

## Benzene-Ring-Substituted 2-Acetyl-1,3-indandiones

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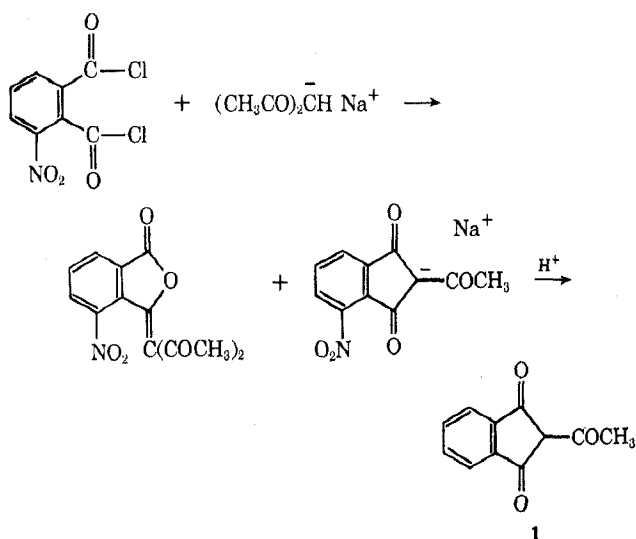
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Received December 16, 1969

2-Acetyl-4-nitro- and 2-acetyl-5-nitro-1,3-indandione (1 and 2) were synthesized by the reaction of 2,4-pentanedione with 3-nitro- and 4-nitrophthalic anhydride, respectively. A possible mechanism for the formation of 1 is presented. 3-(4-Nitrophthalidylidene)-2,4-pentanedione and the following compounds made from 1 and 2 are described: 4- and 5-amino-, 4- and 5-acetamido-, 4-hydroxyamino-, 4-hydroxy-, 4-methoxy-, and 4-acetoxy-2-acetyl-1,3-indandione.

Because direct nitrations of 1,3-indandione<sup>1</sup> and of 2-alkyl-1,3-indandiones<sup>2,3</sup> have failed to effect substitution onto the benzene ring, two indirect methods were investigated to synthesize 2-acetyl-4-nitro-1,3-indandione (1). By following a method developed by Bülow and Deseniss<sup>4</sup> for the preparation of 2-acetyl-1,3-indandione, we found that, when 3-nitrophthaloyl chloride reacted with the sodium salt of 2,4-pentanedione, a mixture of 3-(4-nitrophthalidylidene)-2,4-pentanedione and the sodium salt of 2-acetyl-4-nitro-1,3-indandione was formed (Scheme I).

SCHEME I



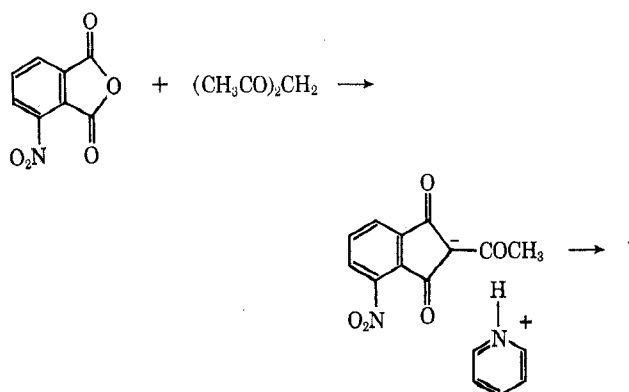
A more practical method for the synthesis of 1, in 76% yield, was found in the reaction of 3-nitrophthalic anhydride with 2,4-pentanedione in the presence of pyridine and a small amount of piperidine at 35–40° (Scheme II).

This reaction is a modification of that developed by Vanag and Oshkaia<sup>5</sup> for 4-nitro-1,3-indandione. It differs principally in the substitution of 2,4-pentanedione for malonic acid.

