methyl, phenyl) followed by catalytic reduction, pyrimidine amino alcohols have been prepared in which the side chain $CHOHCH_2CH_2NR_2$ ($-NR_2$ = dimethylamino, diethylamino) is located at the five position.

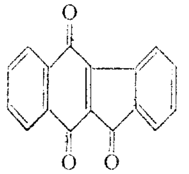
CORVALLIS, OREGON RECEIVED MAY 21, 1945

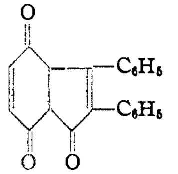
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

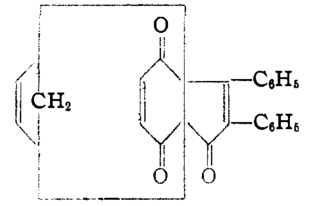
1-Keto-2,3-diphenylindene-4,7-quinone[1]

BY C. F. KOELSCH AND E. J. PRILL

Certain properties of 9-keto-2,3-benzofluorene-1,4-quinone (I)[2] indicated that it would be interesting to study a simpler substance in which a quinoid and a ketocyclopentene ring were fused together. The present paper reports the results of such a study, the compound prepared and studied being 1-keto-2,3-diphenylindene-4,7-quinone (II).


I


II


III

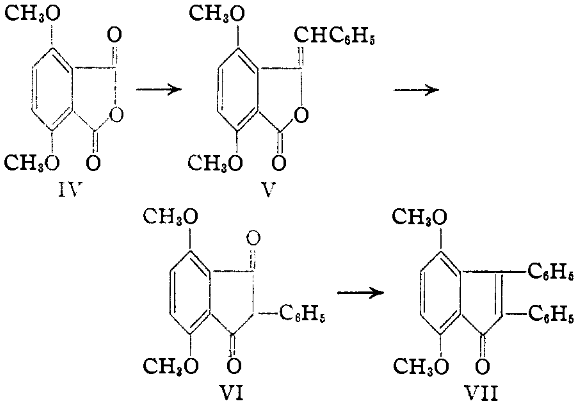
The solid quinone is a yellow crystalline substance, probably a polymer, but in acetic acid or benzene it forms a red solution that becomes purple when it is warmed. Cryoscopic determinations in benzene showed that the solution contains the monomeric quinone; the monomeric nature of the quinone in solution is also indicated by the formation of 4,7-dihydroxy-2,3-diphenylindone by reaction with benzohydroquinone. In benzene the quinone reacts with cyclopentadiene almost immediately, forming a crystalline adduct, presumably III, since it is yellow and not red as are compounds containing a cyclic crossed conjugated system.

In acetic acid, the quinone has a normal oxidation–reduction potential of 0.835 v. Comparison of this value with that reported previously[3] for benzoquinone in acetic acid (0.650 v.), and with that determined in the present research for I (0.623 v.), indicates that fusion of a cyclopentenone ring with a quinone nucleus raises the oxidation potential of the latter by 0.185 v. This increase is nearly independent of the substituents attached to the 2,3-positions of the cyclopentenone ring, for the difference between the oxidation potentials of I and II (0.212 v.) is approximately equal to the usual lowering (0.224 v.)[4] caused by fusion of a benzene ring with a quinone nucleus.

Experimental

The quinone II was obtained through the hydroquinone XIII, from 4,7-dimethoxy-2,3-diphenylindone (VII). This in turn was obtained in three ways.

