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DIECKMANN-SHAPIRO CONDENSATION OF SUBSTITUTED PHTHALIDES

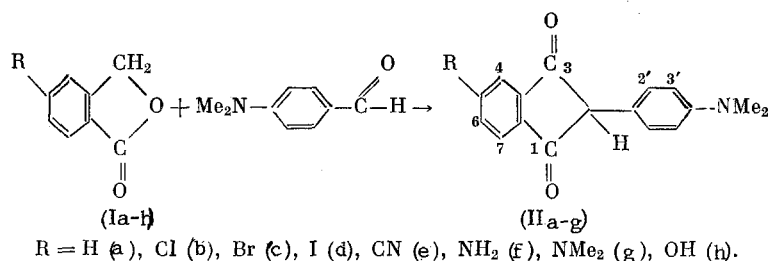
WITH p-DIMETHYLAMINO BENZALDEHYDE

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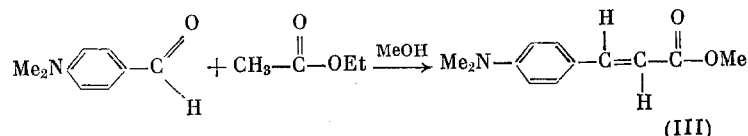
UDC 542.953:547.584:547.571

Dieckmann condensation, modified by Shapiro, is a convenient method for the synthesis of 2-arylindan-1,3-diones. It consists in the reaction of an aromatic aldehyde with a phthalide in an alcohol solution of sodium ethoxide in the presence of ethyl acetate [1]. The condensation of phthalide with various aromatic aldehydes has been studied thoroughly [1]. The literature contains very little information on the reactivities of substituted phthalides [2].

The present research was devoted to an investigation of the condensation of p-dimethylaminobenzaldehyde (DABA) with phthalides Ia-h, which contain substituents that differ with respect to their electronic effects:



The condensation usually proceeds quite rapidly; this is apparent from the dark-cherry-red color of the reaction mixture, which is due to the color of the resulting anions of II. For phthalides Ia-d the reaction is complete in ~1.5 h. In the case of Ie, which contains an electron-acceptor CN group, which increases the activity of the methylene component, the condensation is complete in 5-10 min. An increase in the reaction time to 3-4 h leads to saponification of the cyano group to an amido group. For phthalides If, g, which contain strong electron-donor NH₂ and NMe₂ groups, the condensation proceeds considerably more slowly (~3 h). In this case, the rate of the principal reaction is comparable to the rate of the competing side reaction - Claisen condensation of ethyl acetate with p-dimethylaminobenzaldehyde [3]:



Since the solvent is methanol, methyl p-dimethylaminocinnamate (III) is formed as a result of transesterification. The yields of III for phthalides If, g for a phthalide-benzaldehyde ratio of 1:1 are the same (15.5%). Ester III is formed only in trace amounts in the condensation of Ia-e.

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TABLE 1. IR Spectrum (cm^{-1}) of the Compounds Obtained

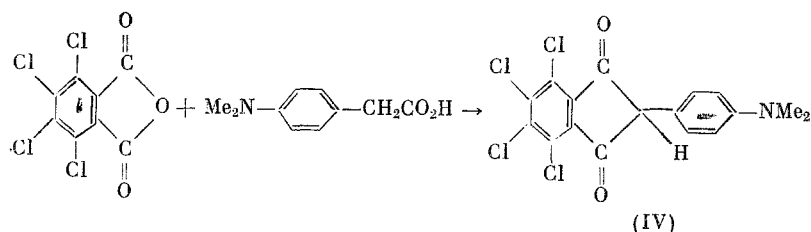
Compound	Color of crystalline form	Dicarbonyl system	Ionized enol and/or aromatic system	+ NH group	Other vibrations
(IIc) *	Red	1710, 1737	1513, 1574, 1600, 1680	2300-2750	
(IIc) *	Black	1710, 1740	1517, 1573, 1610, 1647	2300-2750	
(IId) *	Red	1705	1512, 1560, 1596, 1660	2300-2750	
(IIE) *	Red	1740	1513, 1570, 1608, 1680-1690	2300-2750	2217 (C=N)
(IIf)	Yellow	1683, 1727	1525, 1567, 1593, 1611		1633 ($\delta_{as}\text{NH}_2$) 3240 Assoc. ν NH 3368 ($\nu_s\text{NH}$) 3477 ($\nu_{as}\text{NH}$)
(IIg)	Yellow	1684, 1721	1516, 1556, 1587		
(IV) *	Red	1711	1517, 1583, 1600, 1650	2300-2800	
(Vc)	Yellow	1710, 1738	1511, 1578, 1600		
(Vd)	Yellow	1513, 1739	1513, 1579, 1607		
(Ve)	Black	1707, 1740	1528, 1573, 1601		1635 Assoc. C=O 2221 (C=N)
(Vf)	Yellow	1686, 1724	1513, 1587		3327 Assoc. ν NH 3360 ($\nu_s\text{NH}$) 3460 ($\nu_{as}\text{NH}$)
(Vg)	Yellow	1685, 1720	1510, 1576, 1590		
(VI)	Yellow	1712, 1740	1512, 1599		
(VI)	Black	1712, 1741	1513, 1607		1629 Assoc. C=O

