2-ARYL-4-AZAINDAIN-1,3-DIONES

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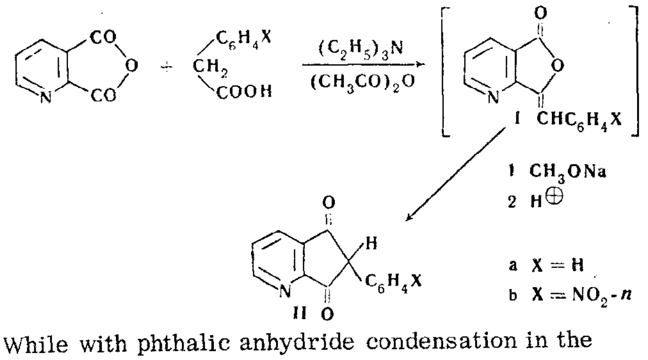
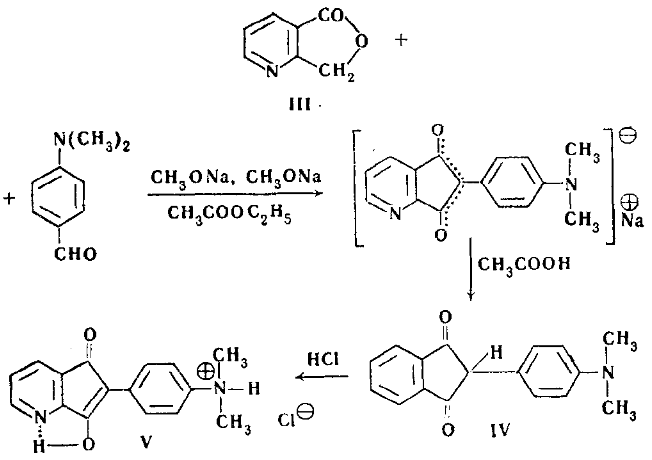
2-Phenyl-4-azaindan-1,3-dione and 2-(p-dimethylaminophenyl)-4-azaindan-1,3-dione are synthesized by condensing 4-azaphthalide with benzaldehyde and p-dimethylaminobenzaldehyde. 4-Azaphthalide reacts with p-nitrobenzaldehyde in hot acetic anhydride to give 3-(p-nitrobenzylidene)-4-azaphthalide, rearranged by sodium methoxide to 2-(p-nitrophenyl)-4-azaindan-1,3-dione. 2-Phenyl- and 2-(p-nitrophenyl)-4-azaindandiones are also obtained by sodium methoxide rearrangement of the products of reaction of quinolinic anhydride with phenylacetic and p-nitrophenylacetic acids. 2-Aryl-4-azaindandiones are deeply colored substances only slightly soluble, and without sharp melting points. They undergo methylation at the nitrogen atom, to give N-methylbetaines. The IR absorption spectra show that 2-aryl-4-azaindandiones exist in a strongly polarized enol form in the solid state.

2-Arylindan-1,3-diones are basically prepared via 3-arylidenephthalides, which latter are obtained either by condensing phthalic anhydride with arylacetic acids in the presence of alkali metal acetates at about 250° (Perkin condensation), or by condensing phthalides with aromatic aldehydes in the presence of sodium methoxide (Dieckman condensation). The first of these methods could not be used to prepare 3-benzylidene-4-azaphthalide (Ia), as quinolinic anhydride decomposes as low as 160°, and below that condensation does not take place. Experiments in which a solvent, acetic anhydride, was used, did not succeed either. The action of quinolinic anhydride with phenylacetic acid in the presence of triethylamine in acetic anhydride solution was also attempted. Using equimolecular amounts of the reactants and of triethylamine, and temperatures 10°–60°, it proved impossible to isolate the desired Ia in a pure state from the condensation product, but the crude product of the sodium methoxide condensation gave on working up, 2-phenyl-4-azaindan-1,3-dione (IIa), in about 12% yield (equation 1)

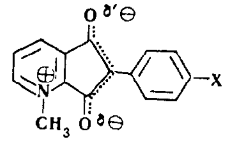


While with phthalic anhydride condensation in the presence of excess triethylamine and at higher temperature gives directly 2-phenylindan-1,3-dione in 50% yield [1], quinolinic anhydride does not give a like result, and chromatography showed the IIa content of the product to be negligible.