The first route to VII involved the reactions



2,3-Dicyanohydroquinone was obtained in 66% yield from 20 g. of quinone and in 50% yield from 100 g. of quinone by the method of Thiele and Meisenheimer,[5] and in 55% yield from 33 g. of quinone by the method of Helferich.[6] The latter preparation is of some interest in view of reports[7] of the complete failure of this relatively inexpensive procedure. From the sodium salt of the hydroquinone and methyl sulfate in water, a 29% yield of 3,6-dimethoxyphthalonitrile was obtained. But when the methylation was carried out in dry xylene using excess methyl sulfate, the excess being subsequently destroyed by boiling for one hour with sodium hydroxide, there was obtained 62.5% of 3,6-dimethoxyphthalonitrile and 24% of 3,6-dimethoxyphthalic anhydride. The nitrile was best hydrolyzed by boiling 20 g. of it with 50 g. of potassium hydroxide in 100 ml. of butyl alcohol and 25 ml. of water for five hours, a yield of 77% of sublimed 3,6-dimethoxyphthalic anhydride (IV), m. p. 261–263° (reported[7a] 259–261°) being obtained.

A mixture of 9.7 g. of 3,6-dimethoxyphthalic anhydride, 9 g. of phenylacetic acid, and 0.5 g. of potassium acetate was heated in an oil-bath at 215–220° for two hours.

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[1] From the Ph.D. Thesis of E. J. Prill, July, 1941.

[2] Koelsch, THIS JOURNAL, **67**, 159 (1945).

[3] Conant and Chow, *ibid.*, **55**, 3745 (1933). This figure was checked in the present investigation.

[4] Conant and Fieser, *ibid.*, **46**, 1864 (1924); Fieser and Dietz, *ibid.*, **53**, 1132 (1931). The figure is an average between the one obtained in water (0.229) and the one obtained in alcohol (0.218).

[5] Thiele and Meisenheimer, *Ber.*, **33**, 675 (1900).

[6] Helferich, *ibid.*, **54**, 155 (1921).

[7] (a) Graves and Adams, THIS JOURNAL, **45**, 2439 (1923); (b) Allen and Wilson, *ibid.*, **63**, 1756 (1941).

There was obtained 7.2 g. of **3-benzal-4,7-dimethoxyphthalide (V)**, yellow needles from acetic acid, m. p. 193.5–195°.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 71.9; H, 4.7.

When 11 g. of V was boiled for two hours with sodium methoxide from 1.5 g. of sodium in 300 ml. of methanol, it yielded 10 g. of **4,7-dimethoxy-2-phenylindandione-1,3 (VI)**, pale yellow needles from xylene, m. p. 240–242°.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.3; H, 5.0. Found: C, 72.6; H, 5.3.

A solution of 7.5 g. of VI in 50 ml. of benzene was boiled for two hours with 45 ml. of 2.6 *N* phenylmagnesium bromide. The mixture was decomposed with iced sulfuric acid, and biphenyl, etc., was removed with steam. The residue was boiled for a few minutes with acetic acid containing 1% sulfuric acid and then distilled at 12 mm. Crystallization from toluene gave **4,7-dimethoxy-2,3-diphenylindone (VII)**[8] in good yield, red prisms and needles, m. p. 182–183°.

Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.7; H, 5.3. Found: C, 81.0; H, 5.1.

From the mother liquor there was obtained a small amount of **4,7-dimethoxy-1,2,3-triphenylindandiol-1,3**, fine white needles from alcohol, m. p. 216–217°.

Anal. Calcd. for $C_{29}H_{26}O_4$: C, 79.5; H, 6.0. Found: C, 79.4; H, 6.0.

When this glycol (0.05 g.) was boiled with 5 ml. of 5% alcoholic sulfuric acid for ninety minutes, it was dehydrated and etherified, giving **1-ethoxy-4,7-dimethoxy-1,2,3-triphenylindene** (0.03 g.), colorless plates from alcohol, m. p. 157–158°.

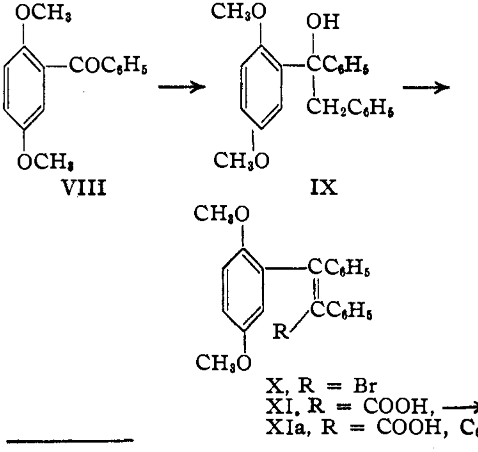
Anal. Calcd. for $C_{31}H_{28}O_3$: C, 83.0; H, 6.3. Found: C, 83.1; H, 6.6.

