of methanol and 2-propanol. The colorless crystals (2.5 g., 28%) melted at 287–288°.

Anal. Calcd. for $C_{19}H_{22}ClN$: Cl, 11.83. Found: Cl, 11.65.

N-(2-Hydroxyethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIf). This compound was prepared by a procedure similar to that described for the methylamino analog from the ketone (V) (9.92 g., 0.04 mole) and ethanolamine (2.14 g., 0.035 mole). The colorless hydrochloride, recrystallized from a mixture of methanol and 2-propanol, amounted to 9.2 g., (80%) and melted at 290–291°.

Anal. Calcd. for $C_{20}H_{24}ClNO$: Cl, 10.75. Found: Cl, 10.89.

N-(2-Chloroethyl)spiro[cyclohexane-1,9'-fluoren]-4-amine hydrochloride (VIIIg). Compound VIIIf (8.0 g.) was mixed with 20 ml. of thionyl chloride. After the initial reaction was over the mixture was heated under gentle reflux for 3 hr. The excess thionyl chloride was evaporated under reduced pressure and the residue was diluted with 100 ml. of dry ether. The crude salt was collected and recrystallized from aqueous methanol as colorless crystals (4.3 g., 51%) which melted at about 355°.

Anal. Calcd. for $C_{20}H_{23}Cl_2N$: Cl, 20.36. Found: Cl, 20.24.

N,N,N-Trimethylspiro[cyclohexane-1,9'-fluoren]-4-ammonium chloride. Compound VIIIb (11.5 g.) and 10% sodium hydroxide solution (100 ml.) were mixed and warmed. The mixture was cooled and the oily amine was extracted with ether. The extract was dried over calcium chloride and the solvent was evaporated. The solid base which remained as a residue (6.0 g.) was sealed in a glass tube with 20 ml. of methyl chloride. The amine dissolved and the quaternary ammonium salt soon began to separate. After standing overnight the almost solid mixture was crystallized from a mixture of methanol and 2-propanol. The colorless crystals (3.2 g., 27%) melted at about 290° with decomposition.

Anal. Calcd. for $C_{21}H_{26}ClN$: Cl, 10.81. Found: Cl, 10.85.

Acknowledgment. The authors wish to express their appreciation to Professor A. L. Allred of Northwestern University for the determination and interpretation of the NMR spectrum.

ELKHART, IND.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

2-Substituted 1,3-Indandiones

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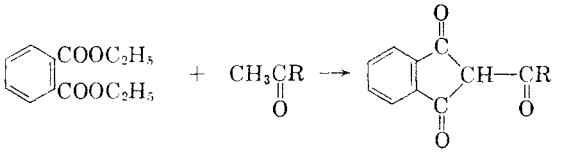
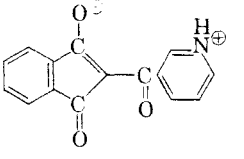
Various 2-aryl- and 2-acyl-1,3-indandiones were prepared. 3-(α-Hydroxy-2,3-dimethoxybenzyl)phthalide (IV) was established as a probable intermediate in the synthesis of 2-(2,3-dimethoxyphenyl)-1,3-indandione (V) from phthalide and 2,3-dimethoxybenzaldehyde. 1,3-Dioxo-2-indancarboxamide (IX) was sought because of its structural relationship with the tetracycline antibiotics. It was accessible from the corresponding nitrile but not from the ethyl ester. Fusion of the sodium enolate of this ester with ammonium acetate gave ethyl 1-imino-3-oxo-2-indancarboxylate (VIII).

