worked up to give 9.0 g of an oil which, on redistillation, yielded 8.0 g (89%) of a colorless liquid, bp 100° (0.6 mm), $n^{24}D$ 1.5264. Glpc showed the purity to be 99+%; nmr ($CDCl_3$), δ 1.31 [6 H, $(CH_3)_2C$], 1.63 (1 H, OH), 3.57 (2 H, CH_2), 3.80 (3 H, CH_3O), 6.72–7.25 (4 H, aromatic, *meta* substitution). *Anal.* ($C_9H_{10}O_2$) C, H.

The alcohol IX, with dry HCl, PBr_3 in Et_2O, or $SOCl_2$ in C_6H_6 gave complex mixtures.

3-(3-Methoxyphenyl)-3-methylbutyronitrile (X).—At 0°, 46.0 g (0.402 mole) of $MeSO_2Cl$ was added dropwise to a solution of 65.6 g (0.364 mole) of IX in 262 ml of dry C_5H_5N. The mixture was allowed to warm to room temperature overnight and poured into 500 ml of H_2O. The suspension was extracted with three 100-ml portions of Et_2O. The extracts were washed once with cold H_2O, cold 10% HCl, and cold H_2O, then dried over $MgSO_4$. Distillation of the solvent in a rotary evaporator left 88.0 g of a colorless, oily mesylate. The ir spectrum (neat, film) showed no OH absorption bands in the 3000–3500-cm^{-1} region. This crude mesylate (83 g, 0.322 mole) was heated and stirred with 19.7 g (0.402 mole) of NaCN and 322 ml of DMSO at 95–100° for 4 days. The cooled mixture was poured into 1 l. of H_2O and extracted with three 250-ml portions of 1:1 Et_2O–C_6H_6 from which, after the usual work-up, 57 g of an amber oil was obtained. Distillation (15-cm Vigreux column) yielded 22.6 g (37%) of colorless oil, bp 99° (0.18 mm), $n^{24}D$ 1.5215. Glpc showed the product to be 98.3% pure; nmr ($CDCl_3$), δ 1.48 [6 H, $(CH_3)_2C$], 2.58 (2 H, CH_2), 3.80 (3 H, CH_3O), and 6.7–7.5 (4 H, aromatic). *Anal.* ($C_{12}H_{13}NO$) C, H, N.

3-(3-Methoxyphenyl)-3-methylbutylamine (XI) Hydrochloride.—Nitrile X, 22.6 g (0.12 mole) in 25 ml of Et_2O, was added dropwise to a stirred suspension of 5.7 g (0.15 mole) of $LiAlH_4$ in 150 ml of Et_2O. After 1.5 hr of refluxing, the mixture was cooled and decomposed with H_2O, and 3 g of filteraid was added; the suspension was filtered through a bed of filteraid. From the filtrate, after removal of the solvent, 23 g (nearly quantitative) of a colorless oil, homogeneous by tlc, was obtained. A sample of this oil was converted to the hydrochloride, as described for IV·HCl. The salt was recrystallized from *i*-PrOH–EtOAc: mp 170–171°; ν_{max}^{Nujol} 3000–2925 (broad), 2000, and 1595 cm^{-1}. *Anal.* ($C_{12}H_{19}NO$·HCl) C, H, Cl.

3-(3-Methoxyphenyl)-3,N,N-trimethylbutylamine (XII) Hydrochloride.—Six grams (0.0311 mole) of XI was treated with 7.13 g (0.156 mole) of HCO_2H and 7.57 g (0.093 mole) of 37% CH_2O, as described for V. After 18 hr of refluxing, 3.5 ml of 12 *N* HCl was added, and the solution was taken to dryness in a rotary evaporator. The white solid thus obtained was slurried in EtOAc and collected by filtration to yield 6.2 g of XII·HCl. This product was recrystallized twice from *i*-PrOH–EtOAc: mp 146–147°; ν_{max}^{KBr} 3000 (broad), 2650, 2550, 2470, 1600, and 1580 cm^{-1}; nmr (DMSO-d_6), δ 1.32 [6 H, $(CH_3)_2C$], 1.71–3.01 [8 H, $CH_2N(CH_3)_2$], 3.80 (3 H, CH_3O), 6.6–7.5 (4 H, aromatic). *Anal.* ($C_{14}H_{23}NO$·HCl) C, H, Cl.