*Admixture of the diketo form [4].

Under the condensation conditions the OH group of phthalide Ih is completely deprotonated. The resulting anion has such an inactive methylene component that the corresponding IIh is not formed at all, and III was isolated in 56% yield.

Thus, the rate of Dieckmann-Shapiro condensation and the ratio of the products depend on the activity of the methylene group in the phthalide, which varies markedly as a function of the electronic effects of the substituents.

An attempt to synthesize 4,5,6,7-tetrachloro-2-(p-dimethylaminophenyl)indan-1,3-dione (IV) by condensation of 4,5,6,7-tetrachlorophthalide with DABA leads to the formation of a difficult-to-separate mixture of IV and other indandiones, which are evidently formed as a result of nucleophilic substitution of Cl atoms by MeO groups. The alternative synthesis of IV was realized by anhydride condensation:

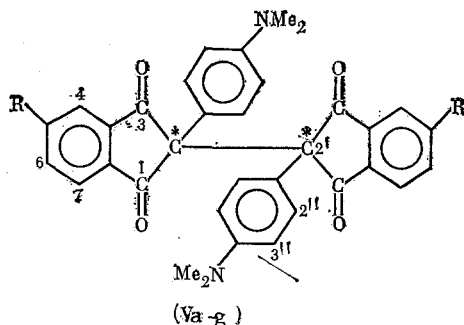


Depending on the solvent used for crystallization, IIB-e and IV, like the previously described IIa [4], may exist in the crystalline state in several polychromic modifications. Thus, IIB-e and IV recrystallized from AcOH are dark-cherry red. Broad absorption bands of an NH^+ group at $2200-2750\text{ cm}^{-1}$, which provide evidence that this form exists in the form of an inner salt, are present in their IR spectra. The vibrations of the indandionyl anionic fragment are difficult to separate from the vibrations of the benzene rings at $1500-1600\text{ cm}^{-1}$ (Table 1). Shiny black crystals - complexes of the inner salts and the enol forms [4] - form in the case of crystallization of IIB, c from ethanol. Regardless of the type of solvent, II f, g give yellow crystals and exist in the diketo form.

Thus the influence of the electronic effects of the substituents in the phthalyl ring on the C-H acidities and associated polymorphism of these compounds is also observed here.

The corresponding dimers Va-g were obtained by oxidation of the anions of indandiones IIa-g; octachlorobisindandione VI is similarly formed from the anion of IV.

All of the dimers obtained are yellow crystalline substances that have a characteristic double absorption maximum of the carbonyl groups at 1685-1740 cm^{-1} (see Table 1). However, dimers Ve and VI were unexpectedly isolated in the form of shiny black crystals. The yellow modifications of these dimers are converted to the black modifications during storage or when they are triturated under a layer of hexane. The low solubilities of the black modifications in benzene and CHCl_3 , in which the other dimers are very soluble,



indicate the existence of additional intermolecular interactions. The intensities of the vibrations of the carbonyl groups are reduced in their IR spectra (1707-1741 cm^{-1}), and additional absorption bands appear at 1629 (VI) and 1635 cm^{-1} (Ve). These new bands are evidently related to the vibrations of associated carbonyl groups as a consequence of the formation of intermolecular charge-transfer complexes of the π - π type. The integral intensities of the absorption bands of the associated and free carbonyl groups are identical, i.e., each dimer molecule is associated with two others through the acceptor indandione and donor p-dimethylaminophenyl fragments. The acceptor properties of the indandione ring of the tetrachloro-containing indan fragment of VI should be more pronounced than in the case of Ve; this is manifested in the greater shift of the absorption band of the carbonyl groups.

