with an optimized column and solvent system.

At first, oxidation of cholesterol was selected as a model reaction from "Organic Syntheses".[6] Chromatographic retention data of the components in the reaction mixture were obtained by using an analytical column. The solvent system for the reversed phase column was optimized experimentally. Acetic acid used for the reaction medium was removed at the same time as the chromates. The loading capacity of the polystyrene gel packed column was large enough to retain and to separate the crude reaction products from a large amount of reagents and reaction medium solvents. The crude reaction mixture, which was directly injected into the preparative column, was separated into its constituents. The colorless crystalline product obtained by evaporation of the eluent was identified as 4-cholestene-3,6-dione by its spectroscopic data. The high purity of the sample was demonstrated by its showing a single peak on an analytical high-resolution column. On the other hand, the specimen obtained by extraction and recrystallization of the product following the procedure described in the literature was a pale yellow crystalline substance which showed several minor peaks on an analytical liquid column chromatography due to impurities. The yield of the reaction was increased from 40% in the literature to 71% in this experiment. These results seem to be due to not only high efficiency fractionation of the main product, but also the removal of chromates at the beginning, which prevents inorganic impurities from contaminating the product during the evaporation under heat. Such contamination is common in conventional separation.

The direct fractionation procedure using reversed phase liquid chromatography was applied further to several typical chromate oxidation reactions described in "Organic Syntheses".[7-11] A few results are shown in Table I. In every case, the purity and yield of these reactions were improved over conventional isolation procedures. Quantitative recovery of the starting material was possible, for instance in the case of the oxidation of naphthalene.[8] Fractions of low purity such as second crop crystals or mother liquors are always given by the traditional techniques. However, with the direct fractionation procedures, only a single, pure fraction is obtained. In a series of these experiments, the same packed column has been used repeatedly to examine the lifetime of the column material. No deterioration of the column function was observed.

The direct fractionation procedure with no pretreatment, which was described above, is simple and fast. It can be automated and waste materials can be minimized by recovering the inorganic and organic reagents, starting materials, and mobile phase solvents. The characteristics of this method are the high purity of the products and the quantitative yield of the reaction products, which are obtainable only by direct fractionation using a high-resolution column. This method can be useful as a general separation procedure for chromate oxidation reaction and as a substitute for the conventional procedure which is now widely utilized.

Experimental Section

General. Starting materials and reagents employed were technical grade chemicals obtained from Wako Pure Chemicals Co., Osaka. Packing material was TSK-gel 110, Toyo Soda Co., Tokyo, spherical porous polymer, diameter of 10 μm for analytical and 30 μm for preparative high performance liquid chromatography. Glass columns (CIG column system,[2] Kusano Scientific Co., Tokyo) packed with a slurry of polystyrene gel–methanol (inter diameter of 4 mm, length of 10 cm for analytical, inter diameter of 15 mm, length of 30 cm for preparative work) were connected with a sample injector valve made of PTFE or glass. The crude reaction mixture obtained was directly injected into the top of the column. The flow rates of the mobile phase consisting of methanol (technical grade, Wako Pure Chemicals Co.) and water were 1 mL/min under pressure of 30 kg/cm^2 for analytical work, and 3 mL/min under pressure of 10 kg/cm^2 for preparative purpose. Chromatographic equipment was assembled from a reciprocating pumping system, KP-9H, Kusano Scientific Co., a 254 nm UV detector, UVILOG, Kusano Scientific Co., and a RI detector, Waters Associates, Mass. Capacity factors in Table I were calculated by $k' = (V_R - V_0)/V_0$ where V_R is the elution volume for the chromatographic peak and V_0 is the column void volume which was measured by *p*-toluenesulfonic acid in water (V_0: 0.8 mL for analytical column, 18 mL for preparative column). The resolution factor of the products was always larger than 1. Yield of the main product shown in Table I was calculated from the weight of the residue obtained by evaporation of the separated fraction. Polar side products which were highly oxidized were eluted from the column with chromates and were not examined precisely in this experiment.

Acknowledgment. We thank Dr. Masaru Hasegawa, Daiichi Pure Chemicals Co., for support of this research.

