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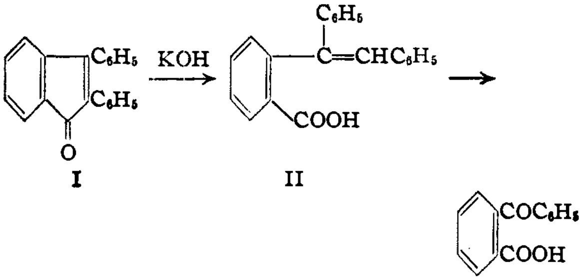
The Formation of 1,3-Diphenylisobenzofuran from 2,3-Diphenylindone

By C. F. H. Allen and J. A. VanAllan

In earlier papers[1,2] it has been shown that alcoholic alkaline reagents give two types of reaction with carbonyl bridge compounds, depending on the nature of the substituent groups at the ends of the bridge. When these groups are phenyl, the bridge is cleaved at one end, a carboxylic acid resulting, whereas the presence of methyl groups favors a reduction of the carbonyl to carbinol. It seemed desirable to learn the behavior of a simpler phenylated ketone with the same sort of reagent.

2,3-Diphenylindone (I) was selected for study, since so many of the possible reaction products were at hand from our earlier work. It was previously known that, upon fusion with potassium hydroxide, the ring is cleaved, with consequent formation of *o*-α,β-diphenylvinylbenzoic acid (II).[3]

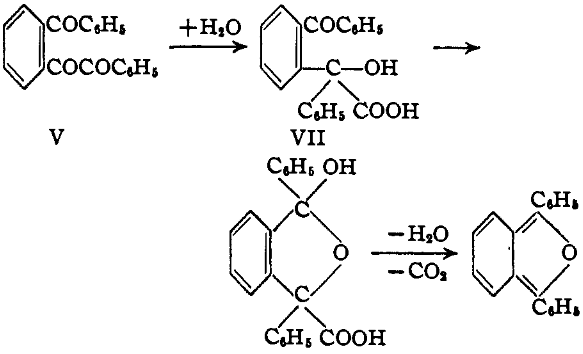


I II III

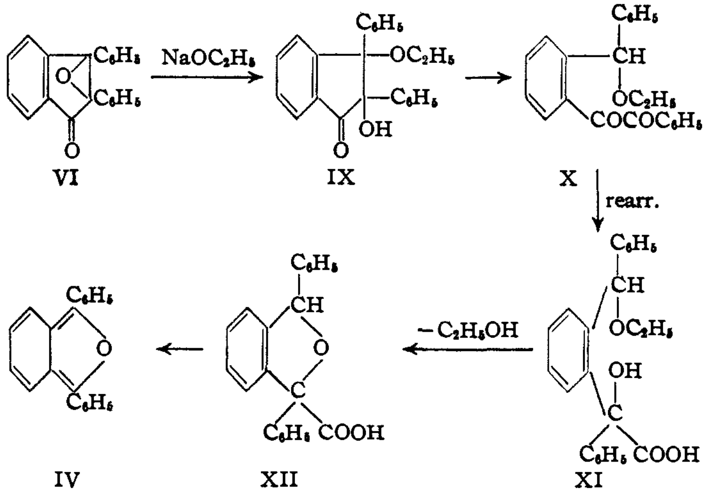
We found that cleavage takes place at the same point when a cymene solution of 2,3-diphenylindone is boiled with sodium amide. Under these conditions, however, the unsaturated acid was not isolated; instead, degradation proceeds to *o*-benzoylbenzoic acid (III).

In view of these observations, it was anticipated that alkaline reagents in solvents such as water or alcohol would bring about the same result. Much to our surprise, however, after acidification, the principal reaction product was found to be 1,3-diphenylisobenzofuran (IV). This same furan was also formed in reactions between ethanolic potassium hydroxide and related substances such as *o*-benzoylbenzil (V) and 2,3-diphenylindone epoxide (VI). In the latter case, the yield is small. It is, thus, apparent that not only has there been a different mode of cleavage, but that it has been accompanied by a rearrangement, for in the furan one phenyl group is attached to each carbon atom directly connected to the ring. The route followed cannot be a simple reaction, since the empirical formulas of the indone and isobenzofuran differ by only one carbon atom.

