THE ALKALI-CATALYSED SELF-CONDENSATION OF ISOPHORONE

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(Received 21 October 1965)

Abstract—The self-condensation of isophorone in the presence of aqueous sodium hydroxide under reflux conditions yields the hydroxyketone (Ib) and a yellow compound $(C_{27}H_{38}O)$ which may result from the condensation of three moles of isophorone less two moles of water. A chemical proof is given for the different hydrogenation products of ketol Ib.

INTRODUCTION

THE base catalysed dimerization of 3-methyl substituted cyclohexenones is brought about by bases such as alkali hydroxides²⁻⁴ or sodium amide.^{5.6} Knoevenagel² discovered the first type of self-condensation and has described the formation of crystalline dimers from 3,5-dimethyl-2-cyclohexen-1-one and from 3-methyl-5-phenyl-2-cyclohexen-1-one upon their treatment with aqueous potassium hydroxide. The structures of the dimers of these cyclohexenones and the one derived from the alkali hydroxide self-condensation of piperitone^{3.4} have been shown to be tricyclic unsaturated hydroxyketones.^{7.8} Structure Ia represents the dimer derived from 3,5-dimethyl-2-cyclohexen-1-one.⁷

The second type of self-condensation was discovered by Ruzicka⁵ who treated 3-methyl-2-cyclohexen-1-one and other cyclohexenones with excess sodium amide in refluxing ether obtaining a mixture of two oily isomers $C_{14}H_{20}O_2$. Ruzicka was not able to separate these two dimers but he suggested an unsaturated hydroxyketone structure for one isomer and for the other a saturated diketone structure. The same



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- ² E. Knoevenagel, E. Reinecke, Ber. Dtsch. Chem. Ges. 32, 418 (1899).
- ³ W. Treibs, Ber. Dtsch. Chem. Ges. 63, 2738 (1930); J. Prakt. Chem. 138, 299 (1933).
- ⁴ L. H. Briggs, C. W. Harland, C. Ralph and H. A. Simmonds, J. Chem. Soc. 3788 (1953).
- ⁶ L. Ruzicka, Helv. Chim. Acta 3, 781 (1920).
- G. Buechi, J. H. Hansen, D. Knutson and E. Koller, J. Amer. Chem. Soc. 80, 5517 (1958).
- ⁷ W. A. Ayer, W. I. Taylor, J. Chem. Soc. 2227 (1955).
- * W. I. Taylor, Chem. & Ind. 252 (1954).

dimerization process was shown to be true of 3,5-dimethyl-2-cyclohexen-1-one and isophorone.

Buechi,⁶ with an elegant investigation, showed the diketone dimer of 3-methyl-2cyclohexen-1-one obtained with sodium amide in boiling ether, to be represented by structure IIa. Buechi proposed analogous structures for the dimers derived from 3,5-dimethyl-2-cyclohexen-1-one and isophorone (IIb). The patent literature^{9,10} describes the dimerization of isophorone brought about by alkali hydroxides leading to an unsaturated hydroxyketone for which structure III is proposed.

RESULTS AND DISCUSSION

The purpose of the present work was the preparation and determination of the structure of the dimer obtained from the self-condensation of isophorone brought about by aqueous alkali hydroxides. Treatment of isophorone with 60% aqueous sodium hydroxide at 150° resulted in a brown reaction mixture, from which a dimer was obtained in 91.5% yield and 65% conversion. From the distillation residue, a yellow compound was separated in 2–3% yield; its analysis and mol. wt. determinations suggested a compound that may have resulted from the condensation of three moles of isophorone less two moles of water, $C_{27}H_{38}O$. The conversions given above represent the equilibrium values for this condensation of isophorone at 150°, 32% yield of isophorone, 61.5% of recovered dimer and 2% yield of the yellow "Trimer" were obtained.

This solid dimer $C_{18}H_{28}O_2$ is characterized by an IR spectrum, which exhibits a hydroxyl band at 3480 cm⁻¹, a single carbonyl band at 1655 cm⁻¹, and an olefinic unsaturation band at 1635 cm⁻¹, see Table 1.