To try another synthetic route, utilizing the Dieckman condensation, to 2-phenyl-4-azaindan-1,3-dione, it is necessary to have available the appropriate azaphthalide, viz. the lactone of 2-hydroxymethylnicotinic acid (4-azaphthalide) (III), or else the lactone of 3-hydroxymethylpicolinic acid. Of recent years the azaphthalide III has attracted attention as a starting material for the synthesis of pharmaceuticals, so that various methods have been developed for preparing it [2–6], and we too have used these. Condensation of III with benzaldehyde in ethyl acetate solution (Dieckman's condensation as modified by Shapiro [7,8]), followed by acidification with acetic acid gave IIa as violet-brown crystals, in approximately 50% yield. 2-(p-Dimethylaminophenyl)-4-azaindan-1,3-dione (IV) was synthesized similarly, and this was generally isolated from the reaction products in the form of its hydrochloride (V). Addition of sodium acetate to an aqueous solution of salt V immediately resulted in separation of black glistening crystals of IV.



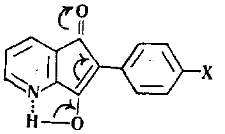
We have prepared 2-(p-nitrophenyl)-4-azaindan-1,3-dione (IIb) via the intermediate 3-(p-nitrobenzylidene)-4-azaphthalide (Ib) by two routes. Unlike phthalide, 4-azaphthalide has enhanced CH acidity and so can be condensed with p-nitrobenzaldehyde, even by just boiling in acetic anhydride, when it gives Ib in approximately 60% yield. The rearrangement of Ib by sodium methoxide also gives an approximately 60% yield. A 28% yield of IIb is obtained by sodium methoxide rearrangement of the product of reaction of quinolinic anhydride with p-nitrobenzaldehyde in acetic anhydride solution in the presence of triethylamine



VI a $X{=}H$; b $X{=}NO_2$; c $X{=}N(CH_3)_2$

(equation 1). All the 2-aryl-4-azaindandiones prepared were deply colored (IIa was violet-brown, IV black, IIb dark-red), and were only slightly soluble and had high melting points, Alkylation of IIa, IIb, and IV with diazomethane led to alkylation of the nitrogen in the pyridine ring, and formation of N-methylbetaines (VIa,b,c). Reaction of the sodium salts of IIa and IIb with dimethyl sulfate also gave respectively VIa and VIb. In no case was formation of O- or C-alkyl derivatives observed. Such a reaction course indicates that the most nucleophilic center in 2-aryl-4-azaindandiones is the nitrogen atom. Analysis of the electronic absorption spectra of IIa also indicate that the nitrogen atom is most readily protonated [9]. The N-methylbetaines VIb by a somewhat enhanced solubility. VIa dissolves in hot water, VIb in ethanol on heating, while only solvents of high solvating capacity, dimethylformamide and dimethylsulfoxide, are suitable for recrystallizing the diones IIa, IIb, and IV.

To elucidate the structures of the compounds prepared, their IR absorption spectra were measured at 1800–1480 and 3600–1800 cm^{-1}, but due to the very limited solubilities, this was done only for the crystalline state (at 1800–1480 cm^{-1} for a paraffin mull, and at 3600–2300 cm^{-1} in hexachlorobutadiene). Judging by the IR spectra, 2-aryl-4-azaindan-1,3-diones are strongly polarized enols with intramolecular hydrogen bonds.