The structure of this ethoxy compound was established by a second synthesis. 4,7-Dimethoxy-2,3-diphenylindone (VII, 3.4 g.) with excess phenylmagnesium bromide gave **4,7-dimethoxy-1,2,3-triphenylindenol** (3.8 g.), colorless prisms from a mixture of chloroform and alcohol, m. p. 176–177°.

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 82.2; H, 5.7. Found: C, 82.6; H, 5.9.

When this indenol was boiled for a few minutes with 1% alcoholic sulfuric acid, it gave 1-ethoxy-4,7-dimethoxy-1,2,3-triphenylindene, colorless plates, m. p. 157–158° alone or mixed with the ether described above.

The second route to 4,7-dimethoxy-2,3-diphenylindone (VII) involved the reactions



VIII IX

X, R = Br

XI, R = COOH, ⟶ VII

XIa, R = COOH, C_6H_5's *trans*

Treatment of 2,5-dimethoxybenzophenone (VIII, 150–175 g.) with benzylmagnesium chloride furnished **IX**, m. p. 110–110.5° (reported[9] 110°) in a yield of 88% when two equivalents or 79% when one equivalent of Grignard reagent was used. Contrary to the statement of Kaufmann, dehydration of IX (10 g.) with ethereal hydrogen chloride did not yield a single product of m. p. 82°, but a mixture of two forms of **α-(2,5-dimethoxyphenyl)-α,β-diphenylethylene (X, R = H)**, probably stereoisomers. These were separated mechanically and crystallized from ether–ligroin, giving 6.9 g. of cubic crystals, m. p. 85.5–86.5°, and 1.8 g. of needles, m. p. 82.5–83.5°. A mixture of the two forms melted completely when it was placed in a bath at 63°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.5; H, 6.3. Found: (cubes) C, 83.7; H, 6.2; (needles) C, 83.4; H, 6.8.

When either of the ethylenes was treated with bromine in cold acetic acid, hydrogen bromide was evolved and a mixture of products was formed. The same mixture was obtained when 33 g. of the carbinol IX was warmed with 17 g. of bromine in 90 ml. of acetic acid. In the latter case there were isolated several grams of an alkali-soluble substance, not further investigated, 2 g. of the bromide X, m. p. 118–119° previously described by Kaufmann, 10 g. of an oily bromide, b. p. *ca.* 245° at 0.1 mm., and 14 g. of a **substance,** colorless cubes from chloroform and alcohol, m. p. 143.5–144.5°, which was apparently an unresolvable complex of the bromide X with a higher bromination product.

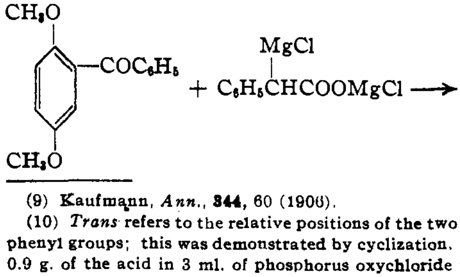
Anal. Calcd. for $C_{22}H_{19}BrO_2 + C_{22}H_{18}Br_2O_2$: C, 61.0; H, 4.3. Found: C, 60.8, 60.7; H, 4.3, 4.5.

Each of the two latter substances (10 g.) yielded a Grignard reagent when it was warmed and stirred for three hours with 1.9 g. of magnesium in 150 ml. of ether containing 4 ml. of ethyl bromide. The solutions were carbonated with solid carbon dioxide, that from the oily bromide giving 35% and that from the complex giving 40–74% of crude acidic product. The crude products (8.8 g.) from several experiments were combined and crystallized from carbon tetrachloride and then from acetic acid, giving faintly colored cubes (2.9 g.) of ***trans***[10]**-β-(2,5-dimethoxyphenyl)-α,β-diphenylacrylic acid** (XI a), m. p. 213.5–215°.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.7; H, 5.6. Found: C, 76.3; H, 5.8.