3-(3-Hydroxyphenyl)-3,N,N-trimethylbutylamine Hydrochloride (XIII·HCl).—Compound XII (5.15 g, 0.02 mole) was refluxed with 150 ml of 48% HBr for 5 hr. The acid was removed in a rotary evaporator leaving a solid residue which was dissolved in 25 ml of H_2O. This solution was made alkaline with NH_4OH, then extracted four times with 15-ml portions of Et_2O. The Et_2O extracts were washed with H_2O and dried over K_2CO_3. The solvent was distilled under reduced pressure, leaving 4.10 g of an amber oil. It was dissolved in 20 ml of *i*-PrOH and excess dry HCl in Et_2O was added. A brown solid, 3.8 g, mp 198–202°, was obtained. Three recrystallizations from *i*-PrOH gave 1.4 g of XIII·HCl as white crystals: mp 201.5–202°; ν_{max}^{KBr} 3280, 3000, 2675, 2520, 2490, 1610, and 1590 cm^{-1}; nmr (DMSO-d_6), 1.28 [6 H, $(CH_3)_2C$], 2.03 (2 H, CH_2), 2.70 [8 H, $CH_2N(CH_3)_2$], 6.8–7.4 (4 H, aromatic), 9.42 (1 H, OH), and 10.23 (1 H, NH^+). *Anal.* ($C_{13}H_{21}NO$·HCl) C, H, Cl.

Acknowledgment.—The microanalyses were obtained by Dr. F. Scheidl and his associates of our Microanalytical Laboratory. The ir spectra were obtained by Mr. S. Traiman and the nmr spectra by Dr. T. Williams of our Physical Chemistry Department, under the direction of Dr. P. Bommer.

Antiinflammatory 2-Aryl-1,3-indandiones[1a]

JOSEPH G. LOMBARDINO AND EDWARD H. WISEMAN

Medical Research Laboratories, Chas. Pfizer & Co., Inc., Groton, Connecticut 06340

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Previously reported antiinflammatory activity for 2-phenyl-1,3-indandione (1) was confirmed in rats. Compound 1 also inhibits blood coagulation *in vivo*, by inhibiting the hepatic synthesis of prothrombin. However, at the time of measurement of antiedema activity (3 hr post-carrageenin injection) neither 1 nor the other anticoagulants warfarin, bishydroxycoumarin, or 2-pivalyl-1,3-indandione had induced a coagulation defect; of these four compounds only 1 had antiinflammatory activity. The aim of this program was the separation of antiinflammatory from anticoagulant activity in some 2-arylindandiones. All compounds were tested in the rat for inhibition of carrageenin-induced paw edema and for inhibition of prothrombin synthesis. Results showed most unclear unsubstituted 2-aryl-1,3-indandiones to be inhibitors in both tests; however, fairly large *meta* substituents on the 2-aryl function diminished anticoagulant activity. In addition, certain substituents in the indane ring successfully removed anticoagulant activity while retaining antiinflammatory activity in many cases. The acidity of those compounds with antiinflammatory activity was found to be restricted to a fairly narrow range.

The property of 2-aryl-1,3-indandiones to inhibit blood coagulation has been thoroughly studied and has led to three analogs with clinically useful anticoagulant activity.[1b] Over the course of some 20 years the greatest amount of interest has centered around the parent 2-phenyl-1,3-indandione (**1**) and its effect on blood prothrombin levels. Extensive structure–activity relationships have been developed[2–7] for analogs of **1** in an attempt to improve the therapeutic index of anticoagulant activity. In addition to anticoagulant

(1) (a) Presented in part before the Medicinal Division at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 12, 1967, Abstract No. P-19; (b) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, The MacMillan Co., New York, N. Y., 1965, pp 1450–1458.

(2) (a) L. Fontaine, M. Odievre, Y. Achet, and B. Drevon, *Therapie*, **16**, 34 (1961); (b) L. Fontaine, M. Grand, Y. Quentin, and S. Merle, *Med. Pharmacol. Exp.*, **13**, 137 (1965).

(3) (a) S. L. Shapiro, K. Geiger, and L. Freedman, *J. Org. Chem.*, **25**, 1860 (1960); (b) S. L. Shapiro, K. Geiger, J. Youdis, and L. Freedman, *ibid.*, **26**, 3580 (1961).

(4) D. Molho, Proceeding of the International Conference on Thrombosis and Embolism, Basel, 1954, p 193.

