Robinson Annelation by Reactions of 2-Methyl 1,3 Diketones with a β-Chloro Ketone

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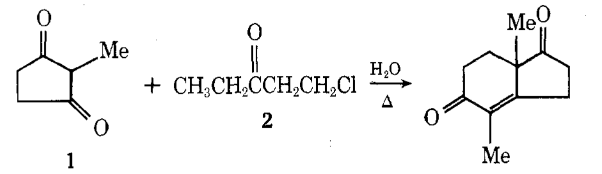
Recently we reported that octalones could be obtained by reaction of a β-chloro ketone[2] with 2-methylcyclohexanone in the presence of an acid in benzene. We now report that a Robinson annelation reaction can be achieved by reaction of 2-methylcyclopentane-1,3-dione (**1**) with 1-chloro-3-pentanone (**2**) in water to afford good yields of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione[3] (**3**). In this method the 1,3 diketone serves as an acid catalyst in the in situ generation of the vinyl ketone, and the generated HCl acts as a catalyst in both the Michael and aldol steps of the reaction.



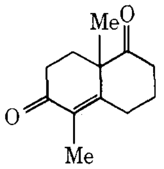
1 **2** **3**

The results of the synthesis of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (**3**) using different molar ratios of **1** and **2** are summarized in Table I. As shown in Table I, the yields of **3** range from 73 to 78%.

Table I. Indandione Formation Using Different Molar Ratios

Molar ratio 1:2	% yield of 3	
	Distilled	Chromatographed
1:1	72.6	62.2
1:1.5	78.1	68

Although the indandione **3** was obtained in good yield as described above, an identical reaction employing 2-methylcyclohexane-1,3-dione and 1-chloro-3-pentanone afforded after column chromatography only 23% of 5,8a-dimethyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione[4,5] (**4**), the major compound being the keto acid[5,6] **5** (41% yield), mp 58–61 °C (known mp 59–61 °C). The keto acid **5** presumably results from opening of the bridged[7] aldol intermediate **6** followed by dehydration of the resulting β-hydroxy ketone.



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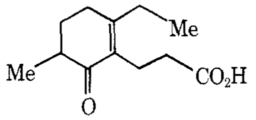

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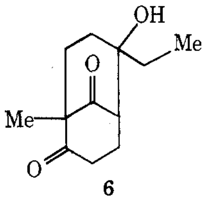

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Experimental Section

7,7a-Dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (3). 2-Methylcyclopentane-1,3-dione (2.5 g, 0.022 mol) and 1-chloro-3-pentanone (4.0 g, 0.033 mol) were added to 20 ml of H_2O. The mixture was stirred at room temperature for 4 h and then refluxed for 16 h. The reaction mixture was poured into a 10% $NaHCO_3$ solution (50 ml); water (100 ml) was added and the resulting mixture was extracted with two 100-ml portions of chloroform. The chloroform extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. Distillation of the residue gave 3.1 g (78.1%) of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (**3**), bp 94–98 °C (0.01 mm). Chromatography of the oil (3.1 g) on silica gel and elution with ether–hexane afforded 2.7 g (68%) of pure **3**: NMR (CCl_4) δ 1.30 (s, angular methyl, 3 H), 1.73 (s, 3 H), 1.78–3.09 (methylenes, 8 H); ir (neat) 1660 and 1745 cm^{-1}.

Registry No.—**1**, 765-69-5; **2**, 32830-97-0; **3**, 28255-09-6; **4**, 28255-08-5; **5**, 60065-15-8; **6**, 60065-16-9; 2-methylcyclohexane-1,3-dione, 1193-55-1.

References and Notes

(1) Undergraduate research participant.
(2) P. A. Zoretic, B. Branchaud, and T. Maestrone, *Tetrahedron Lett.*, 527 (1975).
(3) S. Swaninathon, K. G. Srinivasan, and P. S. Venkataramani, *Tetrahedron*, **26**, 1453 (1970).
(4) Authentic compound prepared by the method of G. Bauduin, H. Christol, and Y. Pietrasanta, *Bull. Soc. Chim. Fr.*, 359 (1973).
(5) Y. Kitahara, A. Yoshikoshi, and S. Oeda, *Tetrahedron Lett.*, 1763 (1964).
(6) We would like to thank Professor A. Yoshikoshi for kindly providing us with the NMR, ir, and an authentic sample of the keto acid **5**.
(7) W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960); K. D. Zwahlen, W. J. Horton, and G. I. Fujimoto, *ibid.*, **79**, 3131 (1957); V. Prelog, L. Ruzicka, P. Barman, and L. Frenkiel, *Helv. Chim. Acta*, **31**, 92 (1948).