$X{=}H$, NO_2, $N(CH_3)_2$

With all the compounds the most intense maximum in the range 1800–1480 cm^{-1} lies in the limits 1580–1530 cm^{-1}. Thus the spectrum picture for IIa, b, and for IV, as well as for the N-methylbetaines VIa, b, c and the alkali metal salts, are wholly of one type, whence it follows that 2-aryl-4-azaindandiones are endowed with a uniform electron density in the system $O{=}C{-}C{=}C{-}O \cdots H \cdots\rightarrow [O \cdots C \cdots C \cdots C \cdots O]^{-} H^{+}$. However in most cases it is less uniform that in betaines, and more uniform that in alkali metal salts. In the 1800–1480 cm^{-1} range not one of the 2-aryl-4-azaindandiones shows absorption above 1680 cm^{-1}, and the first maximum in that region probably corresponds to vibrations of the very abnormal carbonyl group. At the same time it is substantially less intense (as too with the betaines and metal salts) than the above mentioned maximum in the 1580–1530 cm^{-1} region.

EXPERIMENTAL

2-Phenyl-4-azaindan-1, 3-dione (IIa). a) 1.35 g (0.01 mole) 4-azaphthalide III and 1 ml (0.01 mole) benzaldehyde in 20 ml EtOAc was refluxed till the solution became homogeneous. Then a solution of NaOMe, prepared from 0.69 g (0.03 g-at) Na in 10 ml MeOH was added, and the whole refluxed for 1 hr. About 10 ml liquid was next distilled off, and the residue dissolved in 10 ml water. The alkaline solution was tested with actual charcoal and heated. The solution was filtered and the filtrate acidified with AcOH. A violet-brown crystalline precipitate of IIa was formed, yield 1.05 g (47%). It was slightly soluble in EtOH, insoluble in dioxane, nitromethane, and chlorobenzene. It was somewhat more soluble in AcOH. It dissolved in formic acid even in the cold to give a brownish-red solution. It was recrystallized from dimethylformamide, and vacuum-dried at 120°, mp ~ ~290° (decomp). Found: C75.71; H 4.16; N 6.34%. Calculated for $C_{14}H_9NO_2$: C 75.54; H 4.03; N 6.28%. IR spectrum, cm^{-1} (% absorption): 1493(54); 1530(66); 1547(64); 1620(31); 1649(19) hump; 1658 (20); 2580–3013.

b) 1.49 g quinolinic anhydride [10] was heated with 5 ml Ac_2O to dissolve it. The solution was cooled to 10°. Using external ice cooling, 1.4 ml (0.01 mole) dry triethylamine was added, when the solution turned an intense red. It was left standing at room temperature, and after 48 hr was diluted with 10 ml EtOH, and stirred into 10 ml EtOH plus 20 ml crushed ice, and 1 ml conc HCl in a beaker. After 48 hr the precipitate was filtered off, and dried at 50°. The resultant brownish-yellow powder (1.12 g) was covered with a solution of NaOMe prepared from 0.23 g (0.01 g at) Na and 10 ml dry MeOH, and the whole boiled for 30 min. 10 ml water was added to the resultant dark-red solution, which was then shaken with active charcoal, and filtered, the filtrate acidified with AcOH (2 ml), to give a violet-brown precipitate of minute crystals of 2-phenyl-4-azaindan-1, 3-dione yield 0.27 g (12%). It was recrystallized from dimethylformamide and vacuum-dried at 120°, mp about 290° (decomp). Found: C 75.19; H 4.23; N 6.37%. Calculated for $C_{14}H_9NO_2$: C 75.54; H 4.03; N 6.28%.

The compounds obtained by methods a and b had identical IR spectra over the ranges 1800–1480 and 3600–2300 cm^{-1}.