(5) J. Cavallini, A. Milla, A. Grumelli, and F. Ravenna, *Farmaco, Sci. Ed.*, **10**, 710 (1955).

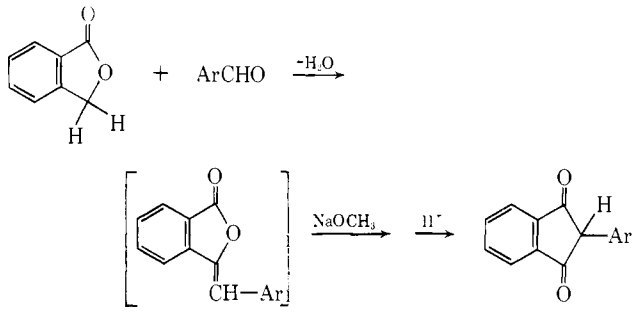
(6) P. Bruciar, *Chem. Zvesti*, **16**, 96 (1962); *Chem. Abstr.*, **59**, 2731 (1963).

(7) H. Kabat, E. F. Soldman, and N. I. Smith, *J. Pharmacol. Exp. Ther.*, **80**, 160 (1944).

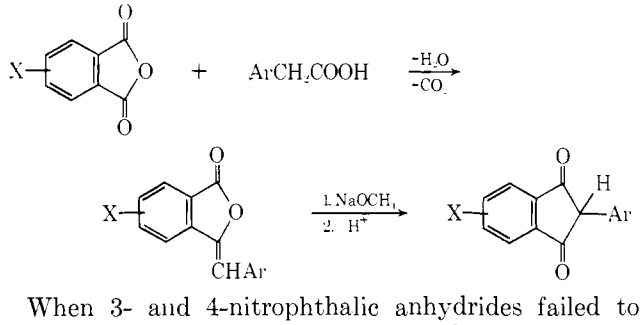
activity, compounds related to **1** exhibit hypermetabolic,[8] analgetic,[9] and uricosuric[10] activity.

In 1961, Fontaine[2a] called attention to the antiinflammatory activity of **1** given orally to rats or guinea pigs and concluded later that this activity was probably mediated through the adrenals.[2b] Possibly because anticoagulant activity would be undesirable in a clinically useful antiinflammatory drug, no further work has been reported on 1,3-indandiones as antiinflammatory agents. It became the objective of this present work to prepare appropriately substituted 1,3-indandiones without anticoagulant activity but retaining the desired antiinflammatory activity.

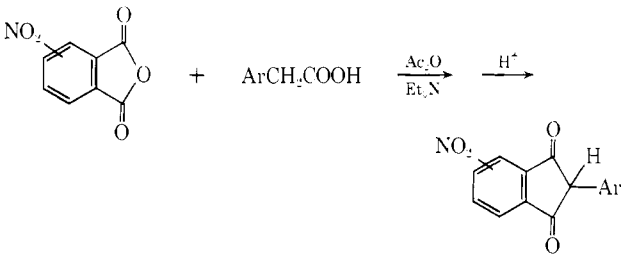
Chemistry.—Preparation of almost all 2-aryl-1,3-indandiones required for this study was accomplished by one of three previously described synthetic pathways. Of greatest utility for preparing analogs with no substituents in the indane ring was the method of Shapiro[3b] which involved condensing aromatic aldehydes with phthalide in the presence of $NaOCH_3$ and ethyl propionate. Yields were usually high (Table I) and purification relatively simple.



Since substituted phthalic acids were more readily accessible than substituted phthalides, a second preparative method was used involving condensation of arylacetic acids with substituted phthalic anhydrides followed by rearrangement in $NaOCH_3$ solution. Yields under these more vigorous conditions were variable but often satisfactory (Table II).

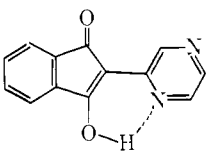


When 3- and 4-nitrophthalic anhydrides failed to produce isolable amounts of 4- and 5-nitro-1,3-indandiones, a milder procedure using actic anhydride and triethylamine according to Oskaja and Vanags[11] was used to condense and rearrange arylacetic acids with nitrophthalic anhydrides. Compounds **54–58** (Table II) were prepared by this procedure.