References and Notes

(1) An example is the series "Organic Syntheses" which deals with standard and reliable procedures. About half of the book is taken up by detailed description of isolation procedures.
(2) S. Hara, *J. Chromatogr.*, **137**, 41 (1977).
(3) S. Hara and M. Nakahata, *J. Liq. Chromatogr.*, **1**, 43 (1978).
(4) Octadecylsilylated silica (ODS) packing is available as a common reversed phase stationary; however, it is deteriorated by the adsorption of chromates on the surface of the remaining silanol groups.
(5) Correlation between retention behavior and solute molecular structure has been systematically investigated in our laboratory. Details will be reported in the future. Cf. D. J. Pietrzyk and Chi-Hung Chu, *Anal. Chem.*, **49**, 757 (1977).
(6) "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1962, p 189.
(7) "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1962, p 713.
(8) "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1962, p 698.
(9) *Org. Synth.*, **55**, 84 (1976).
(10) "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1952, p 449.
(11) "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1952, p 420.

Synthesis and Photochemistry of 2,4,6-Tri-*tert*-butylacetophenone

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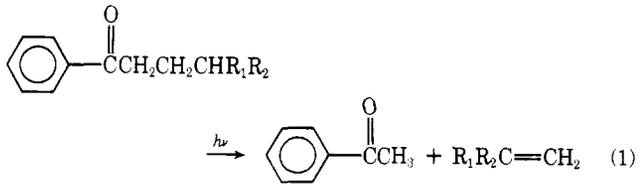
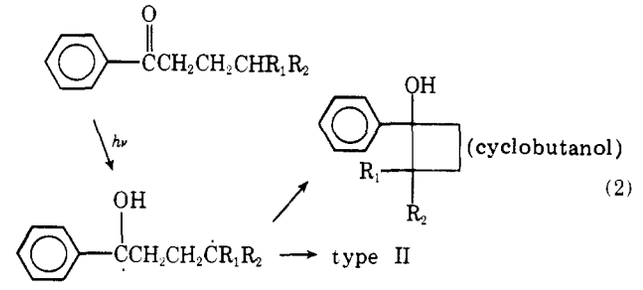
Hydrogen abstraction reactions by excited aromatic carbonyl compounds are generally triplet reactions,[1] and in the case of the Norrish type II reaction of arylalkanones they occur intramolecularly from the γ position of the attached alkyl group. Scission follows and the products are an alkene and a lower molecular weight aryl ketone (eq 1). The type II process



(1)

is accompanied by cyclobutanol formation[2] in the general case (eq 2), and the reaction is known to proceed through biradical intermediates.[2]



(2)

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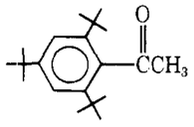
δ-Hydrogen abstraction is substantially slower than γ abstraction,[3] and 1,5 transfers generally predominate over 1,6 or other hydrogen atom transfers in intramolecular reactions of triplet carbonyl derivatives. Nevertheless, there are some specific cases in which δ-hydrogen abstraction is observed. For the most part, these are ketones which have no choice since they contain no γ-hydrogen atoms.[4-8]

Highly hindered free radicals are of significant interest particularly since they are formed from classical inhibitors of chain oxidation and polymerization reactions.[9] Therefore, the stable 2,4,6-tri-*tert*-butylphenyl system is of interest both as a phenoxyl[10] and as an anilino[11] stable radical. The tri-*tert*-butylphenyl radical is also of interest, and its isomerization by hydrogen migration from an ortho *tert*-butyl group has attracted considerable attention as a reaction occurring by quantum mechanical tunneling.[12]

We were interested in the synthesis and photochemistry of 2,4,6-tri-*tert*-butylacetophenone, particularly in view of its highly hindered nature. We wondered if its aromatic carbonyl triplet state would be reactive toward the many adjacent *tert*-butyl hydrogens or if the highly hindered nature of the carbonyl group would be sufficient to force the lowest lying excited state to be π–π^* rather than n–π^* in character. Accordingly, we developed a new synthesis for 2,4,6-tri-*tert*-butylacetophenone (VI) and studied its photochemistry.