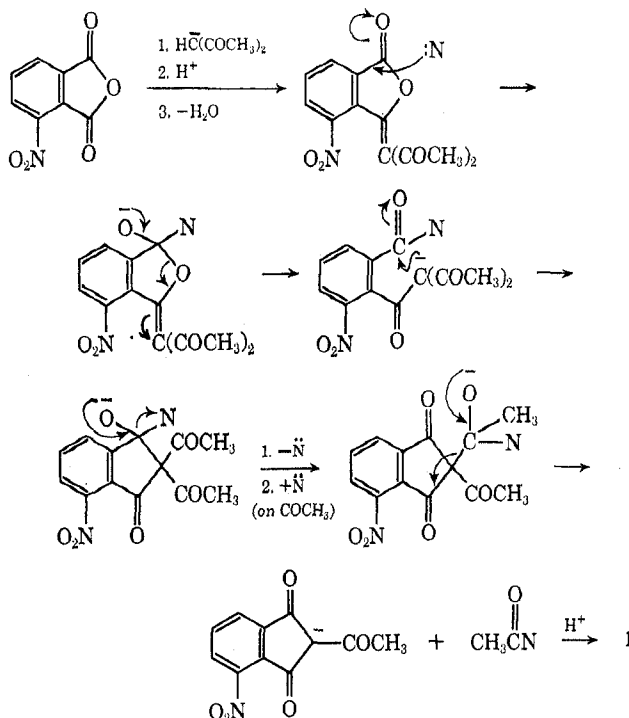
A possible mechanism for the formation of 1 is illustrated in Scheme III.

The 3-(4-nitrophthalidylidene)-2,4-pentanedione, a proposed intermediate in this reaction, was not isolated. However, its formation seems likely if one considers the numerous examples in the literature of phthalide

SCHEME II



SCHEME III

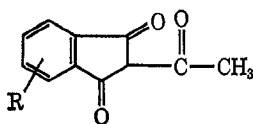


preparation by the condensation of a phthalic anhydride with an active methylene compound.<sup>6,7</sup>

The rearrangement portion of the suggested mechanism is similar to one proposed by Shapiro, Geiger, and Freedman<sup>8</sup> for the base-catalyzed rearrangement of 3-benzylidenephthalide to 2-phenyl-1,3-indandione. The

(1) G. Vanag, *Chem. Ber.*, **69**, 1069 (1936).  
 (2) L. Zalukajevs, *Latv. PSR Zināt. Akad. Vestis*, **1** (54), 147 (1952); *Chem. Abstr.*, **48**, 3942 (1954).  
 (3) T. A. Michelfeld, M. S. Thesis, University of Delaware, 1960.  
 (4) C. Bulow and M. Deseniss, *Chem. Ber.*, **37**, 4381 (1904).  
 (5) G. Vanag and V. Oshkaia, *J. Gen. Chem., USSR*, **28**, 1570 (1958).

(6) S. Gabriel and A. Michael, *Chem. Ber.*, **11**, 1679 (1878).  
 (7) E. Leupold, *ibid.*, **34**, 2836 (1901).  
 (8) S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960).

TABLE I  
 BENZENE-RING-SUBSTITUTED 2-ACETYL-1,3-INDANDIONES


Compd	R	Mp, °C	Recrystn solvent	Empirical formula	Calcd, %			Found, %		
					C	H	N	C	H	N
1	4-NO <sub>2</sub>	148-150	<i>t</i> -BuOH	C <sub>11</sub> H <sub>7</sub> NO <sub>5</sub>	56.65	3.00	6.01	56.94	2.80	5.97
2	5-NO <sub>2</sub>	210.5-211.5	MeOH	C <sub>11</sub> H <sub>7</sub> NO <sub>5</sub>	56.65	3.00	6.01	56.71	2.89	5.83
3	4-NH <sub>2</sub>	127.5-129	EtOH	C <sub>11</sub> H <sub>9</sub> NO <sub>3</sub>	65.02	4.43	6.90	64.88	4.46	6.90
4	5-NH <sub>2</sub>	187-190 dec	Aqueous MeOH	C <sub>11</sub> H <sub>9</sub> NO <sub>3</sub>						
5	4-NHCOCH <sub>3</sub>	179-180	MeOH	C <sub>13</sub> H <sub>11</sub> NO <sub>4</sub>	63.67	4.49	5.71	63.34	4.38	5.85
6	5-NHCOCH <sub>3</sub>	241-241.5	Aqueous MeOH	C <sub>13</sub> H <sub>11</sub> NO <sub>4</sub>	63.67	4.49	5.71	63.49	4.64	5.83
7	4-NHOH	163-165	MeOH	C <sub>11</sub> H <sub>9</sub> NO <sub>4</sub>	60.27	4.11	6.39	60.54	4.02	6.83
8	4-OH	128.5-129.5	EtOH	C <sub>11</sub> H <sub>9</sub> O <sub>4</sub>	64.71	3.92		64.90	3.84	
9	4-OCH <sub>3</sub>	129-130	MeOH	C <sub>12</sub> H <sub>10</sub> O <sub>4</sub>	66.06	4.59		65.66	4.82	
10	4-OCOCH <sub>3</sub>	133-134.5	EtOH	C <sub>13</sub> H <sub>10</sub> O <sub>5</sub>	63.41	4.07		63.16	3.83	

cleavage step is similar to that proposed by Soeder<sup>9</sup> to explain the formation of 2-methyl-1,3-indandione from the methoxide ion catalyzed condensation of dimethylphthalate with diethyl ketone.