The material remaining in the mother liquor was the desired *cis*-acid XI. It crystallized poorly, and was converted directly into the indone VII by allowing a solution of 0.8 g. of it in excess phosphorus oxychloride to stand for ten minutes. The resulting 4,7-dimethoxy-2,3-diphenylindone was washed with aqueous potassium hydroxide and crystallized from toluene, giving red prisms, m. p. 182–183° alone or mixed with the substance obtained from the first series of reactions.

The third route to VII was the most satisfactory for large scale preparations of the compound. It involved the reactions



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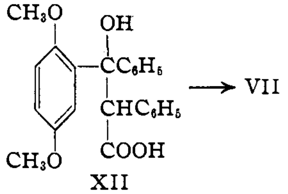
[8] When 1 g. of the indone in 24 ml. of acetic acid was warmed at 100° for one hour with 0.65 g. of chromic anhydride in 6 ml. of water, it was converted into **2-benzoyl-3,6-dimethoxybenzil**, pale yellow plates (0.8 g.) from alcohol, m. p. 168–169°. *Anal.* Calcd. for $C_{23}H_{18}O_5$: C, 73.8; H, 4.8. Found: C, 73.8; H, 5.2.

The triketone condensed readily with alcoholic *o*-phenylenediamine, giving **2′-benzoyl-3′,6′-dimethoxy-2,3-diphenylquinoxaline**, colorless prisms from alcohol, m. p. 206–207°. *Anal.* Calcd. for $C_{29}H_{22}N_2O_3$: C, 78.0; H, 4.9. Found: C, 78.1; H, 5.1.

[9] Kaufmann, *Ann.*, **344**, 60 (1906).

[10] *Trans* refers to the relative positions of the two unsubstituted phenyl groups; this was demonstrated by cyclization. A solution of 0.9 g. of the acid in 3 ml. of phosphorus oxychloride was boiled for three minutes, then poured into water. Extraction of the gum with alcohol, distillation, and crystallization from alcohol gave 0.2 g. of **3-(2,5-dimethoxyphenyl)-2-phenylindone,** orange-yellow prisms, m. p. 132–133°. *Anal.* Calcd. for $C_{23}H_{18}O_3$: C, 80.7; H, 5.3. Found: C, 80.3; H, 5.4.



XII

A solution of 120 g. of phenylacetic acid in 1400 ml. of dry toluene was added to the Grignard reagent from 160 g. of isopropyl chloride and 48 g. of magnesium in 900 ml. of ether.[11] About 500 ml. of the solvent was distilled, then 235 g. of 2,5-dimethoxybenzophenone in 900 ml. of toluene was added, and the mixture was boiled for five hours. Iced sulfuric acid was then added, and the crude acidic product XII (249 g., 75%) was removed from the organic layer with dilute sodium carbonate. From the neutral material there was recovered 60 g. of dimethoxybenzophenone.

Fractional crystallization of a portion of the crude **β-(2,5-dimethoxyphenyl)-α,β-diphenylhydracrylic acid** (XII) from alcohol and carbon tetrachloride showed that it consisted of two forms (diastereoisomeric). The less soluble form, colorless needles, melted at 188–190° dec., or at 191–193° dec., in a bath pre-heated to 185°.

Anal. Calcd. for $C_{23}H_{22}O_5$: C, 73.0; H, 5.8. Found: C, 72.9; H, 6.0.

The more soluble form, colorless needles containing carbon tetrachloride, melted with effervescence in a bath preheated to 110°, then resolidified and melted at 165–167°. When the substance was dried at 100° under reduced pressure, it fell to a powder, m. p. 165–167°.