Air Oxidation of Cyclopentadecane

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The oxidation of hydrocarbons has been thoroughly studied[1–4] and it has been found that the hydroperoxide initially formed decomposes mainly by a nonchain process to yield the alcohol plus ketone.[5] It has been suggested that the alcohol is the initial product, and the ketone is formed by further oxidation. As the reaction proceeds, the alcohol and ketone are consumed with the formation of by-products (eq 1).

$$\mathrm{RH} \xrightarrow{O_2} \mathrm{ROOH} \rightarrow \mathrm{ROH} \rightarrow \text{ketone} \rightarrow \text{by-products} \quad (1)$$

The selectivity of the oxidation of hydrocarbons to alcohol can be improved by the addition of boric acid[6] to the oxidation mixture. This increased selectivity was initially believed to be due to the formation of borate esters of the alcohols which retarded the oxidation of the alcohol and subsequent by-product formation.[4]

It has been proposed, however, that the function of boric acid (metaboric acid) is not solely to esterify the alcohols to protect them against oxidation, but to catalyze the decomposition of the hydroperoxides.[7–9] Indeed, it has been shown that the boric acid esters are as effective as boric acid itself in directing the oxidation of paraffins to alcohols in concentrations as low as 0.2% ester.[10]

In this note, we report our observations on the air oxidation of cyclopentadecane. The products are important precursors in musk synthesis.[11]

Results and Discussion

The results of some experiments on the air oxidation of cyclopentadecane are shown in Table I. The yields of alcohol and ketone from this cyclic hydrocarbon compare well with the yields of alcohol and ketone from the air oxidation of cyclododecane.[12] The results confirm previous observations that product yields and conversions in air oxidations are dependent on air flow rate, boric acid, and temperature among other variables.[4]

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Table I. Air Oxidation of Cyclopentadecane

Expt	Cyclopenta-[a] decane, mol	Boric acid,[b] wt %	Flow rate, ml min^{-1} mol^{-1}	Time of rxn, h	Temp, °C	Convn, %	Yield, %[c,d] Cyclopenta-decanone	Cyclopenta-decanol
1	0.25	5	100	2	150	12.3	8.9	77.2
2	0.25	5	100	5	150	27.9	9.3	71.3
3	0.25	5	100	3	160	21.0	5.7	84.3
4	0.25	5	100	3	170	23.7	4.2	81.0
5	0.25	5	100	6	170	42.2	7.1	58.5
6	0.25	0	100	3	150	23.3	20.8	14.0
7	0.25	0	200	7	140	25.4	25.1	17.0
8	0.71	5	564	2	165	35.8	3.5	71.0
9	0.71	5	310	2	165	34.0	7.0	70.5
10	0.71	5	140	2	165	32.3	3.3	75.2
11	0.71	5	56	5	165	40.4	5.5	72.4
12	0.25	10	100	5	140	12.0	7.4	66.9
13	0.25	10	100	3	170	23.1	3.8	72.4

[a] 99%+ cyclopentadecane twice recrystallized from methanol. [b] Mallinckrodt AR. [c] Yield determined by VPC, 5 ft × 0.125 in. 1% Carbowax on Chromosorb W (180–120 mesh). Program run of 100–160 °C at 8 °C/min. Cyclododecanone and 16-hexadecanolide were used as internal standards. [d] We did not attempt to identify all by-products (except qualitatively by ir).