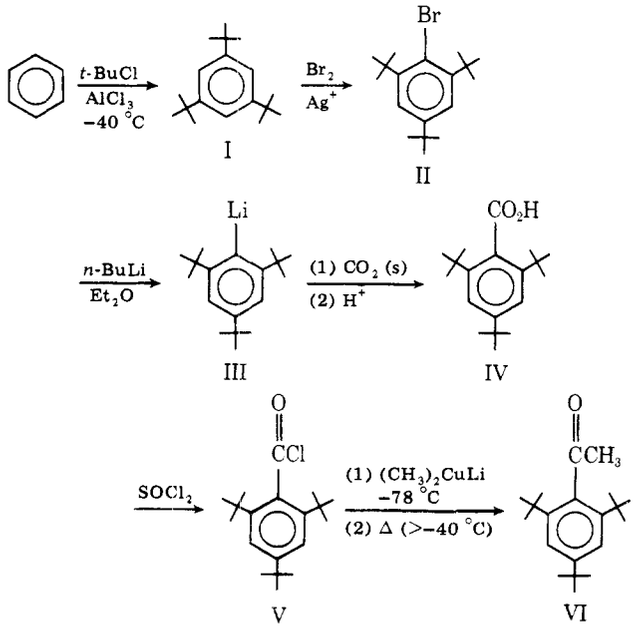
VI

The specific synthesis of VI proved to be more difficult than one might have anticipated. The previously reported synthesis of VI[15] from the acid chloride V using methylmagnesium iodide led predominantly to the coupled product 2,4,6,2′,4′,6′-hexa-*tert*-butylbenzil and less than 3% of the desired ketone.

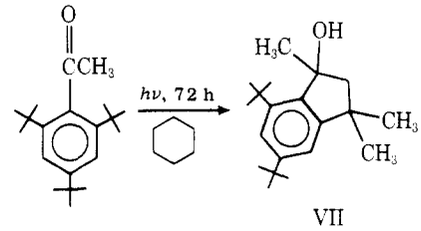
Several alternate routes to VI were attempted, however, and preparation of lithium dimethylcopper in situ at −70 °C and warming (above 40 °C) in the presence of V gave an excellent yield of VI, a reaction known to yield methyl ketones from acid chlorides under mild conditions.[16]

Improvements were also made on the procedures reported previously for the synthesis precursors of IV[13,14] (Scheme I).

Scheme I

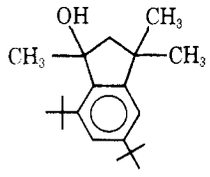


Photolysis through Pyrex of VI (1.2×10^{-2} M in cyclohexane) gave an 89% yield of 1-hydroxy-1,3,3-trimethyl-5,7-di-*tert*-butylindan (VII). The IR spectrum of VII shows a free OH stretching frequency at 3595 cm^{-1}, and the NMR spectrum is consistent with the assigned structure. Heating VII in the presence of catalytic amounts of HCl in C_6D_6 gave a 3:97 mixture of the olefins VIII and IX (eq 4), while heating VII neat in the absence of acid at 210 °C leads to a 39:61 mixture of VIII and IX.

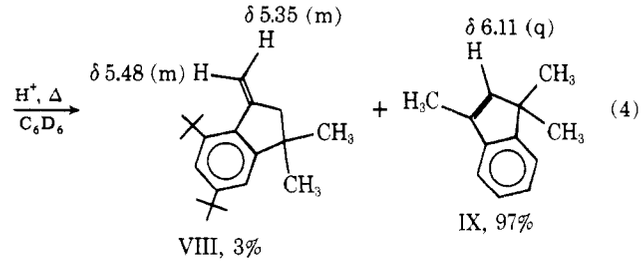


(3)

VII



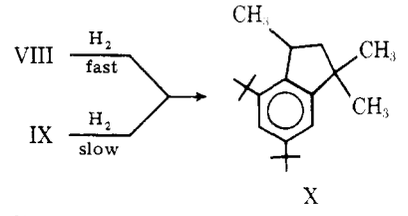
VII



(4)

VIII, 3% IX, 97%

Evidence to support the assignments of VIII and IX was obtained by hydrogenation of the mixture of olefins produced to a single indan (X, eq 5). The NMR absorptions of VIII (δ 5.35, 5.48) disappear first, consistent with a more rapid reduction of VIII followed by a slow reduction of IX, leading to the same product hydrocarbon (eq 5).

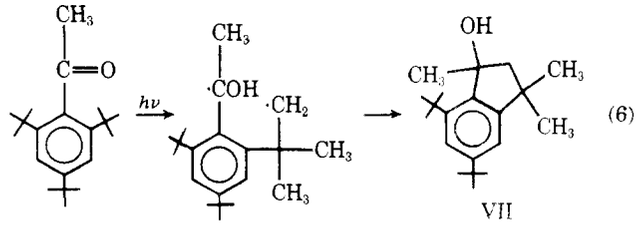


(5)

X

As is readily apparent, 2,4,6-tri-*tert*-butylacetophenone behaves very similarly to other aryl alkyl ketones though hydrogen abstraction from the δ-carbon atom is the only observed reaction. Its efficiency is obviously the result of the fact that the molecule has no alternate choice, and the formed biradical simply ring closes.