Almost all of the indandiones prepared in this work were isolated as their enol form as evidenced by their deep red-violet color following recrystallization from polar solvents such as ethanol. Ir spectra (KBr) exhibited a single carbonyl near 6.0 μ and uv spectra determined in MeOH or MeOH–NaOH were superimposable.[3a] The parent 2-phenyl-1,3-indandione (**1**), however, was a white compound and showed two carbonyl peaks at 5.73 (m) and 5.81 μ (s), indicative of the diketo form.

Apparent acidity constants (pK_a') were determined in 2:1 dioxane–water for a number of these compounds and correlated with antiinflammatory activity (see Table III and discussion below). As has been previously noted,[3a] a 2-(2-substituted aryl) substituent can sterically interfere with coplanarity in the indandione and thus affect the uv absorption spectra.[3b] In the present study a marked effect on pK_a' was observed for the 2-(2-methoxyphenyl)- and 2-(2-chlorophenyl)-1,3-indandione (Table III, 8 and **35**, respectively). A decreased ability to stabilize the conjugate anion in these nonplanar compounds may explain their decreased acidity as compared to closely related analogs. Compound **15**, 2-pyrazinyl-1,3-indandione, is an unusually weak acid possibly due to the hydrogen bond formed between the enol proton and the pyrazinyl nitrogen atom.



15

Pharmacology.—Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (Charles River Strain, average weight 170 g) in response to a subplantar injection of carrageenin. The experimental procedure followed that of Winter, *et al.*[12] Edema formation was measured 3 hr after oral administration of test drug (in aqueous solution), and the response of drug-treated animals was compared with that of animals receiving vehicle alone and animals receiving aspirin (100 mg/kg).

Inhibition of prothrombin synthesis was measured in rats by daily oral administration (two doses) of drug (100 mg/kg in aqueous solution) 8 hr apart. Sixteen hours after the last dose, blood samples were drawn into oxalated syringes from the descending aorta while the animals were maintained under light pentobarbital anesthesia. Plasma was separated by centrifugation, and prothrombin time was determined automatically with a Model 202 clot timer (Mechrolab Inc.) using thromboplastin extract[13] as directed by the manufacturer.

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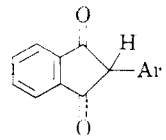
(13) Simplastin®, Warner-Chilcott.