The mechanism of the formation of a diphenylisobenzofuran (IV) from *o*-benzoylbenzil (V) seems obvious. The first step is probably a benzilic acid rearrangement to (VII); this is followed by intramolecular addition, to give the isomeric lactol which is a dihydrofuran (VIII); the last step is the elimination of carbon dioxide and water. The facile elimination of groups from the 1,3-positions of dihydrofurans is well known.[4]



V VII VIII IV



VI IX X XI XII IV

The mechanism of isobenzofuran formation from the epoxide (VI) and alcoholic potassium hydroxide is more complex. A plausible sequence of reactions is as follows: The oxide ring is opened in the presence of the potassium ethoxide, with consequent formation of the glycol ether (IX). The latter, by the reverse of an aldol reaction,[5] forms a benzil (X), which, in the alkaline alcoholic solution, undergoes a benzilic acid rearrangement

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[1] Allen, Jones and VanAllan, This Journal, 68, 708 (1946).

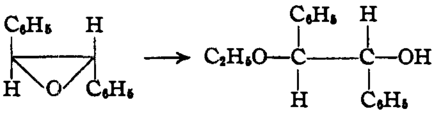
[2] Allen, Jones and VanAllan, *J. Org. Chem.*, 11, 268 (1946).

[3] Meyer and Weil, *Ber.*, 30, 1281 (1897).

[4] Guyot and Catel, *Bull. soc. chim.*, [3] 35, 1126 (1906).

[5] Allen and Gates, This Journal, 65, 1230 (1943).

to give (XI); elimination of alcohol closes the dihydrofuran ring (XII), from which formic acid is lost, to give 1,3-diphenylisobenzofuran (IV).[6] An analogy for the ring opening (VI–IX) is furnished by Read and Campbell's observation[7] that *l-trans*-diphenylethylene oxide, on standing in ethanolic solution, gave the monoethyl ether of *l*-isohydrobenzoin.



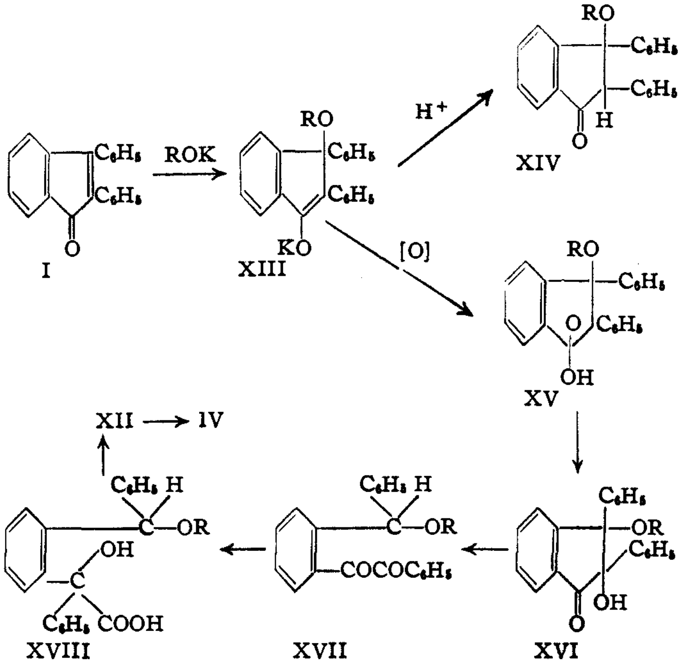
Since 2,3-diphenylindone likewise gives 1,3-diphenylisobenzofuran under the same conditions, it would seem that by some obscure process it must be first converted to either *o*-benzoylbenzil or the epoxide (VI). This indone has been reported to form an epoxide[5] when treated with alkaline hydrogen peroxide in aqueous alcoholic solution, and to form *o*-benzoylbenzil on permanganate oxidation.[8] However, there is no indication of the presence of either in the reaction mixture.