In a search for improved blood anticoagulants in the 1,3-indandione series[2–7] we have prepared a number of new 2-substituted-1,3-indandiones. The 2-acyl derivatives listed in Table I were prepared by the sodium methoxide–catalyzed condensation of diethyl phthalate with the appropriate methyl ketone (Method A).[8,9]



4-Chloroacetophenone and 4-ethylacetophenone reacted satisfactorily in refluxing benzene or toluene, but with methyl 4-chloro-1-naphthyl ketone and 4-hydroxyacetophenone it was necessary to use an excess of diethyl phthalate as the solvent. Methyl 3-pyridyl ketone was unusually reactive; the very high melting point and low solubility of the product suggest that it exists as a zwitterion such as:



It is amphoteric. As an acid it is readily soluble in dilute alkali but as a base it is so feeble that it is precipitated from aqueous solution when diluted to an acid strength less than 3*N*.

The 2-aryl-1,3-indandiones of Table I were prepared by the alkoxide-catalyzed condensation of phthalide with aromatic aldehydes (Method B).[10,11] Even though the yields were low this approach was found to be both versatile and convenient.

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(2) W. H. Seegers, *Pharmacol. Revs.*, **3**, 278 (1951).

(3) J. T. Correll, L. L. Coleman, S. Long, and R. F. Willy, *Proc. Soc. Exptl. Biol. Med.*, **80**, 139 (1952).

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(5) S. R. Heisy, J. P. Saunders, and K. C. Olson, *J. Agr. Food Chem.*, **4**, 144 (1956).

(6) W. Cavallini, E. Milla, E. Grumelli, and F. Ravenna, *Il Farmaco (Pavia), Ed. sci.*, **10**, 710 (1955); *Chem. Abstr.*, **50**, 10707 (1956).

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(8) E. Schwerin, *Ber.*, **27**, 104 (1894).

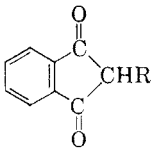
(9) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(10) W. Dieckmann, *Ber.*, **47**, 1439 (1914).

(11) C. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1331 (1936).

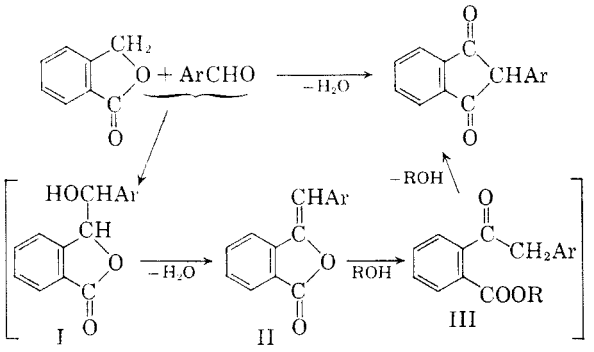
TABLE I

2-SUBSTITUTED-1,3-INDANDIONES

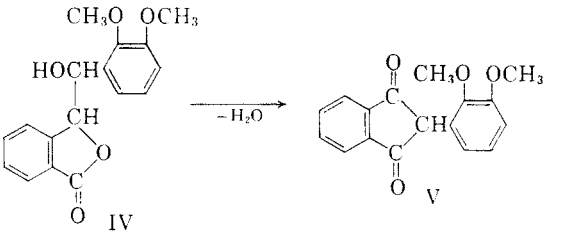


R	Method	Reaction Temp., °	Yield, %	M.P., °[a]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
2-Acyl-1,3-indandiones										
4-Chlorobenzoyl[b]	A	Reflux	5[c]	184	66.5	66.0	3.43	3.34	12.1	12.1
4-Chloro-1-naphthoyl	A	100–120	8[d]	200–201	71.8	71.8	3.31	3.33	10.6	10.8
4-Ethylbenzoyl	A	Reflux	9[e]	87	77.7	77.9	5.07	5.26		
4-Hydroxybenzoyl	A	100–110	60[d]	279	72.2	72.4	3.79	3.76		
Nicotinoyl	A	30–40	7[f,g]	306–308	71.8	72.0	3.63	3.70		
2-Aryl-1,3-indandiones										
2-Chlorophenyl	B	Reflux	31[h]	185	70.2	70.2	3.53	3.53	13.8	13.6
2,6-Dichlorophenyl	B	Reflux	25[h]	158	61.9	61.8	2.77	2.74	24.4	24.2
2,3-Dimethoxyphenyl	B	65	27[h]	148–149	72.3	72.1	5.00	4.93		
4-Hydroxy-3-methoxyphenyl	B	Reflux	17[d]	225–231	71.6	71.9	4.51	4.45		
4-Hydroxyphenyl	B	62	11[d]	178–179[i]	75.7	75.5	4.23	4.42		
2-Methoxyphenyl	B	55	24[d]	172[j]	76.2	76.3	4.80	4.67		
3,4-Methylenedioxyphenyl	B	Reflux	29[h]	160	72.2	72.1	3.79	3.49		