TABLE I

2-ARYL-1,3-INDANDIONES



No.	Ar	Yield, %	Method of prepn[a]	Mp, °C	Cryst solvent[b]	Formula	Analyses or lit. mp, °C
1	C_6H_5		c				
2	3-BrC_6H_4		A	164.5–167.5			165–168[d]
3	3-FC_6H_4		A	158.5–160.5			160[d]
4	4-BrC_6H_4		A	144–145			139–140[d]
5	1-Naphthyl[e]		A	214–216			217–218[d]
6	3-$NO_2C_6H_4$	49	A	224–226	MEK	$C_{15}H_9NO_4$	C, H, N
7	3-$CH_3OC_6H_4$[e]	58	A	147–149	E	$C_{16}H_{12}O_3$	C, H
8	2-$CH_3OC_6H_4$[e]	71	A	170.5–172.5	E	$C_{16}H_{12}O_3$	C, H
9	4-$CH_3OC_6H_4$		A	154–155.5			152–154[f]
10	4-$CH_3C_6H_4$	71	A	143–145	E	$C_{16}H_{12}O_2$	143.5[g]
11	3,4-$Cl_2C_6H_3$	53	A	208–210	IPO	$C_{15}H_8Cl_2O_2$	C, H
12	2-HOC_6H_4	39	B	218–223	E-W	$C_{15}H_{10}O_3$	C, H
13	3,5-$(CH_3O)_2C_6H_3$[e]	65	A	190.5–192.5	E	$C_{17}H_{14}O_4$	C, H
14	4-$(HOOCCH_2O)C_6H_4$	64	A	198.5–200.5	E	$C_{17}H_{12}O_5$	C, H
15	2-Pyrazinyl	22	B	309–310	C	$C_{13}H_8N_2O_2$	C, H; N[h]
16	3-$(C_6H_5CH_2O)C_6H_4$	75	A	129–130	E	$C_{22}H_{16}O_3$	C, H
17	4-$(C_6H_5)C_6H_4$	67	A	200–202	E	$C_{21}H_{14}O_2$	C, H
18	4-ClC_6H_4		A	145–145.5			145[d]
19	3-ClC_6H_4		A	152–153			151[d]
20	3-IC_6H_4		A	176.5–178.5			178[d]
21	4-(CH_3O)-3-$(SO_3^-Na^+)C_6H_3$	9	A	286–288	E	$C_{16}H_{11}NaO_6S\cdot H_2O$	C, H
22	4-$NO_2C_6H_4$		A	216–217			209[d]
23	$(C_2H_5)_2NCH_2CH_2OC_6H_4$	78	A	230–232 dec	E	$C_{21}H_{23}NO_4\cdot H_2O$	C, H, N
24	$CH_3CONHC_6H_4$	54	A	239–241	E	$C_{17}H_{13}NO_3$	C, H, N
25	4-HOC_6H_4	64	B	259–260	M	$C_{15}H_{10}O_3$	C, H
26	3,4-$(HO)_2C_6H_3$	11	B	252–254 dec	A-W	$C_{15}H_{10}O_4$	C, H
27	4-$NH_2C_6H_4$	28	B	227–229	E	$C_{15}H_{11}NO_2$	C, H, N
28	2,3-$(CH_2O_2)C_6H_3$	68	A	159.5–161.5	E	$C_{16}H_{10}O_4$	C, H
29	2-Thienyl	63	A	136–139	IPO-W	$C_{13}H_8O_2S$	C, H
30	3-$CH_3C_6H_4$[i]	75	A	137–139	E	$C_{16}H_{12}O_2$	C, H
31	2-(1-CH_3-pyrrolyl)	14	A	277 dec	E	$C_{14}H_{11}NO_2$	C, H, N
32	α-Naphthyl[e]	68	A	177.5–179.5	E	$C_{19}H_{12}O_2$	C, H
33	2-$(COOH)C_6H_4$		A	246–254			248–254[d]
34	2,4-$Cl_2C_6H_3$		A	144–146			143–145[d]
35	2-ClC_6H_4		A	185.5–187.5			184–186[d]
36	4-(CH_3O)-3-$((CH_3)_2NSO_2)C_6H_3$	15	A	185.5–187.5	E	$C_{18}H_{17}NO_5S$	C, H, N
37	3-Thienyl	37	A	137–139	E-W	$C_{13}H_8O_2S$	C, H
38	3-$CH_3C_6H_4$	18	C	160.5–162.5	E	$C_{16}H_9O_2F_3$	C, H

[a] A, corresponding substituted benzaldehyde was treated with phthalide by the method of Shapiro, *et al.*;[3b] all substituted benzaldehydes were purchased from commercial sources and used as received; B, see Experimental Section; C, the corresponding arylacetic acid was treated with phthalic anhydride as illustrated in the Experimental Section for **40**. [b] MEK = methyl ethyl ketone, E = ethanol, IPO = isopropyl alcohol, W = water, C = chloroform, M = methanol, A = acetic acid. [c] Eastman Organic Chemical. [d] Reference 3a. [e] Mentioned in ref 4 but no analytical data or method of preparation was given. [f] C. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1328 (1936). [g] H. G. Krey, *Pharmazie*, **13**, 619 (1958). [h] C. A. Bruynes, R. F. Rekker, and W. Th. Nauta, *Rec. Trav. Chim.*, **85**, 1259 (1966), report mp 137–138° for this compound but give no analytical data. [i] N: calcd, 12.50; found, 12.03.

Bilateral adrenalectomy was performed through a retroperitoneal incision, while the rats were maintained under light methoxyfluorane[14] anesthesia. Animals were maintained on a normal diet with 0.9% saline in place of drinking water, and were used 5–7 days postoperatively.

Discussion

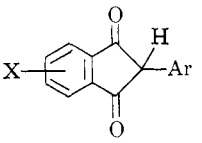
The antiedema activity of 2-phenyl-1,3-indandione (**1**) was recognized by Fontaine[2a] who ascribed an adrenal involvement[2b] to the activity of **1**. In the present work a 100-mg/kg oral dose of **1** gave an antiedema effect in adrenalectomized rats indistinguishable from that in intact rats treated in a similar manner with **1**. We then proceeded on the basis that a useful antiinflammatory agent might be obtained from a group of 2-aryl-1,3-indandiones *if* the known[1b] anticoagulant properties of this family of compounds could be removed by molecular modifications.

In evaluating the uricosuric activity of 5-bromo-2-phenyl-1,3-indandione (**48**) in man, Pasero and Marini[10a] concluded from two clinical cases that this compound did not affect prothrombin time. Later, Masini and Lombardi[10b] reported on one clinical case employing **48** where no changes were found in the prothrombin time. The present work showed **48** to have

(14) Metofane®, Pitman-Moore.