TABLE 1			
	OH cm ⁻¹	CO cm ⁻¹	CC cm ⁻¹
«-Dipiperitone ⁷	3450*	1638*	1615*
3,5-Dimethykcyclohexen-1-one dimer (m.p. 117-8°) ⁷	3472(3450*)	1650(1645*)	1625(1626*)
Isophorone dimer	3480	1650	1635
Isophorone	_	1675	1645
Isophorone "trimer"	<u> </u>	1650	1640

These spectra were taken in a 0.02M solution in CCl₄ or * in KBr disks.

As can be seen from Table 1, the spectral data of the isophorone dimer are in agreement with the ones reported by Ayer and Taylor⁷ for the 3,5-dimethyl-2-cyclohexen-1-one dimer (Ia), and the two spectra are almost superimposable. The compound is an α,β -unsaturated ketone having a hydroxyl group with a very strong intramolecular hydrogen bond to the carbonyl group and must have a structure analogous to the 3,5-dimethylcyclohexen-1-one dimer Ia, i.e. structure Ib. This was confirmed by the following observations.

Treatment of the dimer with several dehydrating agents (such as polyphosphoric acid, phosphoric anhydride, potassium bisulfate and zinc chloride) yielded either the unchanged starting material or decomposition products. A dimer represented by III

⁹ J. G. Fife, Brit. Pat. 560,598 (1944).

¹⁰ S. Ballard, V. E. Haury, U.S. Pat. 2,307,482 (1943), U.S. Pat. 2,406,652 (1946).

should be dehydrated easily to a triene. On the other hand, treatment of the dimer either with conc. hydrochloric acid or thionyl chloride produced a chloride $C_{18}H_{27}ClO$ with the carbonyl band at 1675 cm⁻¹ as in isophorone. This is true also of the acetate, where the ketonic carbonyl band is at 1675 cm⁻¹. Although containing an hydroxyl group, the dimer fails to react with phenyl isocyanate, acetic anhydride with or without sodium acetate, or chromic acid in carbon tetrachloride. Acetylation in cold acetic anhydride and a trace of perchloric acid, or in refluxing acetic acid and a trace of sulfuric acid with azeotropic removal of water afforded a crystalline acetyl derivative. The case by which the chloride is obtained and the difficulty of acetylation indicate the presence of a tertiary alcohol group. The fact that the chloride can be hydrolysed to the hydroxyketone only after long heating under reflux in the presence of silver oxide and that the dimer cannot be dehydrated suggests the presence of a bridge-head hydroxyl group.

The isophorone dimer gives no color with tetranitromethane and does not undergo bromine addition in carbon tetrachloride. It reacts, instead, with bromine in acetic acid liberating hydrobromic acid and yielding a bromide $C_{18}H_{27}BrO$ (Ic). The same bromide could be obtained by Wohl-Ziegler bromination of the dimer. The position of the bromine atom was assigned in analogy with the bromination of Δ^4 -3-ketosteroids, in which bromination takes place in the allylic position in ring B.¹¹

The presence of a double bond conjugated with the carbonyl group is indicated by IR absorption at 1640 cm^{-1} .

Reduction of the ketol Ib with platinum oxide in acetic acid (no hydrogenation takes place in EtOH) furnished the unsaturated alcohol VI ($C_{18}H_{30}O$). To prove that the alcohol VI differs from Ib only by the loss of the ketonic function, the reactions outlined in Table 2 were carried out. Only with sodium borohydride was it possible to obtain the diol IV from Ib. With LAH, or with the Meerwein-Ponndorf-Verley reduction only the diene V was obtained.



The diol, which may be reoxidized to the ketol Ib with the chromium trioxidepyridine reagent,¹² is very acid-sensitive. Thus, by refluxing the diol IV in toluene in ¹¹ C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, J. Amer. Chem. Soc. 72, 4534 (1950).