Table II. Various Workup Procedures for Cyclopentadecane Air Oxidation

No.	Procedure[a]	Yield, g[b] Cyclopenta-decane	Cyclopenta-decanone	Cyclopenta-decanol	Material balance[c]
1	Dissolve in hexane, filter solid[d]	6.92	0.11	1.72	88
2	Dissolve in hexane, wash 10% NaOH, workup	6.74	0.11	1.66	85
3	Dissolve in hexane, wash 20% NaOH, workup	6.34	0.11	1.66	81
4	Stir with 20% NaOH 80 °C 15 min, workup	6.54	0.09	1.68	82
5	Stir with 20% NaOH 80 °C 30 min, workup	6.38	0.10	1.78	83

[a] Reaction conditions same as those of expt 3, Table I. [b] Yield determined by VPC. See footnote *c*, Table I. [c] From 10–15% by-products (acids, polyhydroxy compounds) also present. [d] The solid has mp 197–200 °C. Metaboric acid exists in three modifications having mp 236, 200.9, and 176 °C. Orthoboric acid has mp 170.9 °C. See ref 16.

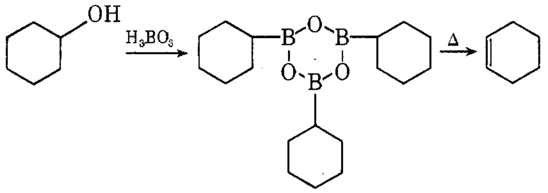
It is apparent from the table that (a) boric acid is necessary for good yields and high conversion to the alcohol; (b) an increase in concentration of boric acid over 5 wt % does not result in improved yields; (c) very high air flow rates are not necessary for good yields and high conversion (although conversion may be slightly faster).

We could detect no hydroperoxide (iodometric titration) when the air oxidation was carried out in the presence of boric acid at 150 °C. In the absence of boric acid (150 °C) a maximum of 6% (of theory) hydroperoxide is formed after 2 h. This rapidly decreases to less than 1% at 3 h. If the maximum of 6% hydroperoxide is added to the yields of products (Table I, expt 6), the total yield of products still falls short of the product yields for the air oxidation in the presence of boric acid.

The experiments were conducted according to the conditions in Table I and worked up by cooling to 80–90 °C, adding 20% sodium hydroxide or water, and refluxing for 1 h. Solvent was then added to the mixture, aqueous and organic phases were separated, and the organic phase was dried and weighed. The products were then determined by VPC.

One air oxidation mixture was split into equal portions and worked up according to the procedures shown in Table II. The yields were determined by VPC. It is immediately obvious that, for the air oxidation of cyclopentadecane under the conditions reported here, *the main portion of the alcohol is not present as a borate ester*. However, boric acid is necessary for high yields of alcohol. Also one cannot discard the possibility that *traces* of borate ester may be present.

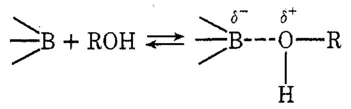
It may be reasonably argued that the borate ester cracks on the VPC column to yield the alcohol, but it is unlikely that this occurs. O'Connor and Nace have shown the borate esters decompose at high temperatures to give olefins in high yield (eq 2).[13,14]



(2)

The results presented here support the rationalization that the function of boric acid (or traces of borate ester[10]) is to catalyze the decomposition of the hydroperoxide to give mainly the alcohol.[15] Consequently, the hydroperoxide is never at a high concentration, and oxidation of the alcohol and ketone to by-products is suppressed. By-products may also arise from the hydroperoxide itself (at high concentration).[4]

We have noted in the air oxidation of cyclopentadecane that as the air oxidation progresses, the metaboric acid goes into solution. If a weak complex is formed (eq 3) or hydrogen



$$>B + ROH \rightleftharpoons >\overset{\delta^-}{B}\text{---}\underset{\displaystyle H}{\overset{\delta^+}{\underset{|}{O}}}\text{—}R \qquad (3)$$

bonding occurs, this may help prevent oxidation of the alcohol.[17] Addition of a nonpolar solvent would precipitate the metaboric acid (Table II).