TABLE II

SUBSTITUTED 2-ARYL-1,3-INDANDIONES



No.	Ar	X	Yield, %	Method of prepn[a]	Mp, °C	Crystn solvent[b]	Formula	Analyses or lit. mp, °C
39	C_6H_5	5-CH_3	65	A	118–120	E	$C_{16}H_{12}O_2$	C, H
40	3-$CF_3C_6H_4$	5-CH_3	21	F	139–140	E	$C_{17}H_{11}F_3O_2$	C, H
41	1-Naphthyl	5-CH_3	52	A	154.5–155.5	E	$C_{20}H_{14}O_2$	C, H
42	3-$CH_3OC_6H_4$	5-CH_3	53	A	100–102	E	$C_{17}H_{14}O_3$	C, H
43	3-$CH_3C_6H_4$	5-CH_3	59	A	114–115.5	E	$C_{17}H_{14}O_2$	C, H
44	2-BrC_6H_4	5-CH_3	40	A	131–133	E	$C_{16}H_{11}BrO_2$	C, H
45	3-ClC_6H_4	5-CH_3	72	A	123–125	E	$C_{16}H_{11}ClO_2$	C, H
46	4-ClC_6H_4	5-CH_3	7	F	144.5–146.5	E	$C_{16}H_{11}ClO_2$	C, H
47	3-FC_6H_4	5-CH_3	68	A	125–217	E	$C_{16}H_{11}FO_2$	C, H
48	C_6H_5	5-Br	19	B	163.5–167	..		167[c]
49	2-Naphthyl	5-Br	47	F	180.5–181.5	E	$C_{19}H_{11}BrO_2$	C, H
50	3-$CF_3C_6H_4$	5-Br	27	B	154.5–155.5	E	$C_{16}H_8BrF_3O_2$	C, H
51	3-FC_6H_4	5-Br	49	B	160.5–161.5	E	$C_{15}H_8BrFO_2$	C, H
52	3-$CH_3C_6H_4$	5-Br	53	B	126–128	E	$C_{16}H_{11}BrO_2$	C, H
53	4-ClC_6H_4	5-Br	54	B	189.5–190.5	E	$C_{15}H_8BrClO_2$	C, H
54	C_6H_5	4-NO_2	35	F	134–135	E	$C_{15}H_9NO_4$	C, H, N
55	3-$CF_3C_6H_4$	4-NO_2	19	C	174–176.5	E	$C_{16}H_8F_3NO_4$	C, H, N
56	C_6H_5	5-NO_2	31	C	205–206	E		201[d]
57	3-$CF_3C_6H_4$	5-NO_2	12	C	190.5–191.5	IPO	$C_{16}H_8F_3NO_4$	C, H, N
58	3-$CH_3C_6H_4$	5-NO_2	21	C	188.5–190.5	E	$C_{16}H_{11}NO_4$	C, H, N
59	3-$CH_3C_6H_4$	5,6-$(CH)_4$	39	F	258–260	A	$C_{20}H_{14}O_2$	C, H
60	3-FC_6H_4	5,6-$(CH)_4$	91	D	329–331 dec	E	$C_{19}H_{11}FO_2$	C, H
61	4-ClC_6H_4	5,6-$(CH)_4$	90	D	335–337 dec	M	$C_{19}H_{11}ClO_2$	C, H
62	3-$CF_3C_6H_4$	5,6-$(CH)_4$	75	D	262–264	E	$C_{20}H_{11}F_3O_2$	C, H
63	2-Naphthyl	5,6-$(CH)_4$	14	D	293–294 dec	E	$C_{23}H_{14}O_2$	C, H
64	C_6H_5	5-CF_3	31	F	173.5–175	IPO–W	$C_{16}H_9F_3O_2$	C, H
65	3-$CF_3C_6H_4$	5-CF_3	50	F	129–131	N	$C_{17}H_8F_6O_2$	C, H
66	2-Naphthyl	5-CF_3	27	E	189.5–191	E	$C_{20}H_{11}F_3O_2$	C, H
67	3-$CH_3C_6H_4$	5-CF_3	38	E	126–128	E–W	$C_{17}H_{11}F_3O_2$	C, H
68	4-ClC_6H_4	5-CF_3	34	E	203–204	IPO–W	$C_{16}H_8ClF_3O_2$	C, H
69	3-$CH_3OC_6H_4$	5-CF_3	33	E	166.5–168	IPO–W	$C_{17}H_{11}F_3O_3$	C, H
70	3-BrC_6H_4	5-CF_3	19	E	172.5–174	E–W	$C_{16}H_8BrF_3O_2$	C, H
71	C_6H_5	4-NH_2	55	F	207–207.5	E	$C_{15}H_{11}NO_2$	C, H, N