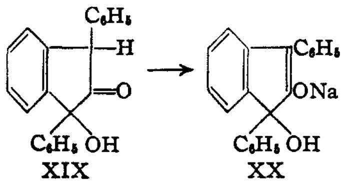
The yield of the isobenzofuran which is isolated from the reaction mixture is 50–55%. Upon concentration, the filtrate deposits two colorless substances. The one obtained in larger amount (25%), upon analysis, gave figures indicating that a molecule of the solvent, isopropyl alcohol, had been added to the indone. The second substance, isolated in a yield of 2–5%, analyzes for a glycol (XXI).

While there are several ways in which an alcohol might be added to the indone (I), it seems highly probable that 1,4-addition of the potassium alkoxide to the conjugated systems of double bonds has occurred, with consequent formation of an enolate (XIII). The free enol would undoubtedly isomerize to the isomeric β-alkoxyketone (XIV), which is the product isolated in 25% yield. This alkoxyketone gives a green color with concentrated sulfuric acid; the alcohol is lost and 2,3-diphenylindone regenerated.

Now it is well known that many enolates undergo spontaneous oxidation to oxanols.[9] In this instance, the oxanol (XV) can be considered as undergoing two successive reactions, each of which is the reverse of an aldol condensation (XV → XVII), to give an ether (XVIII) of a benzilic acid corresponding to (XI); the subsequent ring closure to a dihydroisobenzofuran (XII) and loss of formic acid then proceeds exactly as just outlined. The proposed sequence of reactions, as indicated by formulas XIII–IV, is supported by the observation that when one equivalent of alkoxide is used and the time decreased to one hour, only a very small amount of the isobenzofuran is formed, but the alcohol addition product can be isolated in a good yield.

Dufraisse[10] recently announced that 1,3-diphenylisobenzofuran (IV) resulted when an alkaline solution of 1,3-diphenyl-1-hydroxy-2-indanone (XIX)[11] was treated with air or oxygen (no reaction *in vacuo*); the gas was absorbed very rapidly, which led the authors to assume intermediate formation of an enolate.





In view of our conclusions, it is suggested that his observations can be correctly explained by a similar mechanism, involving oxidation of the metallic enolate (XX) to an oxanol, and so forth, through a dihydrofuran to the isobenzofuran (IV). By an alternative interpretation, the double bond in the enolate could be cleaved by oxidation to give the ketobenzilic acid (VII), with the subsequent steps as already outlined.

The glycol (XXI) is an isomer of one previously described.[5] It exhibits the same halochromism

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(6) In footnote 22 [Bissinger, *et al.*, This Journal, 69, 2955 (1947)], it is noted that 3,4-epoxy-1-butene is opened in both possible ways by methanol under alkaline conditions. Other products that are formed from the 2,3-diphenylindone epoxide are retained in the untractable resinous material that is formed; this probably accounts for the low yield of furan.

(7) Read and Campbell, *J. Chem. Soc.*, 2379 (1930).

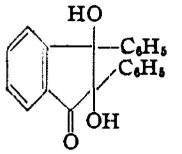
(8) Ivanov and Dalev, *Ann. univ. Sofia, II, faculté phys.-math.*, Livre 2, 33, 305 (1937) [*Chem. Abs.*, 32, 3371 (1938)].

(9) Kohler and Mydans, This Journal, 54, 4668 (1932).

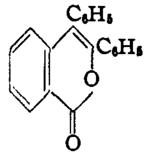
(10) Dufraisse and Ecary, *Compt. rend.*, 223, 1143 (1946).