Anal. Calcd. for $C_{23}H_{22}O_5$ + 0.5 CCl_4: C, 61.9; H, 4.8. Found: C, 61.3; H, 4.9. Calcd. for $C_{23}H_{22}O_5$: C, 73.0; H, 5.8. Found: C, 72.6; H, 6.0.

A mixture of 130 g. of crude XII, 130 ml. of benzene, and 130 ml. of phosphorus oxychloride was kept at 20° for one hour, allowed to stand at room temperature (35°) for four hours, and then poured into water. The benzene was removed with steam, the solid remaining was washed with water and stirred with ether and dilute potassium hydroxide. The indone VII, m. p. 181–182°, remained undissolved; yield 65–80 g. (55–68%).

From the alkaline extract, there was obtained 16 g. of a mixture, separated by fractional crystallization from alcohol and then acetic acid into *trans-* (m. p. 213–215°) and ***cis*-β-(2,5-dimethoxyphenyl)-α,β-diphenylacrylic acid** (XI), colorless needles, m. p. 168.5–169.5°.

Anal. Calcd. for $C_{23}H_{20}O_4$: C, 76.7; H, 5.6. Found: (*cis*) C, 76.2; H, 5.7.

These acids had been encountered previously as intermediates in the second route to VII, but the *cis* acid was not then purified. It was verified that the present samples yielded the corresponding indones on cyclization.

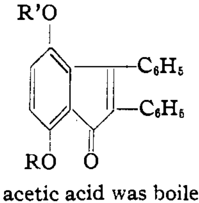
Fractional distillation and fractional crystallization of the neutral material remaining from the cyclization of XII furnished 5.1 g., m. p. 83–84°, and 0.25 g., m. p. 80–81°, of the two forms of α-(2,5-dimethoxyphenyl)-α,β-diphenylethylene (X, R = H). There was also obtained 6.8 g. of 3-(2,5-dimethoxyphenyl)-2-phenylindone, orange prisms, m. p. 133–134°, previously obtained from the *trans*-acid XIa.[10] A seventh product, always obtained in small amount (0.2–0.4 g.) in the cyclization of XII, and separated mechanically from the crystals of the preceding indone, was **6-methoxy-3,4-diphenylcoumarin**,[12] colorless flat needles from alcohol, m. p. 155.5–156.5°.

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.5; H, 4.9. Found: C, 80.3; H, 5.0.

The structure of the coumarin was verified by methylating the compound. Treated with excess alcoholic potassium hydroxide and methyl sulfate, it furnished **methyl *cis*-β-(2,5-dimethoxyphenyl)-α,β-diphenylacrylate**, fine white needles from methanol, m. p. 111.5–112.5°. The same ester was obtained by similar methylation of the acid XI.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 77.0; H, 5.9. Found: C, 77.0; H, 5.8.

4,7-Dihydroxy-2,3-diphenylindone (XIII).—A mixture of 34.2 g. of VII, 100 ml. of 48% hydrobromic acid, and 340 ml. of acetic acid was boiled for twenty-five hours and then cooled. The product was crystallized from acetic acid, giving dark red flat needles (30 g., 95%), m. p. 219–221°.



XIII, R = R' = H
XIV, R = H, R' = CH_3

Anal. Calcd. for $C_{21}H_{14}O_3$: C, 80.3; H, 4.5. Found: C, 79.7; H, 4.8.

4,7-Diacetoxy-2,3-diphenylindone, obtained from XIII with acetic anhydride containing a little sulfuric acid at room temperature, formed dark yellow crystals from alcohol, m. p. 164–165°.

Anal. Calcd. for $C_{25}H_{18}O_5$: C, 75.4; H, 4.5. Found: C, 75.5; H, 4.7.

When the demethylation of VII with hydrobromic acid–acetic acid was carried out during a shorter time (two to eight hours), a mixture of XIII with **7-hydroxy-4-methoxy-2,3-diphenylindone (XIV)**, red needles from acetic acid, m. p. 212–213.5°, was obtained.