¹⁸ G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, J. Amer. Chem. Soc. 75, 422 (1953).

the presence of a trace of acid (sulfuric or acetic acid) or by just leaving an acetic acid solution for 24 hr, water is split off, and the diene V was obtained. The same diene could also be obtained directly from Ib by treating the tosylhydrazone of Ib with sodium ethylene glycolate.¹³ The diene V yielded the alcohol VI by hydrogenation with platinum oxide. The alcohol VI also could be obtained directly from Ib with the Wolff-Kishner reduction of Ib, although in low yield. With a modification of this reduction,¹⁴ i.e. the reduction of the tosylhydrazone of Ib with excess sodium borohydride in dioxan, the alcohol VI was obtained in 63% yield. Compounds V and VI could be converted to the corresponding chlorides with thionyl chloride and hydrolysed again with silver oxide. Compound VI contains a double bond as established by its very weak absorption at 1675 cm⁻¹ and by its color reaction with tetranitromethane. The alcohol VI reacts with NBS, yielding a mixture of bromides, and also with bromine in carbon tetrachloride giving substitution products.

The ketol Ib, with Raney nickel catalyst at $100^{\circ}/125$ atm, was recovered unchanged, but at $180^{\circ}/180$ atm, a liquid unsaturated hydrocarbon (C₁₈H₈₀), the alcohol VI and a saturated alcohol (negative test with tetranitromethane) were obtained. Probably the saturated alcohol is the hydrogenated form of VI.

The 3,5-dimethyl-2-cyclohexen-1-one dimer was chosen as a model substance because its structure has been established.⁷ It was prepared according to the literature² and it was found that two isomeric dimers are formed (m.p. 117–118° and m.p. 93–94°). The IR spectra of both isomers are virtually identical except for the 1000–1300 cm⁻¹ region. The two dimers are not identical and give different 2,4-dinitrophenyl-hydrazones. Buechi⁶ obtained two different diketone dimers from 3,5-dimethyl-2-cyclohexen-1-one with sodium amide in boiling ether but only one dimer from isophorone. The ketol Ia is very soluble in concentrated hydrochloric acid as noticed by Knoevenagel,² but after a certain time, the corresponding chloride precipitates out.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were measured on a Perkin-Elmer model 337 recording spectrometer.

Dimerization of isophorone

(a) A mixture of 280 g (2 moles) isophorone and 70 g 60% NaOHaq was stirred and heated at 155–160° for 2 hr. The brown reaction mixture was cooled, neutralized with HClaq and extracted 3 times with 150-ml portions CHCl₂. The combined CHCl₂-extracts were dried over MgSO₄ and distilled to yield 80 g starting material and 182·3 g Ib (corresponding to a 65% conversion and 91·5% yield); b.p. 136–140° at 0·2 mm m.p. 86–88°. The product was crystallized from petrol ether, b.p. 40–70°. (Found: C, 78·16; H, 10·34. Calc. for C₁₈H₁₈₀O₁: C, 78·21; H, 10·21%.)

The residue of the above distillation was dissolved in 30 ml boiling EtOH and on cooling, 7.6 g deep yellow crystals, m.p. 150–152°, were obtained. (Found: C, 85.81; H, 9.97. Calc. for $C_{17}H_{18}O$: C, 85.66; H, 10.12% Mol. wt. (Rast), Calc. for $C_{17}H_{18}O$: 378.57; Found: 357.)

(b) A mixture of 280 g (2 moles) isophorone and 5.6 g powdered NaOH was stirred and heated at 150–160° for 2 hr. After cooling, the reaction mixture was filtered, diluted with CHCl₂ and washed neutral with water. The CHCl₂-solution was dried over MgSO₄ and distilled to yield 103 g starting material and 146 g Ib, corresponding to 51% conversion and 81.5% yield. The residue, 19.1 g, was dissolved in 30 ml boiling EtOH and on cooling, 10.6 g of the deep yellow isophorone condensation product, m.p. 150–152°, was obtained.