The ease with which nitrophthalic anhydride reacted with 2,4-pentanedione under these mild conditions is probably due to the strong inductive effect exerted by the nitro group. The ease with which the subsequent rearrangement occurred is, in all likelihood, due to the combined presence of the nitro and acetyl groups. That a strongly electron-withdrawing group in the benzene ring facilitates this reaction is indicated by the fact that 3-acetamidophthalic anhydride did not react with 2,4-pentanedione under otherwise identical experimental conditions.

When 4-nitrophthalic anhydride was used in place of 3-nitrophthalic anhydride in the reaction with 2,4-pentanedione, 2-acetyl-5-nitro-1,3-indandione (2) was obtained in 11% yield.

Evidence for the structures of the nitro compounds 1 and 2 is provided by elemental analyses, absorption spectral data, the preparation of the derivatives listed in Table I and the formation of the substituted indeno-[1,2-*c*]pyrazol-4(1H)-ones, which will be described in a subsequent paper.<sup>10</sup>

Nitro compounds 1 and 2, when treated with sodium dithionite in alkaline solution, or reduced catalytically, gave the corresponding amines 3 and 4. These amines are very weak bases. Their hydrochlorides hydrolyzed easily by exposure to air. With acetic anhydride they formed acetyl derivatives (5 and 6). The 2-acetyl-4-hydroxy-1,3-indandione 8, obtained by diazotization of the amine 3, followed by treatment of the diazonium salt with dilute sulfuric acid, gave the typical alkylation and acylation reactions.

### Experimental Section<sup>11</sup>

**2-Acetyl-4-nitro-1,3-indandione (1).** A. From 3-Nitrophthaloyl Chloride.—A suspension in ether of the sodium salt of 2,4-

(9) R. W. Soeder (University of Delaware, Newark), University Microfilms (Ann Arbor, Mich.), Order No. 62-5873; *Diss. Abstr.*, **23**, 2326 (1963).

(10) W. A. Mosher and W. E. Meier, *J. Org. Chem.*, in press.

(11) Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken as nujol mulls on a Perkin-Elmer Infracord Model 137, using sodium chloride plates. Elemental analyses were performed by Dr. A. Bernhardt Microanalytisches Laboratorium in Max-Planck Institut für Kohlenforschung, Mülheim (Ruhr), Germany.

pentanedione was prepared by adding dropwise a solution of freshly distilled 2,4-pentanedione (5 g, 0.05 mol) in anhydrous ether (10 ml) to a stirred suspension of sodium sand<sup>12</sup> (1 g, 0.045 mol) in anhydrous ether (40 ml) and stirring for an additional 24 hr. To this suspension was added a solution of 3-nitrophthaloyl chloride<sup>13</sup> (5 g, 0.02 mol) in a mixture of ether (20 ml) and dioxane (2 ml). The suspension was stirred at room temperature for an additional 36 hr; then the solid product was collected by filtration, dried, and extracted for 16 hr in a Soxhlet extractor with ether. Removal of the solvent from ether extract gave 0.5 g (9%) of 3-(4-nitrophthalidylidene)-2,4-pentanedione, as pale yellow needles, mp 175-177° (ethanol). The ir spectrum shows a carbonyl peak at 1810 cm<sup>-1</sup>.

*Anal.* Calcd for C<sub>13</sub>H<sub>9</sub>NO<sub>6</sub>: C, 56.75; H, 3.27; N, 5.09. Found: C, 56.72; H, 3.50; N, 5.59.

The yellow powder left in the Soxhlet extractor was extracted for 2 hr with methanol and then treated dropwise with 6 *N* hydrochloric acid until it dissolved momentarily. Compound 1 immediately precipitated as a pale yellow solid. This crude product, 1.2 g (26%), was recrystallized from *t*-butyl alcohol to give 1 as fine yellow needles: ir 1730, 1665, 1615, 1595, and 1550 cm<sup>-1</sup>.

**B. From 3-Nitrophthalic Anhydride.**—A mixture of 3-nitrophthalic anhydride (25 g, 0.13 mol), pyridine (25 ml), piperidine (0.2 ml), and 2,4-pentanedione (12.5 g, 0.125 mol) was stirred at 35-40°.