[a] A, the corresponding substituted phenylacetic acid was treated with 4-methylphthalic anhydride as illustrated for compound **40**; B, 5-bromophthalic anhydride was used as illustrated for compound **49**; C, Ac_2O and Et_3N were used as illustrated for **54** in the Experimental Section; D, method used for **59**; E, method used for **64**; F, see Experimental Section. [b] M = methanol; W = water; E = ethanol; IPO = isopropyl alcohol; A = acetone; N = not recrystallized. [c] Footnote *f*, Table I. [d] Reference 11 and J. Klosa, *Pharmazie*, **9**, 682 (1954); *Chem. Abstr.*, **49**, 10252 (1955).

a reduced (compared to **1**) but distinct effect on prothrombin time in rats after nine oral doses (100 mg/kg) 8 hr apart.

At the time of measurement of inhibition of edema (3 hr after oral administration) none of the compounds discussed herein had effected a prolongation of prothrombin time. This was to be expected, since the action of indandione and coumarin anticoagulants (inhibition of hepatic synthesis of prothrombin)[11b] requires 16 hr before an effect on plasma prothrombin is noted.

From a comparison of antiinflammatory and prothrombin activities in a group of nuclear *un*substituted 2-aryl-1,3-indandiones (**1**–**38**, Table III), there appeared a suggestion of diminished prothrombin effects with retention of antiinflammatory activity in certain compounds with 2-aryl groups *meta* substituted with large groups (*e.g.*, **2**, **6**, **7**, **20**). Combination of a *meta*-substituted 2-aryl group with a 5 substituent on a 1,3-indandione produced a group of compounds with no measurable prothrombin effects in rats but which retained useful antiinflammatory activity (*e.g.*, **42**, **44**, **45**, **49**, **57**, **67**, etc., Table III). Furthermore, like **1**, compounds **2**–**4**, **44**, **49**, **67** retained undiminished antiinflammatory activity in adrenalectomized rats at an oral dose of 100 mg/kg.

A further requirement for useful antiinflammatory activity was deduced after determining the apparent acidities (in 2:1 dioxane–water) of almost half of the compounds prepared. With only three exceptions (**15**, **35**, and **16**) all active compounds exhibited a pK_a' of 5.9 or less. Three examples (**54**, **56**, and **65**) with pK_a' as low as 3.5 were also active antiinflammatory agents but one compound (**55**) with $pK_a' = 3.0$ was inactive. When coplanarity in the conjugate base was prevented by a large 2-aryl group (*e.g.*, **8**) or a basic amine function was introduced (*e.g.*, **23**, **27**), pK_a' was increased and antiinflammatory activity was abolished.

TABLE III
PHARMACOLOGICAL ACTIVITY OF 2-ARYL-1,3-INDANDIONES

No.	pK_a'	Antiinflammatory[a] activity	Prothrombin[b] effects	No.	pK_a'	Antiinflammatory[a] activity	Prothrombin[b] effects
1	5.4[c]	++[d]	++	39	5.9	++	++
2	4.6	++[d]	±	40	4.7	++	±
3	4.7	++[d]	++	41		±	++
4	4.7	++[d]	++	42		+	−
5	5.9	−	+	43		+	+
6		±	−	44		++[d]	−
7	5.3	±	+	45		+	−
8	7.6	−	−	46		+	±
9	5.6	+++	++	47		+	+
10	5.9	++	++	48		+	+
11	4.1	+++	+±	49		++[d]	−
12		−	−	50	4.3	++	−
13		−	−	51		++	++
14	5.8	−	−	52	4.8	++	−+
15	7.4	++	++	53	4.5	++	++
16	5.5	−	+	54	3.5	++	++
17	5.2	+	++	55	3.0	−	−
18	4.8	+++	++	56	3.5	++	++
19	4.7	++	++	57		++	−
20	4.7	+	+	58		+	−
21		−	−	59		−	−
22		++	++	60		+	−
23	8.5	−	−	61		−	−
24		−	−	62		±	−
25		−	−	63		−	−
26		−	−	64	4.0	+++	++
27	6.2	−	−	65	3.5	+	−
28	5.4	±	++	66		+	−
29		++	++	67	4.2	+++[d]	−
30	5.7	++	++	68		Lethal at 100 mg/kg	
31		−	−	69		++	−
32	5.2	+++	+	70		+	−
33		−	−	71		−	−
34	5.6	++	++	Bishydroxycoumarin		−	++
35	6.1	++	++	Warfarin		−	++
36		−	−	2-Pivalyl-1,3-indandione		−	++
37		++	++	Phenylbutazone		+++	−
38		++	++				