(11) Koelsch, This Journal, 58, 1324 (1936).

with sulfuric acid, and, like its isomer, is easily converted to the lactone (XXII). It, thus, appears that this is an instance of geometrical isomerism. The new glycol has a much higher melting point and is therefore assigned a *trans* structure. Its origin is not clear, but it probably arises from a *trans* ring opening of a little epoxide formed in the alkaline solution.



XXI

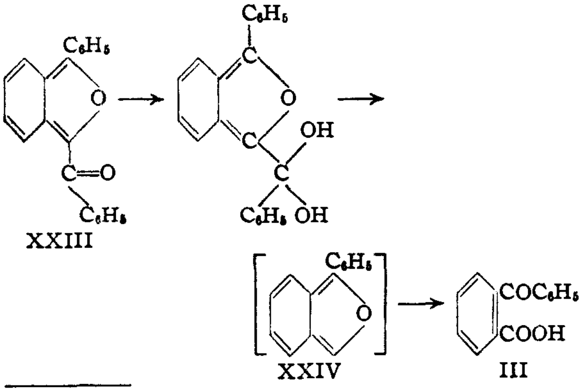


XXII

It has been reported[4] that 1,3-diphenylisobenzofuran in alcoholic solution is oxidized by air alone to *o*-dibenzoylbenzene. This observation has been checked and the time required found to be thirty-four hours. Since a high yield is obtained, the reaction makes available this hitherto relatively inaccessible diketone. The furan can be prepared either from 2,3-diphenylindone (I)[12] as described in this paper, or through Adams and Gold's procedure[13] which starts with a diene synthesis.

This remarkably easy oxidation procedure was applied to 1-phenyl-3-benzoylisobenzofuran (XXIII).[5] The same type of reaction took place, and *o*-benzoylbenzil (V) was obtained in high yield.

It seemed that if potassium hydroxide were added to a solution of 1-phenyl-3-benzoylisobenzofuran before aeration the reaction should not stop with formation of the diketone, but should continue, as described earlier in this paper, to 1,3-diphenylisobenzofuran; the latter would, thus, be obtained in a single operation from 1-phenyl-3-benzoylisobenzofuran. However, *o*-benzoylbenzoic (III) and benzoic acids were formed in excellent yield. Two mechanisms could account for such a result. In the first, an equivalent of water adds to the carbonyl group, after which the reverse of an aldol reaction[6] takes place, to give 1-phenylisobenzofuran (XXIV) and benzoic acid. The furan is then oxidized by air, as in the other instances. By the second mechanism, *o*-benzoylbenzil is produced by aerial oxidation, whereupon the 1,2-diketone is cleaved by further alkaline oxidation. This suggestion seems less likely, for 1,2-diketones are cleaved by alkaline peroxides, rather than through aerial oxidation.



An apparent exception to the easy oxidation of isobenzofurans has been noted in the case of the 1,3-dibenzoyl derivative.[14] This deep red substance was reported as not being further oxidized. Such a discrepancy, along with the unusual color of the substance, suggests that a reinvestigation is in order.

Experimental

Formation of 1,3-Diphenylisobenzofuran (IV). A. From 2,3-Diphenylindone.—To a solution of 1.6 g. of potassium hydroxide in 75 ml. of isopropyl alcohol was added 4 g. of 2,3-diphenylindone,[12] and the mixture was refluxed for ten hours. The red solid slowly dissolved, giving a brownish solution. After pouring into water, the cooled solution was extracted with ether to remove alkali-insoluble material, treated with Norite, and acidified. The yellow solid was taken up in benzene, the solvent evaporated, and the residue triturated with methanol and recrystallized from alcohol. It melted at 127° and showed no depression when mixed with an authentic sample. The yield was 51%; with ethanol as solvent, the yield dropped to 44%, while it was less than 2% with methanol.