The frequencies of the symmetrical stretching vibrations of the carbonyl groups in the dimers correlate with the $(\sigma_p^+ + \sigma_m^+)$ substituent constants [5] in accordance with the equation

$$\nu_s = 7,8 (\sigma_p^+ + \sigma_m^+) + 1733,9 (\text{cm}^{-1})$$

$$r = 0,96, s = 2,2 \text{ cm}^{-1}$$

It should also be noted that the decrease in the frequencies of the stretching vibrations of the carbonyl groups in the spectra of dimer Vf and indandione IIIf is due primarily to the +M effect of the NH_2 group and not to the formation of intermolecular H bonds, as in starting phthalides If and Ig.

The 5-substituted dimers are mixtures of diastereomeric forms — the racemate (2S, 2'S and 2R, 2'R) and meso (2S, 2'R) forms. The PMR spectra of the diastereomers differ in some cases as, for example, in the case of Vg. The ratio of the intensities of the signals of the diastereomers of Vg is about 2:3 (20°C).

Like the previously obtained Va, b [6], solutions of dimers Vc-g and VI become green when heated due to the formation of free radicals.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a Specord 75-IR spectrometer. The PMR spectra of solutions of the compounds in CDCl_3 were obtained with a Bruker WM-250 spectrometer (250 MHz) with tetramethylsilane (TMS) as the internal standard. The phthalides were obtained by the methods in [7, 8].

5-Dimethylaminophthalide (Ig). A 10.43-g (0.07 mole) sample of 5-aminophthalide was heated with 17.8 g (0.14 mole) of Me_2SO_4 at 125-135°C for 1 h, after which the mixture was

poured into 200 g of water, and the liberated oil began to crystallize. The precipitate was separated and recrystallized from aqueous ethanol (with activated charcoal) to give 5.51 g (44.5%) of a product with mp 112-113°C; repeated crystallization gave a product with mp 116-117°C (see [9]).

5-Bromo-2-(p-dimethylaminophenyl)indan-1,3-dione (IIc). A 10.7-g (0.05 mole) sample of 5-bromophthalide and 7.45 g (0.05 mole) DABA were dissolved by heating in 40 ml of dry ethyl acetate, after which a solution of MeONa (from 5 g of Na and 75 ml of MeOH) was added, and the mixture was refluxed for 2 h. It was then evaporated, and the residue was dissolved in 500 ml of water. The aqueous solution was treated with activated charcoal and filtered. The filtrate was acidified to pH 5 with concentrated HCl, and the red precipitate was removed by filtration to give 13.9 g (81%) of a product with mp 216-218°C (decomp., from AcOH). Found, %: C 59.36, H 4.50. $C_{17}H_{14}BrNO_2$. Calculated, %: C 59.32, H 4.10. PMR spectrum (δ , ppm): 2.92 s (CH_3), 4.17 s (H^2), 6.68 d ($H^{3'}$, J = 9 Hz), 7.01 d ($H^{2'}$, J = 9 Hz), 7.91 d (H^7 , J = 8 Hz), 7.99 dd (H^6 , J = 8, J = 1.5 Hz), and 8.18 d (H^4 , J = 1.5 Hz).

5-Iodo-2-(p-dimethylaminophenyl)indan-1,3-dione (IIId). This compound, with mp 107-109°C (from AcOH), was similarly obtained in 96% yield. Found, %: C 51.85, H 3.82. $C_{17}H_{14}INO_2$. Calculated, %: C 52.19, H 3.61. PMR spectrum (δ , ppm): 2.92 s (CH_3), 4.15 s (H^2), 6.70 d ($H^{3'}$, J = 8 Hz), 7.01 d ($H^{2'}$, J = 8 Hz), 7.77 d (H^7 , J = 8 Hz), 8.22 d (H^6 , J = 8 Hz), and 8.43 s (H^4).

