 1 h. To the strongly acid solution was then added diethyl ether (30 ml). The ethereal solution was washed with a 10% aqueous NaOH solution until all acid was removed, then with distilled water (5 × 10 ml) and dried over anhydrous MgSO₄. The alkali washes caused the ethereal solution to change in color from a deep violet to a bright yellow. The drying agent was removed by filtration. The filtrate was concentrated on a rotating evaporator at 5–10 °C (15 torr) to a yellow oil (6; 17 g, 65%) which, on standing for a few minutes at room temperature, changed in color to a deep violet.

IR: $\nu(\text{C-Cl})$ 560 cm⁻¹,
 $\nu(\text{C=O})$ 1730 cm⁻¹,
 No C=C absorption ($\nu = 1605$ cm⁻¹) was present.

¹H NMR (CCl₄): $\delta = 1.7$ (S, 6), 2.15 (S, 3), 2.9 (S, 2).

C₆H₁₁ClO

Calcd	C 53.54	H 8.24,
Found	C 53.39	H 8.29.

The retention time of the compound 6 was identical with that of component X formed during the condensation of acetone using anhydrous hydrogen chloride (see Fig. 1).

Treatment of an ethereal solution of mesityl oxide hydrochloride (6) with a saturated solution of ethanolic KOH until no more sodium chloride precipitated, followed by washes with distilled water (10 × 20 ml), drying over anhydrous MgSO₄, and removal of the solvent on a rotating evaporator at 5–10 °C (10–15 torr) afforded mesityl oxide (5; 12.8 g, 64% based on starting 5, n_D^{25} 1.4423; lit. [36] n_D^{25} 1.4419).

The purity of 5, as determined by gas chromatography, was 100%. No trace of other components could be detected.

Reaction of phorone (4) with anhydrous hydrogen chloride. Preparation of chloride 7

A solution of phorone (4; 4.0 g, 0.029 mol) in anhydrous ether (30 ml) was cooled by an ice/salt bath and saturated with gaseous hydrogen chloride. Following the saturation, the deep violet colored solution was left to stand at room temperature for 30 min. The strongly acidic solution was washed with 10% aqueous NaOH until all acid was removed, then with distilled water (5 × 15 ml), and dried

over anhydrous $MgSO_4$. The alkali washes caused the ethereal solution to change color from a deep violet to a bright yellow. The drying agent was removed by filtration. The filtrate was concentrated on a rotating evaporator at 20–25 °C (15 torr) to a yellow oil (7; 4.4 g, 72%) which, on standing for a few minutes at ambient temperature, changed in color to a deep violet in color.

IR: $\nu(C-Cl) = 550\text{ cm}^{-1}$,
 $\nu(C=O) = 1720\text{ cm}^{-1}$,
 No C=C absorption ($\nu = 1630\text{ cm}^{-1}$) was present.

1H NMR (CCl_4): $\delta = 1.7$ (S, 12), 2.95 (S, 4).

$C_9H_{16}Cl_2O$

Calcd C 51.20 H 7.64,
 Found C 51.23 H 7.69.

The retention time of the compound 7 was identical with that of component Y formed during the condensation of acetone using anhydrous hydrogen chloride (see Fig. 1).

Treatment of an ethereal solution of phorone hydrochloride (7) with a saturated solution of ethanolic KOH until no more sodium chloride precipitated, followed by washes with distilled water (10 × 15 ml), drying over anhydrous $MgSO_4$, and removal of the solvent on a rotating evaporator at 20–25 °C (10–15 torr) afforded phorone (4; 2.8 g, 70% based on starting 4, n_D^{25} 1.4982; lit. [36] n_D^{25} 1.4978). The purity of 4, as determined by gas chromatography, was 100%. No trace of other components could be detected.

Reaction of mesityl oxide (5) with acetone in the presence of anhydrous hydrogen chloride

A solution of mesityl oxide (5; 49.0 g, 0.50 mol) and acetone (29.0 g, 0.50 mol), cooled by an ice/salt

bath, was saturated with gaseous HCl. During the introduction of the gas, the solution became deep violet in color. Following the introduction of HCl, the reaction mixture was left to stand at room temperature for 3 weeks. To this reaction mixture was then added diethyl ether (100 ml), and the ethereal solution was worked up, with both alkali washes, as described in the preceding experiments. There was obtained mesityl oxide (5; 63.0 g, 64% based on acetone and starting 5, n_D^{25} 1.4421; lit. [36] n_D^{25} 1.4419). The purity of 5, as determined by gas chromatography, was 100%. No trace of phorone (4) or other condensation products could be detected.

Reaction of acetone with aluminium chloride.

Preparation of mesityl oxide (5)

To acetone (100.0 g, 1.7 mol), cooled by an ice/salt bath, was gradually added, over a period of 2 h with stirring, aluminium chloride (100.0 g, 0.75 mol). During this addition, the reaction mixture darkened and thickened considerably. The reaction mixture was left to stand at ambient temperature for 16 h. Diethyl ether (200 ml) was then added, and an aqueous 10% NaOH solution was cautiously introduced at 20–25 °C until the aqueous layer became basic to litmus paper. The aqueous layer was drawn off, and the ethereal layer was worked up with both alkali washes, as described in the preceding experiments. There was obtained mesityl oxide (5; 75 g, 85%; n_D^{25} 1.4416, lit. [36] n_D^{25} 1.4419). The purity of 5, as determined by gas chromatography, was 99%. No trace of phorone (4) or other products could be detected.

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