[a] All melting points are corrected. [b] Hemihydrate. [c] Product recrystallized from 80% 2-ethoxyethanol. [d] Recrystallized from 2-ethoxyethanol. [e] Recrystallized from 80% ethanol. [f] The molar ratio of diethyl phthalate, sodium methoxide, and methyl 3-pyridyl ketone was 2:4:1. An exothermic reaction began spontaneously. After 2.3 hr. water was added and extraneous material was removed by extraction with chloroform. The product was precipitated by acidification, washed with acetone, and recrystallized from dimethylformamide. In another run at 100° the yield was 1.5%. [g] Calcd. % N, 5.58. Found, 5.60. [h] Recrystallized from absolute ethanol. [i] Lit. m.p. 174–176° (ref. 6) for material prepared by a different route. [j] Resolidified, then remelted at 175–177°.



Of the indicated intermediates in this condensation the literature provides support for both II and III. Both benzalphthalide[12–15] and methyl 2-phenylacetylbenzoate,[15] prepared by other methods, rearrange in the presence of alkoxides to form 2-phenyl-1,3-indandione. Moreover, both compounds rearrange at the same rate.[15] Dieckmann attempted to isolate benzalphthalide after allowing benzaldehyde and phthalide to react in the presence of milder bases such as amines or potassium carbonate, but was not successful.[10] We have now isolated the probable aldol-type precursor, I, of a substituted benzalphthalide. In the reaction of phthalide with ethanolic solutions of sodium methoxide and 2,3-dimethoxybenzaldehyde the mixture was not refluxed but was held at 65° to see if lower reaction temperatures might give improved yields. In addition to 27% of the expected 2-(2,3-dimethoxyphenyl)1,3-indandione (V) there was also obtained 13% of 3-(α-hydroxy-2,3-dimethoxybenzyl)phthalide (IV). The presence



of hydroxyl and γ-lactone functions was supported by infrared absorption maxima at 2.86 and 5.70 μ.[16] Sodium ethoxide in refluxing ethanol converted the hydroxylactone (IV) to V in 19% yield.

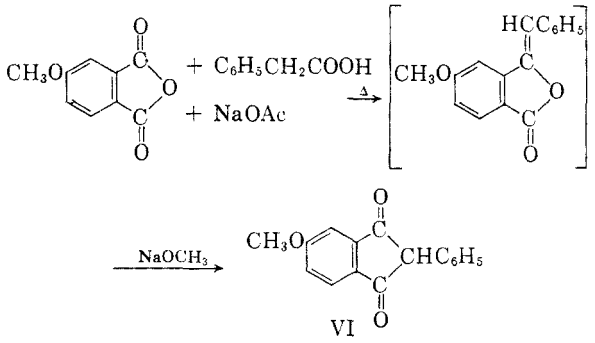
A molecule of water is necessarily generated in the synthesis of V from either the hydroxylactone, IV, or from 2,3-dimethoxybenzaldehyde. It is probable that the low yields obtained in such reactions are due to the saponification of intermediate lactones caused by water produced in the reaction. This view is supported by Nathanson's observa-

(12) F. Nathanson, *Ber.*, 26, 2576 (1893).
(13) A. Eibner, *Ber.*, 39, 2203 (1906).
(14) R. Weiss, *Org. Syntheses*, **Coll. Vol. II**, 61 (1943).
(15) S. Escola, T. Lahikainen, and A. Korhanen, *Suomen Kemistilehti*, 20B, 21 (1947); *Chem. Abstr.*, 41, 7213 (1947).