¹⁸ C. H. DePuy, D. H. Froemsdorf, J. Amer. Chem. Soc. 82, 634 (1960). ¹⁴ L. Cagliotti and P. Grasselli, Chem. & Ind. 153 (1964). (c) A mixture of Ib (160 g) and 60% NaOHaq (40 g) was stirred and heated for 2 hr at 150–160°. The brown reaction mixture was cooled, neutralized with HCl and extracted with CHCl₃. The combined CHCl₃-extracts were dried and distilled to yield 50.8 g isophorone (31.8%) and 101 g starting material (63.2%). The residue (6 g) was dissolved in 15 ml boiling EtOH and on cooling, 2.8 g yellow isophorone condensation product was obtained.

Derivatives of the ketol Ib.

(a) 2,4-Dinitrophenylhydrazone. The derivative was prepared in the conventional method, m.p. 188-189° after crystallization from EtOH. (Found: C, 63.07; H, 7.02; N, 12.37. Calc. for $C_{24}H_{32}N_4O_5$: C, 63.14; H, 7.07; N, 12.27%.)

(b) Semicarbazone. The hydroxyketone (10 g), semicarbazide hydrochloride (10 g) and sodium acetate (10 g) were dissolved in 100 ml MeOH and 30 ml water. The mixture was refluxed for 30 min and kept at room temp for 2 days. The solvents were removed *in vacuo* and the residue extracted with CHCl₃. The CHCl₃-extracts were dried and concentrated. The oily residue was crystallized from a benzene-hexane to yield 2 g semicarbazone (16.6% conversion and 92.5% yield). From the mother liquors, 8.2 g starting material could be recovered. An analytical sample was crystallized from benzene, m.p. 218-219° with dec. (Found: C, 68.37; H, 9.32; N, 12.56. Calc. forC₁₉H_{a1}N $_{3}O_{3}$: C, 68.43; H, 9.37; N, 12.60%.)

Chloride of the ketol Ib

(a) To 100 ml conc. HCl, 5 g Ib was added. The mixture was stirred and a clear solution obtained. Within 10 min the chloride began to precipitate out and after stirring 24 hr, 5.2 g (98%) crude chloride was obtained, m.p. 133-135°. Purification of the product by crystallization from MeOH gave 4.7 g (88.2%) colourless crystals, m.p. 135-136°. (Found: Cl, 11.91. Calc. for $C_{18}H_{17}$ ClO: Cl, 12.0%.)

(b) To a solution of 20 g (0.066 mole) Ib in 50 ml CHCl_s, a solution of 8.25 g (0.07 mole) SOCl_s in 40 ml CHCl_s was added slowly. The mixture was stirred 2 hr at room temp followed by 1 hr heating at 50°. After cooling, the low-boiling materials were removed *in vacuo* and the orange crystalline residue crystallized from MeOH. The crystallization was repeated yielding 17.2 g (81%) pale yellow crystalline product, m.p. 135–136°. A mixed m.p. with the chloride (whose preparation is described above) did not show any depression.

Hydrolysis of the chloride of Ib

A mixture of 14.7 g (0.05 mole) chloride prepared as above, 10 g (0.073 mole) K_aCO_a , 9.4 g (0.055 mole) AgNO_a, 100 ml water and 100 ml EtOH was stirred and refluxed for 24 hr. After cooling, the reaction mixture was washed with ether; the ether washings were dried over MgSO_a and distilled. The fraction distilling as a pale yellow oil at 130–142° (0.2 mm) was retained and crystallized from petrol ether (b.p. 40–70°) to yield 8.6 g (62.5%) Ib, m.p. 86–88°. A mixed m.p. with pure Ib did not show any depression.

Bromo compound Ic

(a) To a solution of 33.1 g (0.12 mole) Ib in 100 ml glacial acetic acid, a solution of 17.6 g (0.22 g atoms) Br₂ in 50 ml glacial acetic acid was added slowly. The mixture was stirred at room temp for 5 hr, whereupon unreacted Br₂ was removed *in vacuo*. The reaction mixture was poured into water and the organic phase extracted with CHCl₂. The CHCl₂-extracts were washed neutral, dried over MgSO₄ and concentrated to leave a yellow oil which was dissolved in 70 ml petrol ether (b.p. 40-70°). Upon standing overnight in the freezer, 12 g (28.2%) pale yellow product was collected, m.p. 106-107°. (Found: C, 60.91; H, 7.72; Br, 22.38. Calc. for C₁₈H₃, BrO₂: C, 60.84; H, 7.66; Br, 22.49%.)