Anal. Calcd. for $C_{22}H_{16}O_3$: C, 80.5; H, 4.9. Found: C, 80.4; H, 5.1.

The monomethyl ether (XIV) formed a red potassium salt, nearly insoluble in water, which was useful in separating the compound from XIII, whose purple potassium salt is easily soluble in water.

1-Keto-2,3-diphenylindene-4,7-quinone (II).—The conversion of XIII to II could not be accomplished with ferric chloride or with potassium nitrate in acetic acid, but lead tetraacetate was a satisfactory oxidizing agent.

A suspension of 1 g. of XIII in 50 ml. of toluene was shaken with 1.42 g. of finely powdered lead tetraacetate. The purple solution was filtered and then cooled in Dry Ice. The resulting light brown amorphous precipitate (0.7 g.) was dissolved in ether and precipitated by the cautious addition of ligroin (28–38°), giving fine yellow needles that slowly darkened when heated, and became brown and melted above 280°. The quinone was obtained in the form of yellow-brown prisms, m. p. above 280°, when its solution in benzene was diluted with ligroin.

Anal. Calcd. for $C_{21}H_{12}O_3$: C, 80.8; H, 3.8; mol. wt., 312. Found: C, 80.7; H, 3.6; mol. wt. (cryoscopic in benzene), 304.

A purple solution of 0.1 g. of the quinone in benzene was treated with 0.04 g. of benzohydroquinone. The benzene and benzoquinone were removed with steam; the red crystalline residue melted at 216–218° alone, or at 217.5–219° when mixed with pure XIII.

A solution of 0.25 g. of the quinone in benzene (75 ml.) became light yellow immediately when 0.1 g. of cyclopentadiene was added. The solution was distilled to 10 ml., and the product was precipitated with ligroin. Crystallization from alcohol gave the **adduct III** (0.22 g.), bright yellow prisms that melted to a red liquid at 188°.

Anal. Calcd. for $C_{26}H_{18}O_3$: C, 82.5; H, 4.8. Found: C, 82.6; H, 5.0.

A yellow addition product was formed from II and butadiene, but it was too unstable to be recrystallized.

Oxidation–reduction measurements were made using a thermionic amplifier between the cell and the potentiom-

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[11] Ivanoff, *Bull. soc. chim.*, [4] **49**, 377 (1931); [5] **4**, 683 (1937).

[12] This coumarin (20 mg.) was also obtained when 0.5 g. of the crude acid XI from the bromide X was boiled for one hour with 0.3 ml. of 48% hydrobromic acid and 0.9 ml. of acetic acid.

eter to avoid polarization and difficulties caused by high resistance of the cell. Potentials were measured at 27° between a saturated calomel electrode and a bright platinum electrode; the latter was immersed in an equimolecular mixture of quinone and hydroquinone at a concentration of about 4 × 10^{-5} molar in buffers prepared according to Conant and Chow.[3] The data are presented in Table I. From graphs of these data, values of E^0_h at $(pH)_{AcOH}$ = 0 were determined. They are, for benzoquinone, 0.650 v.; for I, 0.623 v.; for II, 0.835 v.

TABLE I

POTENTIOMETRIC MEASUREMENTS

Quinone	Buffer[a]	$(pH)_{AcOH}$	E^0_h, v.[b]
Benzoquinone	1	4.24	0.408
	3	2.38	.528
	10	−0.98	.703
1	1	4.24	.371
	3	2.38	.488
	6	1.00	.571
	10	−0.98	.670
II	1	4.24	.588
	3	2.38	.703
	6	1.00	.784
	10	−0.98	.883

[a] Buffer numbers correspond to those used by Conant and Chow. [b] $E^0_h = E_{cell} + 0.098$ v.

