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Comparative Study Between Phthalides and Naphthalides

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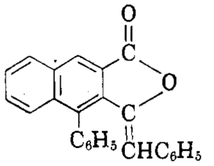
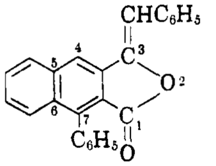
Benzal 7-phenyl-5,6-benzophthalide and 3-benzalnaphthalide are prepared. A marked difference in their behavior towards alkalies, sodium methoxide, phenylmagnesium bromide and photochemical addition with phenanthrenequinone is observed.

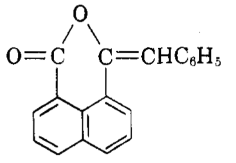
1-Phenylnaphthalene-2,3-dicarboxylic anhydride and naphthalic anhydride condensed with phenylacetic acid in the presence of sodium or potassium acetate to give the corresponding benzal-derivatives (I) and (II), respectively.



Ia



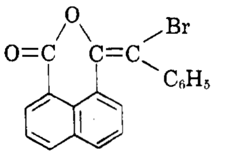
I



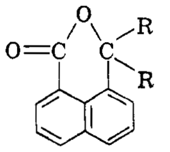
II

Although 1-phenylnaphthalene-2,3-dicarboxylic anhydride is expected to yield on condensation with phenylacetic acid the two isomeric compounds (I) and (Ia), it was possible to isolate, as the main product, only a compound which probably has structure (I) and not (Ia), owing to the steric effect of the phenyl group on the carbonyl group adjacent to it.

The structures of both compounds (I) and (II) are supported by the fact that they are oxidized by chromic acid to the corresponding original anhydrides. They also add bromine in acetic acid giving, in the latter case, an almost colorless product which is believed to have structure (III).



III



IV

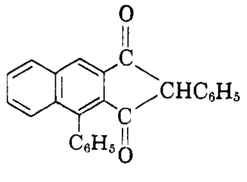
IVa, R = H
IVb, R = C_6H_5

The formation of (III) from 3-benzalnaphthalide (II) appears to take place through the addition of two bromine atoms to the double bond, followed by the loss of one molecule of hydrogen bromide either during the washing with sodium bisulfite, or during crystallization.

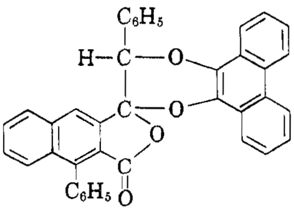
p-Nitrophenylacetic acid failed to undergo condensation under the above mentioned conditions. This may be due to the thermal decarboxylation of *p*-nitrophenylacetic acid prior to the Perkin condensation.

The above anhydrides were recovered unchanged when heated with propionic anhydride in the presence of sodium propionate. This may be due to their comparative insolubility in the medium.

A comparative study between the two unsaturated lactones, benzal 7-phenyl-5,6-benzophthalide (I) and 3-benzalnaphthalide (II), showed a marked difference in their reactivity which may be attributed to the fact that (I) is a γ-lactone (phthalide) while (II) is a δ-lactone (naphthalide). Thus, compound (II) was much more soluble in dilute alkalies and in concentrated ammonia solution than compound (I). It appears that the six-membered lactone (II) is very stable, for although it dissolves easily in alkalies, it is immediately converted to the original naphthalide on acidification. Errera and Azon[1] state that the oxygen ring in the naphthalide (IVa) is more stable than that in phthalides in general, and that it is precipitated unchanged from alkalies on acidification and crystallizes from water unchanged. Similarly, Geissman and Morris[2] found that diphenyl-1,8-naphthalide (IVb) is extremely stable toward a boiling 20% alcoholic potassium hydroxide solution. In conformity with such an observation the authors found that, whereas (I) rearranged to the 1,3-diketone (V) on treatment with a methyl alcoholic sodium methoxide solution, (II) was recovered unchanged. The diketone (V) has a deep red color in the solid state which suggests that it exists in the enol-form.[3] This is supported by its ready conversion to its yellow benzoyl derivative.



V



VI

A marked difference in the reactivity of the double bonds in the two compounds (I) and (II) was also

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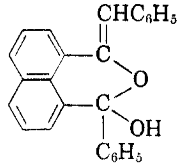
(1) Errera and Azon, *Gazz. chim. ital.* **44**, 11, 92 (1914).