(b) A mixture consisting of 552 g (0.2 mole) Ib, 356 g (0.2 mole) NBS and 0.5 g dibenzoylperoxide in 200 ml CCl₄ was refluxed for 3 hr. After cooling, the reaction mixture was filtered, the filtrate concentrated to dryness and the pale yellow oily residue (74.3 g) dissolved in 100 ml boiling petrol ether (b.p. 40-70°). Upon standing overnight in the freezer, 25 g (35.3%) pale yellow crystals were collected, m.p. 106-107°. A mixed m.p. with the bromide prepared as above did not show any depression.

Acetate of ketol Ib

A solution of 55.2 g (0.2 mole) Ib and 1 g p-toluenesulfonic acid in a mixture of 100 ml benzene and 36 g (0.6 mole) glacial acetic acid was refluxed in a flask equipped with a water trap. After 44 hr, the elimination of water was complete. The mixture was diluted with water and extracted with benzene. The benzene extracts were washed neutral, concentrated to dryness and the crystalline residue crystallized from hexane to yield 52.7 g (83%) acetate, m.p. 125–127°. (Found: C, 75.31; H, 9.45. Calc. for $C_{10}H_{10}O_3$: C, 75.43; H, 9.50%.)

Hydrogenation of ketol Ib

(a) With NaBH₄. To a solution of 69 g (0.25 mole) Ib in 230 ml MeOH, a solution of 5.7 g (0.15 mole) NaBH₄ in 50 ml water containing 11 ml 1N NaOH was added slowly. The reaction mixture was stirred for 80 hr at room temp. Most of the MeOH was removed *in vacuo*, the residue diluted with 150 ml water and extracted 3 times with 200 ml portions ether. The combined ether extracts were dried overnight over MgSO₄. The ethereal solution was concentrated to a 100 ml and kept in the freezer overnight to yield 25.8 g pale yellow crystalline compound m.p. 151–155°. A second crystallization from ether yielded 23.2 g (33.6%) pure IV, m.p. 152–153°. (Found: C, 77.67; H, 10.86. Calc. for C₁₈H₄₀O₃: C, 77.65; H, 10.86% Mol. wt. (Rast) calc. for C₁₈H₄₀O₃: 278.42; Found 282.5.)

The ethereal mother liquors of the above crystallizations were combined, concentrated (39·2 g) and distilled: fraction 1, b.p. 97-105° (0·2 mm) 27·5 g and fraction 2, b.p. 105-120° (0·2 mm) 6·3 g. A second distillation of fraction 1 yielded 25·8 g (40%) of V, b.p. 100-102° (0·2 mm), n_D^{30} 1·5207. (Found: C, 82·93; H, 10·97. Calc. for C₁₀H₃₀O: C, 83·02; H, 10·84%.)

(b) With LAH. To a cooled (ice bath) solution of 4 g (0.1 mole) LAH in 200 ml anhydrous ether, a solution of 55.2 g (0.2 mole) Ib in 300 ml abs ether was added slowly during 2 hr. After 18 hr stirring at 25°, the reaction mixture was decomposed with dil HClaq. The ether solution was removed and the aqueous phase washed 3 times with ether. The combined ethereal washings were washed neutral, dried over MgSO₄ and concentrated to a volume of 80 ml. Upon standing in the freezer overnight, none of the diol whose preparation is described above precipitated out. The ethereal solution was therefore distilled to yield 42.5 g (82%) V: b.p. $100-102^{\circ}$ (0.2 mm), n_D^{00} 1.5207.

(c) With the Meerwein-Ponndorf-Verley procedure. The reduction was carried out using 40 g (0.195 mole) aluminum isopropoxide, 300 ml abs isopropanol and 55.2 g (0.2 mole) lb. When no more acetone was formed, the reaction mixture was hydrolysed and extracted with ether. The ethereal extracts were combined, dried over MgSO₄ and concentrated to a volume of 80 ml. Upon standing in the freezer overnight, no IV precipitated. The ethereal mixture was therefore distilled to yield 37.9 g (74%) V: b.p. 100-102° (0.2 mm), n_{20}^{20} 1.5208.