From a similar-sized run, in which one equivalent of sodium isopropoxide was used, and the time reduced to one hour, under 0.1 g. of isobenzofuran was obtained. The oily material is easily separated from 0.2 g. (3%) of the glycol (XXI) but crystallizes very reluctantly. The solid that does separate is a mixture of the alcohol addition product (XIV) (31%) and unchanged starting material (5%).

B. From *o*-Benzoylbenzil.—A mixture of 1.2 g. of *o*-benzoylbenzil[8] and 10 ml. of 10% potassium hydroxide in ethanol was refluxed for one and one-half hours, and worked up as in A. It gave an 85% yield of the 1,3-diphenylisobenzofuran.

C. From the Epoxide (VI).—Following the same procedure, but using 2 g. of the epoxide, resulted in formation of the isobenzofuran in a yield of only 10–11%.

3-Isopropoxy-2,3-diphenylindanone (XIV; R = i-C_3H_7).—The ethereal extract from A (above) was evaporated to dryness and the residue extracted twice with ligroin (b. p. 90–120°). The crude crystals deposited from the ligroin were recrystallized from a mixture of petroleum ether and benzene, when the melting point was 127–128°.

Anal. Calcd. for $C_{24}H_{22}O_2$: C, 84.3; H, 6.4. Found: C, 84.8; H, 5.8.

When 0.2 g. of this ether was added to 2 ml. of concentrated sulfuric acid, it gave a green solution; after a half hour this was poured into water. The bright red crystals were removed and found to be 2,3-diphenylindone by mixed melting point.

2,3-Dihydroxy-2,3-diphenylindanone (XXI).—The residue, insoluble in ligroin, was triturated with benzene, filtered, and recrystallized from benzene. It melted to a red liquid at 233–235° with decomposition; the yield was 4.2%.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.7; H, 5.1. Found: C, 79.4; H, 5.1.

This is the *trans* glycol, corresponding to the *cis* form obtained from the epoxide.[5]

Both the *cis* and *trans* glycols give a red halochromism with concentrated sulfuric acid, which soon changes to

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(12) Allen, Gates and VanAllan, "Organic Syntheses," **27**, 30 (1947).

(13) Adams and Gold, This Journal, **62**, 56 (1940).

(14) Weiss and Sonnenschein, *Ber.*, **58**, 1043 (1925).

pale yellow. On dilution and appropriate manipulation, the same lactone (XXII) is obtained from both; it was identical with a previously prepared specimen.[5]

Formation of 1-Phenyl-3-benzoylisobenzofuran (XXIII).—The yield of this substance from the glycol (XXI)[5] has been improved (90%) by modifying the procedure as follows: A mixture of 8 g. of the glycol, 0.3 g. of potassium hydroxide, and 50 ml. of alcohol is refluxed for three hours and worked up as usual.

Formation of *o*-Benzoylbenzoic Acid. A. From the Indone.—A mixture of 1.4 g. of 2,3-diphenylindone, 0.39 g. of sodium amide, and 10 ml. of xylene was refluxed for twelve hours. It was then diluted first with alcohol, then with water, and 1 ml. of 40% sodium hydroxide, and the xylene distilled with steam. The residual alkaline solution was treated with Norite and acidified. After some time, *o*-benzoylbenzoic acid separated in a yield of 50%, and was identified by comparison with an authentic specimen.

B. From 1-Phenyl-3-benzoylisobenzofuran (XXIII).—A mixture of 1.5 g. of the furan, 0.5 g. of potassium hydroxide, and 75 ml. of absolute alcohol was heated in a current of oxygen for five hours. The next day the solvent was removed *in vacuo*, the residue taken up in water, treated with Norite, acidified, and extracted with benzene. The acid was caused to crystallize by the addition of ligroin; the yield was 0.98 g. (93%); it was shown to be *o*-benzoylbenzoic acid by mixed melting point.