Experimental Section

A 100-ml resin flask was fitted with a heated water condenser (~65 °C), a mechanical stirrer (600 rpm), a fritted glass gas addition tube (25–50 μ pore size), and a thermometer. Cyclopentadecane (99%, 52.6 g, 0.25 mol) and 2.5 g of boric acid were placed in the flask and the reaction mixture heated slowly to 150–155 °C. The water present was driven off with the aid of air or nitrogen. The mixture was then heated to a given temperature (±2 °C) and air bubbled through the molten hydrocarbon for the required time. The reaction mixture was then cooled to ~95 °C and 25 ml of water added. (For the experiments in Table II only hexane was added.) After stirring at 95 °C for 1 h, the reaction mixture was cooled and hexane added. The mixture was transferred to a separatory funnel and the aqueous and organic layers separated. The organic phase was washed with water once more, weighed, and analyzed by VPC according to the conditions given in footnote *c*, Table I.

Registry No.—Cyclopentadecane, 295-48-7; cyclopentadecanone, 502-72-7; cyclopentadecanol, 4727-17-7.

References and Notes

(1) C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957.
(2) W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966.
(3) G. A. Russell, *J. Chem. Educ.*, **36**, 111 (1959).
(4) N. M. Emanuel, E. T. Denison, and Z. K. Maizus, "Liquid Phase Oxidation of Hydrocarbons", Plenum Press, New York, N.Y., 1967.
(5) Reference 4, p 344.
(6) Boric acid exists as metaboric acid at 140–170 °C under the conditions of most air oxidations.
(7) A. N. Bashkirov, *Khim. Nauka Promst.*, **1**, 273 (1956).
(8) Y. B. Chertkov, *Zh. Prikl. Khim.*, **32**, 363 (1959).
(9) B. G. Freiden, *J. Appl. Chem. USSR (Engl. Transl.)*, 1263 (1954).
(10) D. Dimitrov, S. Voynova, and N. Pencev, *C. R. Acad. Bulg. Sci.*, **19**, 811 (1966).
(11) P. Z. Bedoukian, *Am. Perfum. Cosmet.*, **80**, 23 (1965).
(12) F. Broich and H. Grasemann, *Erdoel Kohle*, **18**, 360 (1965).
(13) G. L. O'Conner and H. L. Nace, *J. Am. Chem. Soc.*, **77**, 1578 (1955).
(14) A reviewer has suggested that the following reactions may occur on the VPC column:

$$(ROBO)_3 \rightarrow B_2O_3 + (RO)_3B$$
$$2(RO)_3B + H_3BO_3 \rightarrow (ROBO)_3 + 3ROH$$

We feel that these reactions are not significant here for the following reasons: (a) The metaboric acid (expt 1, Table II) was filtered before analysis. (b) No significant tailing of the alcohol peak was observed (which should occur if the above reactions take place on the column). (c) In the presence of boric acid, significant quantities of the olefin[13] should be observed, lowering the yield of the alcohol. Cyclopentadecene was not observed as a significant product.
(15) P. F. Wolf and R. K. Barnes, *J. Org. Chem.*, **34**, 3441 (1969).
(16) N. P. Nies and G. W. Cambell in "Boron, Metallo-Boron Compounds and Boranes", R. M. Adams, Ed., Interscience, New York, N.Y., 1964.
(17) See review for discussion of various suggested mechanisms: W. G. Woods and R. J. Brotherton, *Prog. Boron Chem.*, **3**, 1 (1970).

Synthesis of Authentic Tri-*O*-benzylphloroglucinol

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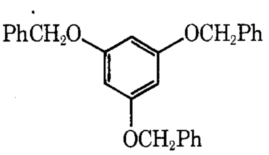
It is surprising that such a simple compound as the tri-*O*-benzyl ether of phloroglucinol, allegedly prepared first in 1900, has actually been synthesized as a pure, individual compound only in the present work.

The tribenzylphloroglucinol (mp 39–41 °C) reported by Kaufler[1] and quoted in the literature as such[2,3] is a mixture of several components as shown by repetition of the description[1] and TLC of the product.

Tri-*O*-benzylphloroglucinol (**1**), which is a promising intermediate in the synthesis of specially substituted flavonoids and *C*-methyl flavonoids, is obtainable by benzylation of phloroglucinol in the presence of sodium hydride. Separation from the by-product, *C*-benzyltri-*O*-benzylphloroglucinol (2,4,6-tribenzyloxydiphenylmethane) (**2**), has been achieved by TLC and column chromatography.