Tosylhydrazone of ketol Ib

The method of DePuy and Froemsdorf was used for preparation of the tosylhydrazone.¹⁸ To a solution of 46.5 g (0.25 mole) *p*-toluenesulfonylhydrazine in 500 ml EtOH containing 15 ml conc. HClaq, 69 g (0.25 mole) Ib was added. The mixture was stirred until the solids dissolved, and then refluxed 1 hr. After cooling, the reaction mixture was filtered and the pale yellow product crystallized from EtOH to yield 9.2 g (82%) of the tosylhydrazone, m.p. 212–213°. (Found: C, 67.32; H, 8.12; N, 6.44; S, 7.10. Calc. for C₁₅H₂₆N₃SO₆: C, 67.53; H, 8.16; N, 6.30; S, 7.22%.)

Decomposition of the tosylhydrazone

A solution of 9 g (0.02 mole) tosylhydrazone of Ib in 40 ml ethylene glycol containing dissolved 0.7 g (0.03 mole) Na was heated to 160°, at which temp a strong N_s evolution began. After 15 min, no more N_s evolution was noticed; the reaction mixture was cooled, diluted with 100 ml water and extracted with ether. The combined ether extracts were washed neutral, dried and distilled to yield 4.9 g (93%) V, b.p. 90-95° (0.1 mm), n_D^{30} 1.5205.

Oxidation of diol IV

A solution of 4.9 g (0.0175 mole) IV in 40 ml pyridine was added to 5.2 g (0.052 mole) CrO₄ in 55 ml pyridine in the cold. The flask was stoppered and magnetically stirred at room temp for 18 hr.

The reaction mixture was poured into water and extracted with $CHCl_{9}$. The combined $CHCl_{9}$ extracts were washed with water, dried and concentrated. The black residue was extracted with ether and from the ethereal extracts, 3.2 g (65%) Ib was obtained, m.p. 85–87°. The 2,4-dinitrophenylhydrazone, m.p. 188–189° and mixed m.p. with the 2,4-dinitrophenylhydrazone of pure Ib did not show any depression.

Chloride of V

The diene V upon treatment with SOCl₂ in CCl₄ yielded the corresponding chloride, b.p. 80–85° (0.1 mm), n_{10}^{20} 1.5238, m.p. 48-49°. (Found: Cl, 12.80. Calc. for C₁₈H₂₇Cl: Cl, 12.72%.)

Diene V from diol IV

Two solutions of each 2.78 g (0.01 mole) V in 20 ml toluene were prepared, the first of which was treated with 3 drops acetic acid and the second with 3 drops H_3SO_4 . Both mixtures were stirred and refluxed for 4 hr, cooled, washed neutral and distilled. In both cases, 1.8 g (69%) V, b.p. 90-95° (0.1 mm), n_{20}^{20} 1.5205 was obtained. These dienes could be converted to the chloride, m.p. 48-49°.

Hydrogenation of V

The diene V (10 g) in 40 ml glacial acetic acid took up 1 mole H_s in the presence of 0.1 g PtO_s. The alcohol VI distilled at 101-105° (0.1 mm), n_D^{so} 1.5065 and was crystallized to a white product m.p. 84-85°. (Found: C, 82.30; H, 11.55. Calc for C₁₈H_{so}O: C, 82.38; H, 11.52%.)

Compound VI from ketol Ib

(a) To a solution of 9 g (0.02 mole) Ib tosylhydrazone in 200 ml abs dioxan, 19 g (0.5 mole) NaBH₄ was added. The mixture was refluxed for 18 hr, concentrated to dryness and excess NaBH₄ decomposed with dil H₃SO₄. The aqueous phase was extracted with CHCl₃, the CHCl₃-extracts were dried and distilled to yield 3.3 g (62%) VI, b.p. 101-106° (0.1 mm), n_{20}^{20} 1.5070. Upon crystallization, the crystalline form of VI, m.p. 84-85°, was obtained. Upon treatment with SOCl₃, this alcohol yielded the corresponding chloride, m.p. 60-61°.