Sodium salt of IIa. 0.23 g (0.001 mole) IIa was dissolved with heating in 3 ml MeOH containing 0.04 g (0.001 mole) NaOH, the solution filtered, and ether added to the filtrate, to precipitate the red Na salt of 2-phenyl-4-azaindan-1, 3-dione, yield 0.20 g (82%). It was readily soluble in water and EtOH. Found: N 5.45%. Calculated for $C_{14}H_8NNaO_2$: N 5.71%. IR spectrum, cm^{-1} (% absorption): 1493(50) hump, 1513–1527(54), 1591(48), 1610(42) hump, 1637(37).

N-methylbetaine (VIa). a) 0.25 g (0.001 mole) sodium salt of 2-phenyl-4-azaindan-1, 3-dione and 3 ml freshly distilled Me_2SO_4 were heated together on a water-bath for 30 min, then left overnight at room temperature. The reaction products were diluted with ether and filtered, the precipitate washed with 1% Na_2CO_3, then with water. Yield of VIa 0.19 g (79%). VIa was soluble in acetone, $CHCl_3$, and hot water. It was recrystallized from water, when it gave brown needles, mp ~240° (decomp). Found: C 75.68; H 4.53; N 5.96%. Calculated for $C_{15}H_{11}NO_2$: N 5.90%. IR spectrum, cm^{-1} (% absorption): 1498(58), 1546(70), 1563(63), 1610(65), 1656(40).

b) 0.22 g (0.001 mole) 2-phenyl-4-azaindan-1, 3-dione was suspended in 6 ml ether, and 0.5 ml dimethylformamide, and with ice cooling an ethereal solution of diazomethane added (prepared from 1.0 g N-nitrosomethylurea). After 24 hr the precipitate of IVa was separated off, yield 0.18 g (75%).

3-(p-Nitrobenzylidene)-4-azaphthalide (Ib). 0.54 g (0.004 mole) 4-azaphthalide and 0.60 g (0.004 mole) p-nitrobenzaldehyde were refluxed together in 3 ml Ac_2O for 6 hr. After a day the yellow crystals of azaphthalide Ib were filtered off, and washed with benzene, yield 0.62 g (58%), recrystallized from dioxane-EtOH, mp 270–276°. Found: N 10.44%. Calculated for $C_{14}H_8N_2O_4$: N 10.46%. IR spectrum, cm^{-1} (% absorption): 1507(71), 15.78(64), 1596(58) hump, 1656(48), 1777(84).

2-(p-Nitrophenyl)-4-azaindan-1, 3-dione (IIb). a) A solution of NaOMe prepared from 0.04 g (0.0017 g at) Na and 20 ml MeOH was added to 0.40 g (0.0015 mole) finely powdered 3-(p-nitrobenzyldene)-

4-azaphthalide, with ice cooling, after which the mixture was allowed to stand at room temperature being shaken from time to time. After 30 min the red solution was filtered, and acidified with HCl, when a red precipitate of 2-(p-nitrophenyl)-4-azaindan-1,3-dione was obtained, yield 0.25 g (62%). Recrystallized from dimethylformamide, mp about 340° (decomp). Found: C62.85; H 3.11; N 10.34%. Calculated for $C_{14}H_8N_2O_4$: C 62.69; H 3.01; N 10.46%. IR spectrum, cm^{-1} (% absorption): 1493(65), 1545(77), 1560(60) hump, 1583(62) hump, 1628(45), 1673(47), 2664–2794.

b) 1.67 g (0.01 mole) quinolinic acid [11] and 7 ml Ac_2O were heated together at 120–130° for 1 hr, cooled to 90°, and 1.80 g (0.01 mole) p-nitrophenylacetic acid added. After the latter had dissolved, 2.8 ml (0.02 mole) dry Et_3N was added at such a rate that the temperature did not exceed 50°. The products were left overnight, and next day the dark red solution of condensation product was poured onto 40 g crushed ice and 2 ml concentrated acid in a beaker. The dark oil which separated quickly solidified. After filtering off, the solid was carefully dried and finely powdered, and 2.15 g suspended in 15 ml dry MeOH, and a solution of NaOMe (ex 0.23 g Na and 15 ml MeOH) added, the whole refluxed for 10 min, cooled, and 2–3 ml HCl added, when a dark red precipitate of compound IIb formed, yield 0.75 g (28%). The compounds prepared by methods a and b had identical IR spectra.