From a synthetic point of view, the photochemical δ-hydrogen abstraction in this case provides a most satisfactory route to the hydroxyindan. Attempts to generalize this reac-



(6)

VII

tion are under way in our laboratories.

In summary, 2,4,6-tri-*tert*-butylacetophenone undergoes an efficient δ-hydrogen abstraction reaction from its triplet n–π* state. Ring closure of the formed diradical produces a single product, 1-hydroxy-1,3,3-trimethyl-5,7-di-*tert*-butylindan (VII, eq 6).

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 grating infrared spectrophotometer, ultraviolet spectra on a Beckman Acta MIV spectrophotometer, and nuclear magnetic resonance spectra on either a Varian Associates CFT-20 or A-60 NMR spectrophotometer. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

1,3,5-Tri-*tert*-butylbenzene (I). Benzene (15.6 g, 0.2 mol) and 194 g of *tert*-butyl chloride (2.1 mol) were mixed in a 500-mL, three-neck, round-bottom flask fitted with a mechanical stirrer. Aluminum trichloride (13.2 g, 0.1 mol) was added to the mixture with stirring over a 20-min period at −40 °C. The temperature was allowed to slowly rise to −15 °C, and the reaction was maintained at −15 °C for 2 h. During this period, a color change from creamy white to bright yellow was observed. The resulting solution was poured over 800 g of ice water and stirred. The pinkish organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate, and the excess *tert*-butyl chloride was removed at reduced pressure. The residue was recrystallized from methanol to give 32.5 g (66%) of a white solid: mp 69–71 °C (lit.[17] 73 °C); NMR ($DCCl_3$) δ 7.32 (s, 3) and 1.37 (s, 27). Similar runs resulted in yields of 61, 61, 62, and 66%.

2,4,6-Tri-*tert*-butylbromobenzene (II). 1,3,5-Tri-*tert*-butylbenzene (35 g, 0.14 mol) was dissolved in 1.2 L of glacial acetic acid and 0.3 L of dioxane. A solution of silver nitrate (35 g, 0.2 mol), 10 mL of nitric acid and 760 mL of water and then 35 g (0.22 mol) of bromine were added to this solution. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with 5 L of water, decolorized with sodium bisulfite, and extracted with pentane. The pentane solution was washed with 10% sodium hydroxide and with water and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. The product was recrystallized from ethanol to yield 13.5 g (30%) of white crystals: mp 171–173 °C (lit.[17] 173–174 °C); NMR ($DCCl_3$) δ 7.48 (s, 2), 1.59 (s, 18), and 1.32 (s, 9). In subsequent runs, yields of 25, 27, 29, and 31% were obtained.

2,4,6-Tri-*tert*-butylbenzoic Acid (IV). *n*-Butyllithium (4.5 mL of a 2.2 M hexane solution, 0.01 mol) was added to a solution of 1.4 g (4 mmol) of 2,4,6-tri-*tert*-butylbromobenzene in 25 mL of ether (freshly distilled from lithium aluminum hydride). The solution was maintained at reflux for 1 h under nitrogen and then was poured over dry ice and allowed to stand for 8–10 h. The organic solution was washed with dilute hydrochloric acid and with water and dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure. The product was recrystallized from petroleum ether to give a fine, white powder in 46% yield (0.58 g): mp 291–293 °C (lit.[13] 297 °C); NMR ($DCCl_3$) δ 7.51 (s, 2), 1.50 (s, 18), and 1.32 (s, 9).

2,4,6-Tri-*tert*-butylbenzoyl Chloride (V). Freshly distilled thionyl chloride (4 g, 0.03 mol) and a few drops of pyridine were added to a solution of 3 g (0.01 mol) of 2,4,6-tri-*tert*-butylbenzoic acid in 80 mL of dry ether. The solution was allowed to stand at room temperature for 24 h. The resulting solution was filtered through scintered glass under a nitrogen atmosphere, and the solvent was removed from the filtrate under reduced pressure. The white solid was used without further purification or storage. The melting point range of this material was 140 to 150 °C (lit.[15] 151–155 °C).