(b) To a solution of $82 \cdot 8$ g (0.3 mole) Ib in diethylene glycol, 46 g (0.7 mole) powdered KOH followed by 30 ml 85% hydrazine hydrate was added. The mixture was stirred and refluxed 2 hr, excess water was removed until the reaction mixture temp had reached 180°, when refluxing was continued for 2 hr. After cooling, the reaction mixture was diluted with 100 ml water, neutralized with HCl and extracted with ether. The combined ether extracts were dried and distilled and the fraction, b.p. 95–115° (0.1 mm) (16.2 g) was collected. After 2 crystallizations from petrol ether (b.p. 40–70°), 12.5 g (15.9%) VI, m.p. 84–85°, was obtained.

(c) The ketol Ib (20 g) in 30 ml glacial acetic acid took up 2 moles H_1 at 1 atm. press. and room temp in the presence of 0.2 g PtO₁. The H_1 uptake was very slow and lasted 100 hr. The alcohol VI, 14.7 g (73.5%) distilled at 98–106° (0.1 mm) and crystallized from petrol ether (b.p. 40–70°), m.p. 84–85°.

(d) The ketol Ib (138 g, 0.5 mole) in 170 ml MeOH was hydrogenated at 180° and 160-140 atm. H₃. After 26 hr, the uptake of H₃ ceased and 0.75 mole H₃ was consumed. Upon distillation, 131.8 g (96%) colorless oil was collected at 100-110° (0.1 mm), n_{10}^{30} 1.5058. The oil was dissolved in 100 ml boiling petrol ether (b.p. 40-70°) and upon standing in the deep freezer overnight, 62.7 g (47.5%) VI, m.p. 84-85°, was obtained. The mother liquors were concentrated and fractionated: fraction 1, b.p. 84-86°(0.1 mm), n_{10}^{30} 1.4936, 20.3 g; fraction 2, b.p. 100-110° (0.1 mm), n_{10}^{30} 1.5058, 30.1 g; fraction 3, b.p. 100-117° (0.1 mm), n_{10}^{30} 1.5038, 18.1 g. Fraction 1 was distilled again and 15.6 g product boiling at 85-86° (0.1 mm) n_{10}^{30} 1.4931 (positive test with tetranitromethane) was obtained. (Found: C, 87.62; H, 12.08; Calc. for $C_{18}H_{80}$: C, 87.73; H, 12.27%. Mol. wt. (cryoscopic): calc. for $C_{18}H_{30}$: 246.42; Found: 236.)

Fraction 3 was distilled again and 25.3 g product b.p. 114-116° (0.1 mm) n_{10}^{50} 1.5034 (negative test with tetranitromethane) was obtained. (Found: C, 81.83; H, 12.08. Calc. for C₁₈H₃₃O: C, 81.75; H, 12.20.)

Chloride of VI

(a) To 500 ml conc. HCl, 30 g VI was added. The mixture was stirred at room temp for 48 hr (no solution obtained) and filtered. The white precipitate was washed with water until neutral, dried and distilled. The chloride was collected at $80-83^{\circ}$ (0.05 mm), n_{20}^{30} 1.5023 to yield 25 g (78%). After crystallization from MeOH, the product melted at 60-61°. (Found: Cl, 12.53. Calc. for $C_{18}H_{12}Cl$: Cl, 12.62.)

(b) To a solution of 13.1 g (0.05 mole) VI in 30 ml CCl₄, a solution of 7.2 g (0.06 mole) SOCl₅ in the same solvent was added slowly at room temp. After 2 hr stirring at room temp and another 2 hr at 50°, the mixture was concentrated *in vacuo*. The residue was crystallized from MeOH to yield 10.3 g (72%) chloride, m.p. 60-61°.