(2) Geissman and Morris, *J. Am. Chem. Soc.*, **63**, 1111 (1941).

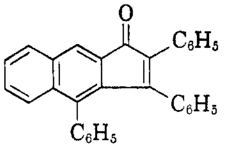
(3) Koelsch, *J. Org. Chem.*, **10**, 366 (1945).

observed. Thus, whereas phenanthrenequinone failed to add to (II), it gave a colorless adduct (VI) with (I). The structure of this adduct is based on: (*1*) its similarity to phenanthrenequinone addition products with other benzalphthalides,[4] (*2*) the fact that it is colorless, and (*3*) the analytical data.

Benzal 7-phenyl-5,6-benzophthalide (I) and 3-benzalnaphthalide (II) behave differently in their reaction with the Grignard reagent. Thus, the naphthalide (II) reacted with phenylmagnesium bromide to yield a pale yellow product, which gives a yellow color with sulfuric acid and analyzes for the hemiketal (VII). Geissman and Morris[2] obtained only the hemiketal product when they allowed the naphthalide (IVb) to react with an excess of the Grignard reagent. They attributed the failure of their naphthalide (IVb) to react further than the monoaddition stage (the hemiketal stage) to the great stability of the *peri*-ring.



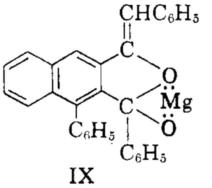
VII



VIII

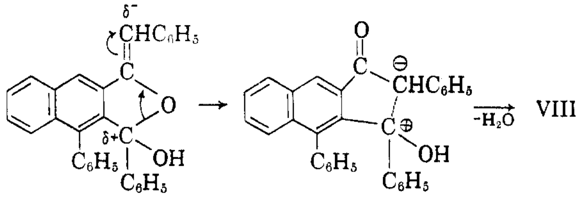
However, the phthalide (I) reacted with phenylmagnesium bromide under the same conditions to give an orange product, which gave a 2,4-dinitrophenylhydrazone derivative and analyzed for the indone (VIII). This is in complete agreement with the work of Lowenbein and Ulich,[5] who found that diphenyl indone is produced by interaction of phenylmagnesium bromide and benzalphthalide. We found that the indone (VIII) was always produced even when a fivefold excess of the Grignard reagent was used. This demonstrates conclusively that the indone is not produced during the reaction but only after hydrolysis, otherwise it would react with excess of the reagent.

It seems plausible to suggest that only one molecule of phenylmagnesium bromide enters into reaction with the phthalide (I) giving rise to the complex (IX), in which the magnesium is coordinated with the two oxygen atoms thus preventing further reaction.



IX

Hydrolysis of the complex (IX) would then lead to the production of the hemiketal (X) which might well rearrange according to the following scheme:



X

In our opinion, the failure of the naphthalides (IVb) and (II) to react with excess Grignard reagent beyond the hemiketal stage cannot be attributed to the stability of the oxygen ring (*peri*-ring), but is largely due to the formation of such magnesium complexes as described above. This seems to be a feasible assumption since, in general, phthalides, which are known to have a less stable oxygen ring, react with only one molecule of the Grignard reagent.

The difference in stability between the hemiketal products, in both phthalides and naphthalides, manifests itself only after hydrolysis of the metal complex.

EXPERIMENTAL[6]

Benzal 7-phenyl-5,6-benzophthalide (I). A mixture of 1-phenylnaphthalene-2,3-dicarboxylic anhydride[7] (5 g.), phenylacetic acid (2.5 g.) and freshly fused sodium acetate (0.2 g.) was placed in a wide Pyrex tube and heated in a metal bath at 220° for 1 hr. The warm reaction mixture was extracted with boiling acetic acid, treated with charcoal, filtered and concentrated. Recrystallization of the solid so obtained from acetic acid gave 4.5 g. (69%) of benzal 7-phenyl-5,6-benzophthalide as yellow plates, m.p. 236–238°.

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.2; H, 4.6. Found: C, 85.7; H, 4.8.

The product was sparingly soluble in hot dilute sodium hydroxide solution. A solution of (I) in acetic acid absorbed bromine and furnished, on dilution with water, a colorless material, m.p. 160–170°, which could not be obtained in a crystalline form.