Sodium salt of IIb. 0.54 g (0.002 mole) IIb was rearranged in the cold with NaOMe (ex 0.07 g Na and 5 ml dry MeOH). After 15 min the dark red solution was filtered off, and washed with MeOH, yield 0.15 g (28%), recrystallized from dimethylformamide and MeOH. Found: N 9.37%. Calculated for $C_{14}H_7N_2NaO_4$: N 9.65%. IR spectrum, cm^{-1} (% absorption): 1506(47), 1544(83), 1582(73), 1600(63), 1654(21).

N-methylbetaine VIb. This was prepared similarly to VIa, using methods a and b. 0.29 g Na salt of IIb and Me_2SO_4 gave 0.22 g (78%) N-methylbetaine (VIb). Reaction of IIb with diazomethane gave VIb, 80% yield. Violet-brown crystals (ex dimethylsulfoxide), mp 335° (decomp). Found: C 64.25; H 3.51%. Calculated for $C_{15}H_{10}N_2O_4$: C 64.83; H 3.58%. IR spectrum, cm^{-1} (% absorption): 1495(28) hump, 1552–1582(57), 1620(52), 1665(15).

2-(p-Dimethylamino)-4-azaindan-1,3-dione (IV). Hydrochloride V. 1.35 g (0.01 mole) 4-azaphthalide and 1.49 g (0.01 mole) p-dimethylaminobenzaldehyde were boiled together in 15 ml dry EtOAc. About 3 ml liquid was distilled off, and a NaOMe solution ex 0.25 g (0.011 g at) Na and 15 ml MeOH was added, and the whole refluxed for 1 hr. The products were filtered, and about 5 ml AcOH added to the violet-red filtrate; after 2 min crystals of IV separated (0.90 g, 34%). A few drops of conc HCl were added to the filtrate. A red precipitate of 2-(p-dimethylaminophenyl)-4-azaindan-1,3-dione hydrochloride V formed suddenly, yield 0.75 g (24%, calculate on the 4-azaphthalide). It was recrystallized from dilute HCl (1:1). Found: N 9.40; Cl 11.48%. Calculated for $C_{16}H_{14}N_2O_2 \cdot HCl$: N 9.25; Cl 11.71%. IR spectrum, cm^{-1} (% absorption): 1511(59), 1549(81), 1562(80) hump, 1631(46), 1669(36).

0.37 g hydrochloride V was dissolved in 10 ml hot water, and a hot solution of NaOAc (0.34 g $NaOAc \cdot H_2O$ + 3 ml H_2O) added. Black crystals of indandione IV separated, and after 2 hr were filtered off. Yield 0.27 g. IV had low solubilities in EtOH, dioxane, and water, but it was readily soluble in dimethylformamide. It was recrystallized from dimethylformamide-EtOH (1:1), and dried at 100°, mp 240–245° (decomp). Found: C 72.07; H 5.28; N 10.80%. Calculated for $C_{16}H_{14}N_2O_2$: C 72.17; H 5.30; N 10.52%. IR spectrum cm^{-1} (% absorption): 1512(64), 1531(68), 1606(50), 1645(24) hump, 1664(28); 2600–2705; 2805; 2887; 3050–3085.

N-methylbetaine (VIc). Prepared from 0.27 g (0.001 mole) IV and diazomethane, similarly to VIa, using method b. Yield 0.22 g (79%) VIc. Recrystallized from EtOH, mp 270–275° (decomp). Found: C 73.02; H 5.65; N 9.88%. Calculated for $C_{17}H_{16}N_2O_2$: C 72.83; H 5.75; N 10.00%. IR spectrum, cm^{-1} (% absorption): 1516–1545(70), 1602(72), 1653(28).

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