Hydrolysis of the chloride of VI

A mixture of 8.4 g (0.03 mole) chloride derived from VI, 6 g (0.043 mole) K_2CO_3 , 5.9 g (0.035 mole) AgNO₃, 45 ml water and 45 ml EtOH was stirred and refluxed for 24 hr. After cooling, the reaction mixture was concentrated to dryness and the residue extracted with ether. The ether extracts were dried over MgSO₄ and distilled. The fraction b.p. 103–104° (0.1 mm) was collected and crystallized from 4 ml petrol ether (b.p. 40–70°) to yield 5.1 g (65%) product, m.p. 82–85°. A second crystallization yielded the pure alcohol, m.p. 84–85°.

Titration of alcohol VI

The alcohol VI can be titrated with Br_2 in CCl_4 ; it does not add Br_3 , but one of its hydrogens is replaced by Br. The procedure adopted by us is a modification of the Shell method.¹⁵ The sample was dissolved in CCl_4 , water was added and the flask cooled in an ice-bath for 10 min. Then the Br-reagent was added and the flask stored in the dark and in the ice-bath for 10 min, whereupon approx. 3-4 g Hg metal was added. The flask was shaken well and the HBr formed was titrated with 0-1N NaOH in the presence of methyl orange. By this procedure, values corresponding to 102-104% of the theoretically formed HBr were found.

By simply titrating the Br_3 , which was consumed during the reaction, values corresponding to 95-96% of the theoretically consumed Br_3 were found.

Dimerization of 3,5-dimethyl-2-cyclohexan-1-one

The dimerization of 3,5-dimethyl-2-cyclohexen-1-one, prepared according to the literature,¹⁴ either with a 60% NaOHaq or with powdered NaOH was carried out as previously described for isophorone. The crude product, b.p. 143–148° (0.5 mm) melted at 109–111°. After crystallization from aqueous EtOH it melted at 117–118°—reported' 120°, and the 2,4-dinitrophenylhydrazone melted at 189–190°, reported' 191°.

The aqueous ethanolic mother liquors of the crystallizations were combined and concentrated. The residue, upon repeated crystallizations from petrol ether (b.p. 40-70°) yielded the low-melting isomer of the dimer, m.p. 93-94°. (Found: C, 77.24; H, 9.61; Calc. for $C_{16}H_{16}O_{3}$: C, 77.32; H, 9.74%. Mol. wt. (Rast) calc. for $C_{16}H_{16}O_{3}$: 248, Found 232.)

The low-melting dimer formed a 2,4-dinitrophenylhydrazone, m.p. 199–200°. The m.p. of the two 2,4-dinitrophenylhydrazones was depressed on admixture. (Found: C, 61.60; H, 6.62; N, 13.12. Calc. for $C_{11}H_{18}N_4O_5$: C, 61.66; H, 6.59; N, 13.08%.)

Chloride of Ia, high-melting isomer

To 100 ml conc. HCl, 5 g high-melting dimer Ia was added. The mixture was stirred at room temp and a clear solution was obtained. Stirring was continued and after 18 hr the chloride started to come out. After 4 days stirring the white precipitate was collected by filtration, washed with conc. HCl and water and dried to yield 4.9 g (91.5%) crude chloride. A 2 days' reaction time gave the chloride in only 69% yield. Purification of the crude product by crystallization from aqueous MeOH gave the pure chloride, m.p. 102-103°. (Found: C, 71.85; H, 8.54; Cl, 13.14. Calc. for C₁₆H₁₁₀ClO: C, 72.02; H, 8.69; Cl, 13.29%.)

The chloride could be hydrolysed to Ia by treatment with Ag₃O as previously described for the chloride of the isophorone dimer.

Acknowledgment—The authors wish to thank W. R. Grace & Co. for their permission to publish this work, and in particular, Dr. R. Gabler for his encouragement and suggestions.

¹⁵ S. Siggia, Quantitative Organic Analysis via Functional Groups, p. 298. J. Wiley, New York, N.Y. (1963).

¹⁴ E. C. Horning, M. O. Denekas, R. E. Field, Organic Syntheses Coll. Vol. II; p. 317 (1955).