(16) The infrared spectrum was determined in chloroform solution by Mrs. Cecilia Jorgensen.

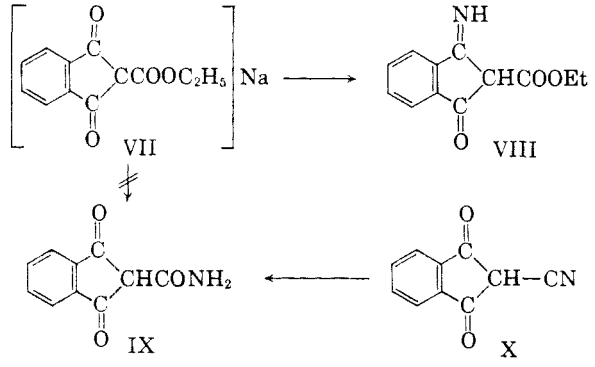
tion that benzalphthalide in absolute ethanol could be rearranged almost quantitatively to 2-phenyl-1,3-indandione, but in 96% ethanol the yield was only one fourth as great.[12]

5 - Methoxy - 2 - phenyl - 1,3 - indandione (VI) was prepared as follows:



This method[6,12,14] was not successful with phthalic anhydrides substituted in the 4-position with hydroxyl-, benzoyl- or sulfonic acid groups.

A consideration of the 1,3-dioxo-2-carboxamide grouping in the tetracycline antibiotics suggested that 1,3-dioxo-2-indancarboxamide (IX) might show antibacterial activity. An attempt to prepare this amide by treating the sodium salt of ethyl 1,3-dioxo-2-indancarboxylate[17] (VII) with concentrated ammonia in an autoclave at 100° was unsuccessful. When VII was fused with ammonium acetate the product obtained was not an amide,



but an imino ester, VIII.[18] In another approach diethyl phthalate and acetonitrile were condensed to give 1,3-dioxo-2-indancarbonitrile (X),[19] an enolic acid with a pK_a of 2.9. The nitrile (X) was readily hydrolyzed to the desired amide (IX) by dissolving it in concentrated sulfuric acid and pouring this solution into cold water. This amide was active *in vitro* against a variety of gram-positive and gram-negative bacteria, but only at relatively high concentrations (*ca.* 1 mg./ml.).[20]

The anticoagulant activities of the compounds listed in Table I will be reported separately.[21]

EXPERIMENTAL

Method A. 2-(4-Hydroxybenzoyl)-1,3-indandione. A well stirred suspension of 48.6 g. (0.9 mole) of sodium methoxide in 300 ml. (1.52 moles) of diethyl phthalate was heated to about 70° during the cautious addition of a solution of 40.8 g. (0.3 mole) of *p*-hydroxyacetophenone in 100 ml. of diethyl phthalate. After stirring at 100–110° for 7 hr. the mixture became too thick to stir. This temperature was maintained for another 6 hr., the mixture was allowed to cool, and 300 ml. of water and 100 ml. of benzene were added. The mixture was warmed until the solids had dissolved, the organic (upper) layer was extracted with 100 ml. of water and the resulting organic (lower) layer was discarded. The combined aqueous solutions were washed with 50 ml. of benzene, diluted with 400 ml. of 95% ethanol, heated to boiling, acidified with 80 ml. of concd. hydrochloric acid, and chilled to 10°. The solid product was washed with ethanol, with water, and then with more ethanol; 48.1 g. (60%), m.p. 279° dec., unchanged after recrystallization from 2-ethoxyethanol.