A dark solution was formed in a short time and a bright yellow precipitate began to form. After 6 hr the reaction mass was cooled and the very thick crystalline product was collected by filtration, washed with ether and dried to give 33.2 g (82.2%) of the crude pyridinium salt of 1. This salt, treated with 6 *N* hydrochloric acid (100 ml), gave a yellow crystalline precipitate, which, collected by filtration, washed with water, and dried, yielded 19.0 g (76% overall yield) of 1 as fine yellow needles. A mixed melting point taken with compound 1, obtained from 3-nitrophthaloyl chloride as described under A, showed no depression.

**2-Acetyl-5-nitro-1,3-indandione (2).**—A mixture of 4-nitrophthalic anhydride<sup>14</sup> (5 g, 0.025 mol), 2,4-pentanedione (2.5 g, 0.025 mol), anhydrous pyridine (5 ml), and piperidine (3 drops) was stirred at 35-40° for 7 hr and then filtered. The solid was washed with ether and dried to give 4 g (30%) of the pyridinium salt of 2, which, treated with hydrochloric acid, as in the above procedure for compound 1, yielded 2.5 g (11%) of 2 as pale yellow crystals: ir 1730, 1660, 1610, 1595, and 1545 cm<sup>-1</sup>.

**2-Acetyl-4-amino-1,3-indandione (3).** A. Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> Reduction.—To a stirred solution of concentrated ammonium hydroxide (50 ml) in water (300 ml) were added nitro compound 1 (3.8 g, 0.016 mol) and then a solution of sodium dithionite (10 g, 0.043 mol) in water (50 ml). The solution immediately turned deep orange and slightly warm. After 1 hr concentrated hydrochloric acid was added at room temperature to make the reac-

(12) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., p 125.

(13) V. J. Chambers, *J. Amer. Chem. Soc.*, **25**, 607 (1903).

(14) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **95**, 208 (1909).

tion mixture strongly acidic. The precipitate was collected by filtration, washed with water, and dried to give 1.8 g (54%) of **3** as yellow crystals:  $\nu$  3520, 3400, 3250, 1710, 1660, 1630, 1610, and 1590  $\text{cm}^{-1}$ .

**B. Catalytic Reduction.**—A suspension of **1** (10 g, 0.043 mol) and 10% Pd-C (1 g) in absolute ethanol (250 ml) was hydrogenated at 50 psi (Paar shaker) at room temperature until the calculated amount of hydrogen was absorbed. The reduction was somewhat exothermic. Then the catalyst was removed immediately by filtration. The filtrate on cooling gave 5.6 g (64%) of **3** identical with the amine obtained under A, by mixture melting point and by comparison of the infrared spectra.

The hydrochloride of **3**, which hydrolyzed quickly to the free base on contact with air, was formed as white crystals, by bubbling dry hydrogen chloride into an ether solution of **3**.

Treatment of a solution of **3** (2.5 g, 0.012 mol) in anhydrous methanol (25 ml) with methyl iodide (4 ml, 0.064 mol) and sodium bicarbonate (2.5 g, 0.030 mol) at reflux for 16 hr gave (2-acetyl-1,3-dioxo-4-indanyl)trimethylammonium iodide as yellow crystals, which decomposed at 238–240°.

Upon treating a concentrated aqueous solution of the above iodide with a few drops of 70% perchloric acid, the perchlorate was obtained as pale yellow crystals which decomposed at 282–285°.

*Anal.* Calcd for  $\text{C}_{14}\text{H}_{16}\text{ClNO}_7$ : C, 48.70; H, 4.64. Found: C, 48.63; H, 4.72.

**2-Acetyl-5-amino-1,3-indandione (4)**, was obtained by treating the nitro compound **2** (6 g, 0.026 mol) with sodium dithionite (23 g, 0.13 mol) and ammonium hydroxide (200 ml), as described in procedure A for the isomer **3**. In this case the reaction mass was heated to 50° on a steam bath and then allowed to return to room temperature. A 36% yield of **4**, as bright yellow crystals was obtained. These crystals darkened quickly upon exposure to air. Recrystallization from aqueous methanol gave brown crystals:  $\nu$  3550, 3425, 3300, 1710, 1650, 1620, 1600, 1580  $\text{cm}^{-1}$ .