5-Cyano-2-(p-dimethylaminophenyl)indan-1,3-dione (IIe). A 4.77-g (0.03 mole) sample of 5-cyanophthalide and 4.47 g (0.03 mole) of DABA were dissolved by heating in 20 ml of dry ethyl acetate, a solution of MeONa (from 3 g of Na in 45 ml of MeOH) was added, and the mixture was refluxed for 10 min. It was then worked up as in the preceding case to give 8.51 g (98%) of a product with mp 230-233°C (from AcOH). Found, %: C 74.01, H 5.13. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.68, H 4.90.

5-Amino-2-(p-dimethylaminophenyl)indan-1,3-dione (IIIf). A 5.96-g (0.04 mole) sample of 5-aminophthalide and 5.96 g (0.04 mole) of DABA were dissolved by heating in 24 ml of ethyl acetate, a solution of MeONa (from 4 g of Na and 60 ml of MeOH) was added, and the mixture was refluxed for 3 h. It was then evaporated, and the residue was dissolved in 400 ml of water. The precipitate was removed by filtration and washed with water to give 1.27 g (15.5%) of methyl p-dimethylaminocinnamate (III) with mp 132-133°C (ethanol, yellow crystals; mp 135-136°C [3]). Found, %: C 70.48, H 7.55. $C_{12}H_{15}NO_2$. Calculated, %: C 70.22, H 7.37. IR spectrum (ν , cm^{-1}): 1698 (C=O), 1620 (C=C), 1600, 1527 (C=C_{arom}), 1160 (C-O), 984 (δ C-H, trans-CH-CH), and 812 (δ C-H); 1,4-substituted benzene ring. PMR spectrum (δ , ppm): 2.81 s (NMe), 3.69 s (OMe), 6.14 d (H^2 , J_{trans} = 16 Hz), 6.56 d ($H^{2'}$, J = 8 Hz), 7.32 d ($H^{3'}$, J = 8 Hz), and 7.60 d (H^3 , J_{trans} = 16 Hz). The mother liquor was neutralized to pH 7 with concentrated HCl, and the yellow precipitate was removed by filtration to give 5.51 g (46%) of IIIf. Compound IIIf was purified with a chromatographic column packed with silica gel [benzene-ethyl acetate (1:1)] to give yellow crystals with mp 230-232°C (decomp.). Found, %: C 72.80, H 5.99. $C_{17}H_{16}N_2O_2$. Calculated, %: C 72.83, H 5.75.

5-Dimethylamino-2-(p-dimethylaminophenyl)indan-1,3-dione (IIg). This compound, with mp 195-197°C (decomp.), was similarly obtained in 43% yield. Found, %: C 73.90, H 6.50. $C_{19}H_{20}N_2O_2$. Calculated, %: C 74.00, H 6.54. PMR spectrum (δ , ppm): 2.91 s (NMe), 3.16 s (5-NMe), 4.10 s (H^2), 6.71 d ($H^{3'}$, J = 9 Hz), 7.04 d ($H^{2'}$, J = 9 Hz), 7.07 s (H^4), 7.08 d (H^6 , J = 9 Hz), and 7.89 d (H^7 , J = 9 Hz).

4,5,6,7-Tetrachloro-2-(p-dimethylaminophenyl)indan-1,3-dione (IV). A 5.52-g (0.02 mole) sample of tetrachlorophthalic anhydride and 3.58 g (0.02 mole) of p-dimethylaminophenylacetic acid were dissolved in 120 g (1.2 moles) of Ac_2O with stirring and heating on a water bath, 12 g (0.12 mole) of Et_3N was added, and the mixture was heated for 15 min. It was then poured into a mixture of 200 g of ice and 60 ml of concentrated HCl, and the aqueous mixture was neutralized to pH 5 with NaOH solution. The cherry-red-brown precipitate was removed by filtration to give 6.30 g (79%) of product. The dried product was refluxed thoroughly in $CHCl_3$ and recrystallized from AcOH to give a product with mp 248-250°C. Found, %: C 50.66, H 2.83. $C_{17}H_{11}Cl_4NO_2$. Calculated, %: C 50.65, H 2.75.