Method B. 2-(2,3-Dimethoxyphenyl)-1,3-indandione (IV). Hot solutions of 83.1 g. (0.5 mole) of 2,3-dimethoxybenzaldehyde in 50 ml. of absolute ethanol and 67.1 g. (0.5 mole) of phthalide in 50 ml. of absolute ethanol were combined, cooled to 20°, and maintained at this temperature during the gradual addition of a solution of 27.0 g. (0.5 mole) of sodium methoxide in 100 ml. of absolute ethanol. The reaction mixture was loosely stoppered and kept for 50 hr. in an oven maintained at about 65°. The resulting thick red slurry was diluted with 150 ml. of ethanol, heated to boiling, then acidified by the gradual addition with stirring of a slight excess (51 ml.) of concd. hydrochloric acid. The mixture was chilled to 5°, the solid collected, washed with ethanol and then with water. Two recrystallizations from ethanol gave 38.5 g. (27%) of elongated prisms, m.p. 148–149°.

Analogous reactions run at the reflux temperature (Table I) were stopped after 1–3 hr. The higher yields were obtained with the shorter reaction times.

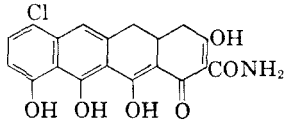
3-(α-Hydroxy-2,3-dimethoxybenzyl)phthalide (IV). The acidic, alcoholic filtrate from the above reaction mixture was allowed to stand for 2 weeks in an unstoppered, wide-mouthed flask. It had then deposited 19.6 g. (13%) of large, tan prisms. Two recrystallizations from ethanol, using decolorizing charcoal, gave 14.1 g. of prisms, m.p. 141°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.38; mol. wt., 300.3. Found: C, 67.6, 67.7; H, 4.91, 4.99; mol. wt., 321.

A solution of 0.051 g. (0.0022 mole) of sodium in 3.5 ml. of absolute ethanol was combined with 0.601 g. (0.002 mole) of the above hydroxyphthalide (IV) and heated under reflux for 20 min. The resulting thick orange slurry was cooled, agitated during the dropwise addition of 1.9 ml. of concd. hydrochloric acid, then evaporated to dryness. Extraction with 4 ml. of chloroform, evaporation of the extract, and crystallization of the residual sirup from 2 ml. of ethanol gave 0.105 g. (19%) of rods, m.p.

(17) W. Wislicenus, *Ber.*, 20, 593 (1887).

(18) In later work in these laboratories, directed toward the total synthesis of tetracycline antibiotics, the product isolated from a similar fusion of a keto ester with ammonium formate was not an imine, but was the desired keto amide,



[J. H. Boothe, A. S. Kende, T. L. Fields, and R. G. Wilkinson, *J. Am. Chem. Soc.*, 81, 1006 (1959)].

(19) This compound was first prepared in another investigation by Dr. R. S. Long.

(20) Antibacterial testing was done by Mr. A. C. Dornbush and his co-workers in the Microbiology Department of these laboratories.

(21) V. Downing *et al.*, to be published.

147–148°. Admixture with 2-(2,3-dimethoxyphenyl)-1,3-indandione (V) did not depress the melting point.

5-Methoxy-2-phenyl-1,3-indandione (VI). A mixture of 13.9 g. (0.078 mole) of 4-methoxyphthalic anhydride, 11.8 g. (0.087 mole) of phenylacetic acid, and 0.5 g. of freshly fused sodium acetate was stirred at 230–245° for 2 hr.; about 1 ml. of a distillate was collected. The partially cooled mixture was diluted with 100 ml. of absolute ethanol, the temperature was adjusted to about 60° and a solution of 4.9 g. (0.091 mole) of sodium methoxide in 50 ml. of hot absolute ethanol was slowly added. After heating the mixture at 70–80° for 5 min. there were added 70 ml. of water and (slowly) 50 ml. of 2*N* hydrochloric acid. The mixture was allowed to stand at 5°, the solid was collected by filtration and washed with water until free of halides; 14.9 g. (76%), m.p. 183–185°. Recrystallization from ethanol gave 12.7 g., m.p. 187°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.80. Found: C, 76.1; H, 4.98.