**4-Acetamido-2-acetyl-1,3-indandione (5)**.—A mixture of amine **3** (0.5 g, 0.003 mol) and acetic anhydride (1 ml, 0.01 mol) refluxed for 3 min gave, after cooling to 0°, a yellow precipitate, which was purified by sublimation under a high vacuum at 120°. A 58% yield of **5** as pale yellow powder was obtained:  $\nu$  3400, 1725, 1700, 1650, 1620, and 1600  $\text{cm}^{-1}$ .

**5-Acetamido-2-acetyl-1,3-indandione (6)** was obtained in 54% yield by treating amine **4** with acetic anhydride as described above for the isomer **5**. Sublimation at 210° (1.5 mm) and recrystallization from aqueous methanol gave pale yellow crystals:  $\nu$  3400, 1725, 1700, 1655, 1625, 1605, and 1540  $\text{cm}^{-1}$ .

**2-Acetyl-4-hydroxyamino-1,3-indandione (7)**.—A suspension of **1** (13 g, 0.056 mol) and 10% Pd-C (1g) in absolute ethanol (250 ml) was hydrogenated at 12 psi (Paar shaker) at room temperature until the calculated amount of hydrogen was absorbed. Then the catalyst was removed by filtration and the filtrate was

diluted to 500 ml with water, and cooled in a Dry Ice-acetone mixture to give 9 g of crude **7** contaminated with amine **3**. The amine was removed by washing the crude with ether. Recrystallization of the residue, 7 g (57%), from methanol gave **7** as yellow orange crystals:  $\nu$  3370, 1715, 1695, 1650, 1610, and 1585  $\text{cm}^{-1}$ .

**2-Acetyl-4-hydroxy-1,3-indandione (8)**.—A solution of **3** (5 g, 0.025 mol) in a mixture of acetic acid (50 ml) and concentrated sulfuric acid (20 ml) was added dropwise to a stirred and cooled (below 10°) solution of nitrosylsulfuric acid, prepared from sodium nitrite (5 g, 0.07 mol) and concentrated sulfuric acid (25 ml) following the standard procedure. After stirring for an additional 0.5 hr at 10° the reaction mass was added slowly to a stirred and warm (80°) solution of concentrated sulfuric acid (30 ml) in water (90 ml). The precipitate was collected and purified by sublimation at 100° under a high vacuum to give 2.5 g (49%) of **8** as pale yellow crystals:  $\nu$  3450, 1705, 1655, and 1610  $\text{cm}^{-1}$ .

The methoxy derivative **9** was obtained in 93% yield by adding dimethyl sulfate (0.7 ml, 0.07 mol) to a stirred mixture of **8** (1 g, 0.005 mol), sodium hydroxide (0.4 g, 0.01 mol), and water (30 ml), heating to 35° for 15 min, cooling to room temperature, and stirring for 2 days. The infrared spectrum of the collected pale yellow precipitate showed peaks at 1720, 1660, 1630, 1595, and 1280  $\text{cm}^{-1}$ .

The acetoxy derivative **10** was formed by adding **8** (0.5 g, 0.003 mol) to 97% acetic anhydride (3 ml, 0.03 mol). The mixture was refluxed for 15 min, the excess of acetic anhydride and acetic acid evaporated under vacuum, and the residue triturated with petroleum ether (bp 60–70°) to give, after several crystallizations from ethanol, 0.46 g (75%) of **10**, as silky colorless crystals:  $\nu$  1770, 1730, 1670, 1635, and 1610  $\text{cm}^{-1}$ .

**Attempted Preparation of 4-Acetamido-2-acetyl-1,3-indandione from 3-Acetamidophthalic Anhydride.**—2,4-Pentanedione (2.5 g) and 2 drops of piperidine were added to a stirred mixture of 3-acetamidophthalic anhydride (5 g) and anhydrous pyridine (5 ml). The mixture was maintained at 40° for 24 hr. Only starting materials were recovered.

**Registry No.**—**1**, 25125-04-6; **2**, 25125-05-7; **3**, 25125-06-8; **4**, 25125-07-9; **5**, 25125-08-0; **6**, 25125-09-1; **7**, 25125-10-4; **8**, 25125-11-5; **9**, 25125-12-6; **10**, 25125-13-7; 3-(4-nitrophthalidylidene)-2,4-pentanedione, 25125-14-8; (2-acetyl-1,3-dioxo-4-indanyl)trimethylammonium iodide, 25125-15-9; (2-acetyl-1,3-dioxo-4-indanyl)trimethylammonium perchlorate, 25125-16-0.

**Acknowledgment.**—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.