General Method for the Preparation of Dimers Va-g and VI

A 0.002-mole sample of substituted 2-(p-dimethylaminophenyl)indan-1,3-dione was added to a solution of MeONa (from 0.05 g of Na and 6 ml of MeOH), and 0.25 g (0.002 mole) of I_2 was then added after the solid had dissolved completely. The mixture was stirred for 1.5 h

(for 15 min in the case of IIe and IV), after which the precipitate was removed by filtration and washed with 0.1 N $\text{Na}_2\text{S}_2\text{O}_3$ solution and water. The yields ranged from 60 to 80%. The products were purified with a chromatographic column packed with silica gel [benzene-ethyl acetate (1:1)] or by recrystallization from CHCl_3 -EtOH.

2,2'-Bis[5-bromo-2-(p-dimethylaminophenyl)indan-1,3-dione] (Vc). This compound had mp 178-180°C (decomp.). Found, %: C 59.67, H 3.93. $\text{C}_{34}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_4$. Calculated, %: C 59.50, H 3.81. PMR spectrum (δ , ppm): 2.93 s (Me), 6.57 d ($\text{H}^{3''}$, J = 9 Hz), 6.97 d ($\text{H}^{2''}$, J = 9 Hz), 7.70 d (H^7 , J = 8 Hz), 7.80 d (H^6 , J = 8 Hz), and 7.97 s (H^4).

2,2'-Bis[5-iodo-2-(p-dimethylaminophenyl)indan-1,3-dione] (Vd). This compound had mp 164-165°C (decomp.). Found, %: C 52.28, H 3.40. $\text{C}_{34}\text{H}_{26}\text{I}_2\text{N}_2\text{O}_4$. Calculated, %: C 52.33, H 3.36. PMR spectrum (δ , ppm): 2.93 s (Me), 6.59 d ($\text{H}^{3''}$, J = 9 Hz), 6.97 d ($\text{H}^{2''}$, J = 9 Hz), 7.55 d (H^7 , J = 8 Hz), 8.03 d (H^6 , J = 8 Hz), and 8.20 s (H^4).

2,2'-Bis[5-cyano-2-(p-dimethylaminophenyl)indan-1,3-dione] (Ve). This compound had mp 210-220°C (decomp.). Found, %: C 74.55, H 4.80. $\text{C}_{36}\text{H}_{26}\text{N}_4\text{O}_4$. Calculated, %: C 74.73, H 4.53.

2,2'-Bis[5-amino-2-(p-dimethylaminophenyl)indan-1,3-dione] (Vf). This compound had mp 360°C (DMFA-EtOH) and was insoluble in benzene, CHCl_3 , and EtOH but soluble in DMSO. Found, %: C 72.43, H 5.72. $\text{C}_{34}\text{H}_{30}\text{N}_4\text{O}_4$. Calculated, %: C 73.11, H 5.41.

2,2'-Bis[5-dimethylamino-2-(p-dimethylaminophenyl)indan-1,3-dione] (Vg). This compound had mp 203-205°C (decomp.). Found, %: C 74.28, H 6.23, N 9.03. $\text{C}_{38}\text{H}_{38}\text{N}_4\text{O}_4$. Calculated, %: C 73.24, H 6.23, N 9.11. PMR spectrum (δ , ppm) (the first values presented are the chemical shifts of the diastereomer that predominates in the mixture): 2.91 s (Me), 3.03 and 3.01 s (5-NMe), 6.58 d ($\text{H}^{3''}$, J = 8 Hz), 6.85 and 6.89 d (H^6 , J = 8 Hz), 6.96 and 6.90 s (H^4), 7.13 and 7.14 d ($\text{H}^{2''}$, J = 8 Hz), and 7.63 and 7.68 d (H^7 , J = 8 Hz).

2,2'-Bis[4,5,6,7-tetrachloro-2-(p-dimethylaminophenyl)indan-1,3-dione] (VI). This compound had mp 210-220°C (decomp.). Found, %: C 51.55, H 2.67. $\text{C}_{34}\text{H}_{20}\text{N}_2\text{O}_4\text{Cl}_8$. Calculated, %: C 50.78, H 2.51.

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CONCLUSION

In the Dieckmann-Shapiro condensation of phthalides with p-dimethylaminobenzaldehyde the reaction rate decreases with an increase in the electron-donor effect of the substituent in the phthalide and becomes comparable to the rate of a competing reaction - Claisen condensation of ethyl acetate with the aldehyde.

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