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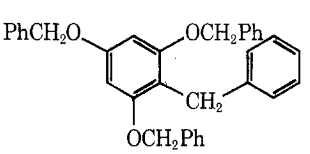

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Rather simple spectra were obtained by NMR as evidence for the structures of **1** and **2**. These were verified by MS data.

Hydrogenation of the compound **1** in the presence of 10% Pd on carbon in glacial acetic acid yielded the starting material (phloroglucinol) which proved to be identical according to ir, TLC, and melting point with the authentic phloroglucinol.

Experimental Section

Benzylation of Phloroglucinol in the Presence of NaH. A 50% dispersion of sodium hydride in oil (1.44 g, 720 mg of NaH, 30 mmol) was gradually added to a stirred solution of anhydrous phloroglucinol (1.26 g, 10 mmol) in dimethyl sulfoxide (40 ml). After the evolution of hydrogen had ceased, benzyl chloride (3.6 ml, 30 mmol) was added to the reaction mixture. The temperature rose to about 50 °C. After stirring for about 40 min, the greenish suspension was then poured on ice (400 g), and allowed to stand overnight. The yellow powder (1.06 g) which precipitated was recrystallized from ethanol to give white needles (300 mg), mp 76–78 °C. This product was a mixture of two compounds (**1** and **2**) as shown by TLC in a 60:40 benzene–petroleum ether (bp 60–80 °C) mixture (R_f 0.6 and 0.7). Separation of this mixture by preparative TLC yielded pure tribenzylphloroglucinol, mp 96–97 °C (from ethanol), R_f 0.6, and *C*-benzyl-tri-*O*-benzylphloroglucinol, mp 101–103 °C (from ethanol), R_f 0.7. The two compounds were also separated on a silica gel column (0.05–0.20 mm) with the above solvent mixture.

$C_{27}H_{24}O_3$ (396) (compound **1**): m/e 396 (M^+), 91 (base); NMR ($CDCl_3$, Me_4Si) δ 5.13 (s, 6, OCH_2), 6.43 (s, 3, ArH), 7.57 (s, 15, ArH).

$C_{34}H_{30}O_3$ (486) (cmmpound **2**): m/e 486 (M^+), 91 (base); NMR ($CDCl_3$, Me_4Si) δ 4.21 (s, 2, $ArCH_2$), 5.16 (s, 2, OCH_2), 5.18 (s, 4, OCH_2), 6.49 (s, 2, ArH), 7.37–7.57 (m, 20, ArH).

Catalytic Debenzylation of Tri-*O*-benzylphloroglucinol. Pd/carbon (10%, 114 mg) in glacial acetic acid (20 ml) was prehydrogenated, then a solution of tribenzylphloroglucinol (63 mg, 0.16 mmol) in glacial acetic acid (10 ml) was added and the hydrogenation was continued at room temperature; 11 ml of hydrogen was absorbed (theoretical 11.5 ml). The catalyst was removed and the solution evaporated to dryness to obtain a product (18 mg), mp (after drying at 110 °C) 211–216 °C (lit. 219 °C) (anhydrous phloroglucinol), which proved to be identical with authentic phloroglucinol (TLC, ir).

Registry No.—1, 59434-20-7; **2,** 59434-21-8; phloroglucinol, 2041-15-8.

References and Notes

(1) F. Kaufler, *Monatsh. Chem.*, **21**, 993 (1900).
(2) "Beilsteins Handbuch der Organischen Chemie", Vol. 6, 1923, p 1103.
(3) I. Heilbron et al., Ed., "Dictionary of Organic Compounds", Vol. 5, 4th ed, Eyre and Spottiswoode, London, 1965, p 2737.

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A Simple Method for Converting Nitriles to Amides. Hydrolysis with Potassium Hydroxide in *tert*-Butyl Alcohol

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Many years ago it was reported that nitriles could easily be converted into amides by heating them in weakly basic medium in the presence of hydrogen peroxide.[1–3] Treatment of a nitrile with sodium hydroxide and hydrogen peroxide in aqueous ethanol has become a standard synthetic[4] and qualitative analytical procedure.[5]