Chromic acid oxidation of (I). An excess of a saturated solution of chromium trioxide in acetic acid was added portionwise to a hot solution of (I) (0.5 g.) in acetic acid (50 ml). The colorless material which was precipitated on dilution of the cold reaction mixture with water was proved to be 1-phenylnaphthalene-2,3-dicarboxylic anhydride, by m.p. and mixed m.p.

3-Benzalnaphthalide (II). A mixture of naphthalic anhydride (13 g.), phenylacetic acid (10 g.), and fused sodium acetate (0.3 g.) was rapidly heated to 230–240°, and maintained at that temperature for 2 hr. The hot melt was rapidly poured into a mortar and crushed to a fine powder. On extraction with boiling alcohol, 15 g. (84%) of 3-benzalnaphthalide was obtained as brownish-orange needles, m.p. 205–208°. Recrystallization from boiling alcohol (charcoal) yielded orange needles, m.p. 210–212°.

Anal. Calcd. for $C_{19}H_{12}O_2$: C, 83.8; H, 4.4 Found: C, 82.9; H, 4.5

The substance was fairly soluble in concentrated ammonia solution and in dilute sodium hydroxide solution; the solution in both cases acquired a brownish-red coloration and the substance was recovered unchanged on acidification.

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[4] Schönberg and Mustafa, *Chem. Revs.*, **40**, 190 (1948).

[5] Lowenbein and Ulich, *Ber.*, **58B**, 2662 (1925).

[6] Microanalysis was carried out by Alfred Bernhardt, Germany. Melting points are not corrected.

[7] Bucher, *J. Am. Chem. Soc.*, **30**, 1244 (1908).

Bromination of (II). A solution of 3-benzalnaphthalide (II) (0.5 g.) in carbon tetrachloride–acetic acid mixture (2:1) (100 ml) was treated at room temperature with a solution of bromine in carbon tetrachloride. The addition of the bromine was continued until the reaction mixture acquired a faint reddish-brown coloration. The carbon tetrachloride solution was washed with an aqueous solution of sodium bisulfite, washed with water, dried, and concentrated. Recrystallization of the solid obtained from carbon tetrachloride (charcoal), gave 0.2 g. (33%) of benzalnaphthalide monobromide (III) as almost colorless rectangles, m.p. 194–195°.

Anal. Calcd. for $C_{19}H_{11}BrO_2$: C, 64.9; H, 3.1; Br, 22.5. Found: C, 64.4; H, 3.2; Br, 21.63.

Chromic acid oxidation of (II). A solution of 3-benzalnaphthalide (0.2 g.) in acetic acid (20 ml) was treated with an excess of a saturated solution of chromium trioxide in acetic acid and the mixture was gently warmed. When the reaction subsided, the reaction mixture was poured into water and the precipitated solid collected on a filter. Crystallization from acetic acid gave colorless needles which proved to be naphthalic anhydride by m.p. and mixed m.p. The aqueous filtrate was extracted with ether which was reextracted with sodium bicarbonate solution. Acidification of the bicarbonate solution precipitated a solid, which proved to be benzoic acid by m.p. and mixture m.p.

Attempted condensation with p-nitrophenylacetic acid. A mixture of 1-phenylnaphthalene-2,3-dicarboxylic anhydride (6 g.) or naphthalic anhydride (5 g.), *p*-nitrophenylacetic acid (4 g.), and fused sodium acetate (0.2 g.) was heated up rapidly to 170°. The temperature was then raised slowly to 220° and maintained there for 2 hr. The warm melt was extracted with boiling acetic acid and the solution concentrated. Both anhydrides were recovered unchanged.

Attempted condensation with propionic anhydride. A mixture of 1-phenylnaphthalene-2,3-dicarboxylic anhydride (5 g.) or naphthalic anhydride (4 g.) and propionic anhydride (5 g.) was heated to 160–170°. Fused sodium propionate (1.2 g.) was then added, in portions, during 0.5 hr. Heating was continued at 180–190° for a further 4 hr. Both anhydrides were insoluble in the medium and were recovered unchanged.