2,4,6-Tri-*tert*-butylacetophenone (VI). Methyllithium (27 mL of a 1.6 M solution in ether, 43 mmol) was added to a stirred solution of 3.95 g of copper(I) iodide (21 mmol) in 125 mL of dry ether at 0 °C under a nitrogen atmosphere. After 10 min, the solution was cooled to −78 °C and 1.8 g of the acid chloride V (5.5 mmol) dissolved in 25 mL of ether was added. The solution was allowed to slowly warm to room temperature. After ~2 h, the solution was filtered and the filtrate was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure, and the product was purified by column chromatography and then recrystallization from methanol. A yield of 0.73 g (44%) was obtained: mp 120.5–122 °C (lit.[15] 121–123 °C); NMR ($DCCl_3$) δ 7.50 (s, 2), 2.68 (s, 3), 1.39 (s, 18), and 1.33 (s, 9).

Photolysis of 2,4,6-Tri-*tert*-butylacetophenone. Ketone VI (20 mg, 0.7 mmol) was added to 8 mL of cyclohexane, and the resulting degassed solution was irradiated in a Rayonet reactor (313.0-nm lamps). After 72 h, the solvent was removed at reduced pressure and the products were purified by thick-layer chromatography. 1-Hydroxy-1,3,3-trimethyl-5,7-di-*tert*-butylindan (VII) was obtained in 89+% yield. The data are the result of four runs and were determined by NMR spectroscopy using methylene chloride as an internal standard: NMR ($DCCl_3$) δ 7.16 (m, 2), 1.95 (s, 2), 1.68 (s, 3), 1.64 (s, 9), 1.32 (s, 9), 1.27 (s, 3), and 1.24 (s, 3); IR ($HCCl_3$) 3595 (m), 3050–2850 (s), 1580 (m), 1250 (br s), 1165 (s), 1110 (m), 1060 (m), 935 (m), 915 (m), 890 (m), and 730 (m) cm^{-1}; UV (95% EtOH) 239 nm (ε 1677), 266 (346), and 307 (78).

Dehydration of 1-Hydroxy-1,3,3-trimethyl-5,7-di-*tert*-butylindan. The alcohol VII (100 mg, 0.35 mmol) was placed in an NMR tube, with C_6D_6 as solvent, a drop of dilute hydrochloric acid was added, and the tub was placed in an oil bath at 80 °C. After being heated overnight, the tube was allowed to cool and an NMR spectrum was obtained: ($DCCl_3$) δ 7.35 (d, J = 2 Hz, 1), 7.18 (d, J = 2 Hz, 1), 6.11 (q, J = 2 Hz, 1), 2.44 (d, J = 2 Hz, 3), 1.49 (s, 9), 1.35 (s, 9), 1.33 (s, 3), and 1.25 (s, 3). This structure is consistent with formation of 1,3,3-trimethyl-5,7-di-*tert*-butylindene (VIII).

When VII was melted and heated neat at 210 °C for 90 min in the absence of acid, a mixture of two alkenes was formed: NMR ($DCCl_3$) δ 7.36 (m, 5 units), 7.20 (d, 3), 7.10 (d, 2), 6.11 (q, 3), 5.48 (m, 2), 5.35 (m, 2), 2.61 (t, 4), 2.48 (d, 9), and 1.50–1.25 (several sharp singlets). These data are consistent with a 3:2 mixture of the internal alkene VIII and external alkene 1-methylene-3,3-dimethyl-5,7-di-*tert*-butylindan (IX), respectively.

Support for the identity of these alkenes is provided by their hydrogenation to 1,1,3-trimethyl-4,6-di-*tert*-butylindan (X). The mixture above was subjected to hydrogenation over 10% palladium on carbon at 1 atm. The hydrogenation was followed by NMR. Those peaks due to the exocyclic olefin IX disappeared first. Then the peaks due to the internal olefin VIII began to disappear, and the indan X was obtained as the sole product: NMR ($DCCl_3$) δ 6.83 (d, J = 1 Hz, 1), 6.55 (d, J = 1 Hz, 1), 3.31 (m, 1), 2.00 (m, 1), 1.95 (m, 1), and 1.42–1.26 (m, 27). Anal. Calcd for $C_{18}H_{32}$: C, 87.02. Found: C, 87.02.

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Registry No.—I, 1460-02-2; II, 3975-77-7; IV, 66415-27-8; V, 20208-55-3; VI, 22744-29-2; VII, 68854-37-5; VIII, 68875-58-1; IX, 68854-38-6; X, 68854-39-7; benzene, 71-43-2.

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