Oxidation of Isobenzofurans to 1,2-Aroylbenzenes. A. *o*-Dibenzoylbenzene.—A solution of 0.4 g. of 1,3-diphenylisobenzofuran in 15 ml. of benzene was refluxed for thirty-four hours in a slow current of oxygen. When the fluorescence had disappeared, the solvent was evaporated and the residue recrystallized from methanol. The yield of *o*-dibenzoylbenzene was 0.37 g. (86%); m. p. 145–147°. It was identified by comparison with a sample at hand.

B. *o*-Benzoylbenzil (V).—A solution of 1 g. of 1-phenyl-3-benzoylisobenzofuran in 20 ml. of alcohol was refluxed in a current of air for seven hours, the solvent removed, and the residue crystallized from acetic acid. The yellow crystals (0.55 g.) melted at 96°; a mixed melting point with a stock sample was not depressed.

Summary

1,3-Diphenylisobenzofuran is easily obtained by the action of alcoholic potassium hydroxide upon 2,3-diphenylindone, its epoxide, and *o*-benzoylbenzil. Mechanisms are proposed to account for the reactions.

1,3-Disubstituted isobenzofurans are slowly but completely oxidized by air or oxygen, in refluxing alcoholic solutions, to *o*-diaroylbenzenes.

1-Phenyl-3-benzoylisobenzofuran, in an alkaline alcoholic refluxing solution, is oxidized to *o*-benzoylbenzoic acid. This same acid also results when 2,3-diphenylindone is cleaved by sodium amide in boiling xylene.

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[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Morphine Studies. 2-(2',3'-Dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone

BY E. C. HORNING, M. G. HORNING AND E. J. PLATT[1]

One of the chief structural characteristics of morphine and many of its derivatives is the presence of a quaternary carbon, identified in the Gulland–Robinson formula as C-13 of the octahydrophenanthrene system. Methods for the synthesis of octahydrophenanthrenes of this kind are quite limited; few such compounds have been made, and attempted applications of known methods to the synthesis of morphine derivatives have not been successful.

It was recognized by Cook[2] that octahydrophenanthrenes could be obtained from 2-arylcyclohexanones by an apparently general method involving a Reformatsky reaction, followed by dehydration, hydrogenation and cyclization. This method was applied by the English workers to 2-phenylcyclohexanone, and we have used it with 2-(2',3'-dimethoxyphenyl)-cyclohexanone.[3]

We have been interested in the application of Cook's procedure to the synthesis of certain morphine derivatives, and for this purpose it has first been necessary to investigate the preparation of a dimethoxyarylcyclohexanone containing an appropriately substituted carbon in the 2-position. The reactions employed are indicated on the diagram; the starting material was prepared by the sodamide alkylation of 2,3-dimethoxyphenylacetonitrile with δ-chlorovaleronitrile. Continued study of this reaction has led to the inclusion of certain apparently minor modifications which result in consistent yields of 80–83%. The product, 2-(2',3'-dimethoxyphenyl)-pimelonitrile, is a dinitrile which can undergo cyclization to a six-membered β-iminonitrile, but which can also be alkylated directly by the sodamide method. This situation apparently arises through the structural factors which affect the cyclization. In the case of pimelonitriles, cyclization does not occur so readily as in the case of adiponitriles, and structural modifications may impose added difficulty in the way of the reaction. In the cyclization of α-(2,3-dimethoxyphenyl)-pimelonitrile (I) with sodium,[3] the cyclizing agent will produce a carbanion by removal of the most acidic hydrogen, which in this case is that associated with the phenylacetonitrile system. If a carbanion of this structure is formed, however, cyclization may follow directly only by addition of a completely substituted carbanion carbon to the nitrile group at the other end of the chain. The effective steric hindrance presented toward this addition is a barrier which in similar cases usually is sufficient to prevent cyclization. It is not known whether

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(1) Rohm and Haas Research Assistant.

(2) Cook, Hewett and Lawrence, *J. Chem. Soc.*, 71 (1936).

(3) Horning, Horning and Platt, This Journal, 69, 2929 (1947).