Action of sodium methoxide. (a) Benzal 6-phenyl-5,6-benzophthalide (I) (0.3 g.) was dissolved in a 2% methyl alcoholic solution of sodium methoxide (100 ml) and the solution heated under reflux for 30 min. The reaction mixture was diluted with water, filtered, cooled, and acidified with ice cold dilute hydrochloric acid. Crystallization of the precipitated product from alcohol gave 0.2 g. (66%) of 2,4-diphenyl-5,6-benzindan-1,3-dione (V) as deep red prisms, m.p. 200°,

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.2; H, 4.6. Found: C, 85.5; H, 4.8.

(b) Benzalnaphthalide (II) (0.3 g.), when similarly treated gave a brownish-red solution from which it was recovered unchanged on acidification.

Photo-addition with phenanthrenequinone. A mixture of benzal 7-phenyl-5,6-benzophthalide (I) (0.6 g.) and phenanthrenequinone (0.4 g.) in dry thiophene-free benzene (30 ml.) was placed in a Schlenck tube[8] under a carbon dioxide atmosphere and exposed to sunlight for six days. The precipitated colorless solid was filtered off. Crystallization from benzene gave 0.3 g. (31%) of the adduct as colorless needles, m.p. 320–322°.

Anal. Calcd. for $C_{39}H_{24}O_4$: C, 84.2; H, 4.4. Found: C, 84.5; H, 4.6.

Under similar conditions, and even after a longer period of exposure to sunlight, 3-benzalnaphthalide (II) was recovered unchanged (m.p. and mixture m.p.).

Action of Grignard reagent. (a) A solution of benzal 7-phenyl-5,6-benzophthalide (I) (1 g.) in dry benzene (50 ml.) was added to an ethereal solution of phenylmagnesium bromide (from bromobenzene, 1.6 g. and magnesium, 0.2 g.) and the reaction mixture was heated under reflux for 2 hr., then left overnight. Decomposition of the reaction mixture with aqueous concentrated ammonium chloride solution produced a deep red color which rapidly changed to light orange on shaking. On concentration of the benzene extracts and addition of petroleum ether (40–60°), a light orange product was obtained. Recrystallization from benzene-methyl alcohol gave 0.4 g. (36%) of 2,3,4-triphenyl-5,6-benzindone (VIII) as orange slender needles, m.p. 242–244°.

Anal. Calcd. for $C_{31}H_{20}O$: C, 91.1; H, 4.94. Found: C, 90.8; H, 5.38.

The substance gave a permanganate color with concentrated sulphuric acid. It also gave a *2,4-dinitrophenylhydrazone* which crystallized from alcohol–ethyl acetate mixture in deep red needles, m.p. 306–308°.

Anal. Calcd. for $C_{37}H_{26}H_4O_4$: N, 9.5. Found: N, 9.33.

(b) A solution of benzalnaphthalide (II) (1 g.) in dry benzene (100 ml.) was added to an ethereal solution of phenylmagnesium bromide (from 1.8 g. of bromobenzene and 0.3 g. of magnesium) and the reaction mixture was heated under reflux for 4 hr. then left overnight. Decomposition with aqueous ammonium chloride solution, and concentration of the previously washed and dried benzene extracts followed by addition of petroleum ether (40–60°), gave a pale yellow product. Recrystallization from benzene–petroleum ether mixture (1:1) gave 0.2 g. (17%) of 1-phenyl-1-hydroxy-3-benzalnaphthalide (VII) as pale yellow plates, m.p. 177–178°.

Anal. Calcd. for $C_{25}H_{18}O_2$: C, 85.7; H, 5.2. Found: C, 85.45; H, 5.3.

The substance gave a pale yellow coloration with concentrated sulfuric acid.[2]

Benzoylation of (V). The hydroxybenzindone (0.5 g.) was shaken with a 10% aqueous solution of sodium hydroxide (50 ml.) and benzoyl chloride (3 ml.). The reaction was exothermic, the red solid dissolved gradually, and soon the mixture precipitated a yellow solid. Recrystallization from methyl alcohol gave 0.4 g. (66%) of the benzoyl derivative as yellow needles, m.p. 225°.

Anal. Calcd. for $C_{32}H_{20}O_3$: C, 84.9; H, 4.4. Found: C, 85.3; H, 4.6.

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[8] Houben, *Die Methoden der Organischen Chemie*, 2nd ed., Vol. 4, Georg Thieme, Leipzig, 1924, p. 960.