Potentiometric titration at 28° of 20 ml. of a solution of the hydroquinone corresponding to I (13.1 mg., 75 ml. of alcohol, 0.7 g. of lithium chloride, 4.0 ml. of concd. hydrochloric acid, and sufficient water to make 100 ml.) with 0.0139 *N* ceric sulfate gave a curve (end-point, 1.44 ml. oxidant) at the mid-point of which $E = E_{cell} + E_{s.c.e.} = 0.398 + 0.246 = 0.644$ v. Titration of a similar solution of benzohydroquinone gave a curve (end-point, 1.41 ml. oxidant) with mid-point $E = 0.687$ v., whence, using 0.710 v.[13] as E_0 for benzoquinone in 75% alcohol at 28°, the *p*H at the mid-point was 0.4. With $E = E_0 - \frac{RT}{F}pH$, and assuming the mid-point *p*H to be the same in both titrations, I had $E_0 = 0.668$ v. in 75% alcohol.

Summary

Three methods of synthesizing 4,7-dimethoxy-2,3-diphenylindone are described. Demethylation of this substance and oxidation of the resulting dihydroxy compound yields 1-keto-2,3-diphenylindene-4,7-quinone. The quinone is yellow and presumably polymeric in the solid state, but its solutions are red and contain the monomer. It readily forms a 1:1 adduct with cyclopenta diene, and it has the high oxidation potential of 0.835 v.

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[13] Conant and Fieser, THIS JOURNAL, 44, 2489 (1922).

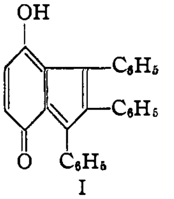
MINNEAPOLIS, MINNESOTA RECEIVED APRIL 30, 1945

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

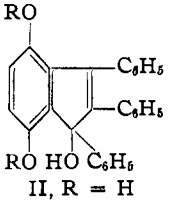
The Reaction of Phenylmagnesium Bromide with 4,7-Dihydroxy-2,3-diphenylindone[1]

BY C. F. KOELSCH AND E. J. PRILL

In order to investigate the possibility of forming a trans-nuclear quinoid compound (I) related to indene, it was desired to obtain 1,2,3-triphenylindenetriol-1,4,7 (II). The project had to be abandoned, however, for II could not be prepared either by demethylation of 4,7-dimethoxy-1,2,3-triphenylindenol-1 (III),[2] or by the action of phenylmagnesium bromide on 4,7-dihydroxy-2,3-diphenylindone.

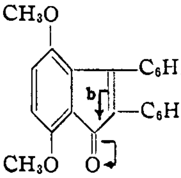


I

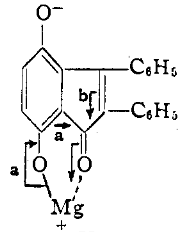


II, R = H
III, R = CH_3

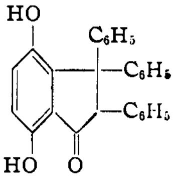
Demethylation failed because of the formation of tarry substances from III and strong acids. The Grignard synthesis failed because only 1,4-addition occurred, giving VI. This 1,4-addition was surprising in view of the exclusive 1,2-addition of phenylmagnesium bromide to all 2,3-diarylindones hitherto studied. But formulas IV and V indicate a possible explanation for the difference in behavior of the two compounds represented.



IV



V



VI

In IV, process b is weakened by conjugation with the phenyl groups, and the principal cationoid center is developed on C_1. In V, however, the cationoid properties of C_1 are largely neutralized by the strong resonance a, leaving C_3 as the main, even though still weak, cationoid center.

Experimental

No new C–C linkage was formed when phenylmagnesium bromide reacted with 4,7-dihydroxy-2,3-diphenylindone in ether, and decomposition of the complex gave back the indone. The reaction was carried out under forcing conditions. A warm solution of 1.57 g. of the indone in 100 ml. of toluene was treated with 12 ml. of 2 *N* phenylmagnesium bromide. The mixture was boiled for fifteen minutes, and then decomposed with iced acid. The solvents and biphenyl were removed with steam in the presence of a little sodium hydrosulfite, and the residue was crystal-

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[1] From the Ph.D. Thesis of E. J. Prill, July, 1941.

[2] Koelsch and Prill, THIS JOURNAL, 67, 1296 (1945).