Ethyl 1-imino-3-oxo-2-indancarboxylate (VIII). To a beaker containing 231.2 g. (3.0 moles) of partially molten ammonium acetate at 100° there was added with stirring 72.1 g. (0.3 mole) of the powdered sodium salt of crude ethyl 1,3-dioxo-2-indancarboxylate (VII).[17] After continuous manual stirring at 110–115° for 40 min. the original yellow dough was all liquefied. Mechanical stirring at 110–115° was continued for 1.4 hr. The hot melt was poured with swirling into 450 ml. of hot water. The dark solid which separated on cooling was collected by filtration and the filtrate extracted twice with chloroform. Solids had separated overnight from both the aqueous solution and the chloroform extracts. These solids and the earlier, dark solid were recrystallized repeatedly from dimethylformamide (2.5 ml./g.) or 2-ethoxyethanol (15 ml./g.), combining fractions as purity warranted. Two insoluble, orange by-products were also encountered; one was almost infusible, the other melted at 239–240° dec. The product amounted to 7.2 g. (13%) of yellow-orange crystals, m.p. 242–244° dec.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.10; N, 6.45; O, 22.1. Found: C, 65.8, 66.0; H, 4.41, 4.70; N, 6.47; O, 21.9.

1,3-Dioxo-2-indancarbonitrile (X).[19] A mixture of 216 g. (4.0 moles) of sodium methoxide, 205 g. (5.0 moles) of acetonitrile, and 444 g. (2.0 moles) of diethyl phthalate was stirred under reflux for 6 hr. (After 2 hr. the mixture had become so thick that it was diluted with another 200 ml. of acetonitrile.) The mixture was cooled and 400 ml. of ether was added. The solid was collected by filtration, washed with ether, dried, dissolved in 3.6 l. of water, acidified with 250 ml. of concd. hydrochloric acid, and allowed to stand at 5° for several hours. The product was collected and washed with water; 232 g. (68%), bright yellow, m.p. 194–195° dec. Recrystallization from tetrahydrofuran-benzene, using decolorizing charcoal, raised the m.p. to 202–204° dec. An analytical sample was obtained by sublimation at 0.2 mm. and *ca.* 180°; m.p. 205–206° dec.

Anal. Calcd. for $C_{10}H_5O_2N \cdot {}^1/_2H_2O$: C, 66.66; H, 3.36; N, 7.78; moisture, 5.00%; neut. equiv., 180. Found: C, 66.71; H, 3.52; N, 8.13; moisture (Karl Fischer), 4.24%; neut. equiv., 190; pK_a 2.9. The infrared absorption spectrum[22] showed an intense peak at 4.51 μ, confirming the presence of the nitrile function.

1,3-Dioxo-2-indancarboxamide (IX). Eight ml. of concd. sulfuric acid was kept cold while 2.0 g. of unpurified 1,3-dioxo-2-indancarbonitrile was dissolved therein. The deep orange solution was allowed to stand overnight, then poured into 200 ml. of cold water. The resulting solid was collected, washed with water and ethanol, and recrystallized from dimethylformamide-water to give 0.9 g. of yellow-orange needles; these sintered from 160 to 220°. After extraction with 200 ml. of boiling benzene the extract was allowed to stand at 5°. It deposited 0.2 g. of an orange powder which sintered from 180 to 220°.

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.5; H, 3.73; N, 7.41. Found: C, 63.9; H, 4.00; N, 7.42.

The infrared spectrum[22] showed no absorption in the nitrile range (4–5 μ); absorption maxima at 2.90, 2.98, and 6.05 μ were compatible with the presence of a primary amide grouping.

Acknowledgment. The authors express appreciation to Drs. R. P. Parker, J. J. Denton, and P. F Dreisbach for their helpful suggestions and encouragement, to Mr. O. A. Sundberg and his associates for the microanalyses, and to Mr. B. A. Heiser and Drs. E. Baumgarten and E. Conroy for 2,6-dichlorobenzaldehyde, 4-methoxyphthalic anhydride, and methyl 3-pyridyl ketone.

PEARL RIVER, N. Y.

(22) Solids were pressed with potassium bromide for infrared spectral determinations.