[a] Antiinflammatory activity is reported as a mean inhibition of edema in the treated animals within the range of 0.5–1.5 times that of the mean inhibition of concurrently treated animals receiving aspirin (100 mg/kg *po*); +, drug given at 100 mg/kg; ++, drug given at 33 mg/kg; +++, drug given at 10 mg/kg *po*. Compounds with antiinflammatory activity (at 100 mg/kg) of less than 0.5 times aspirin are reported as −. [b] +, prolongation of prothrombin time 16 hr after administration of nine oral doses, 8 hr apart (100 mg/kg *po*); ++, prolongation of prothrombin time 16 hr after administration of two oral doses, 8 hr apart (100 mg/kg *po*); −, no prolongation of prothrombin time after nine oral doses (100 mg/kg *po*). [c] For comparison, J. Linabergs and A. Neis [*Latvijas PSR Zinatnu Akad. Vestis*, **No. 2**, 213 (1962); *Chem. Abstr.*, **58**, 8443 (1963)] report a pK_a of 4.2 for 1 in water-1% methanol. In the present work all pK_a' values were determined in 2:1 dioxane–water (v/v). [d] Identical results were obtained with these compounds in both adrenalectomized and nonadrenalectomized rats dosed at 100 mg/kg *po*.

Experimental Section[15]

Most compounds were prepared by one of three known methods as indicated in Tables I and II. Preparative methods differing from the known techniques are described below.

2-(2-Hydroxyphenyl)-1,3-indandione (**12**).—A solution of 1.0 g (0.004 mole) of 2-(2-methoxyphenyl)-1,3-indandione (**8**) in 25 ml of 48% HBr was refluxed for 3.5 hr. After cooling, the dark red solids were filtered and recrystallized from a small amount of EtOH yielding a tan solid, 0.34 g (30%).

Similarly, 2-(4-hydroxyphenyl)- and 2-(3,4-dihydroxyphenyl)-1,3-indandione (**25** and **26**) were prepared from the corresponding 2-(methoxyphenyl)-1,3-indandione analogs by a procedure analogous to that described above.

2-Pyrazinyl-1,3-indandione (**15**).—To a solution of 12.3 g (0.110 mole) of potassium *t*-butoxide in 150 ml of dry DMF was added 4.7 g (0.050 mole) of 2-methylpyrazine. To this deep red solution was slowly added 11.1 g (0.050 mole) of diethyl phthalate in 20 ml of DMF. After 3 hr at room temperature, the blue-green solution was evaporated to dryness under reduced pressure. After partitioning between H_2O–Et_2O, the H_2O layer was acidified with HCl to produce a yellow solid, 6.2 g. Recrystallization from 1 l. of $CHCl_3$ yielded 2.5 g (22%) of pure **15**.

2-(4-Aminophenyl)-1,3-indandione (**27**).—A suspension of 2.8 g (0.010 mole) of 2-(4-acetamidophenyl)-1,3-indandione (**24**) in 100 ml of 6 *N* HCl was refluxed for 4 hr. After filtration the tan insolubles were dissolved in aqueous NaOH and the red solution was acidified with AcOH to pH 6. Filtration of the red precipitate and recrystallization from EtOH yielded 0.76 g (28%) of **27**, mp 227–229.[16]

5-Methyl-2-(3-trifluoromethylphenyl)-1,3-indandione (**40**).—A thoroughly mixed combination of 4.8 g (0.030 mole) of 4-

(15) Melting points were determined in a Thomas–Hoover capillary melting point apparatus using a calibrated thermometer and are corrected. Potentiometric titrations were carried out in 2:1 dioxane–H_2O (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH. The apparent pK_a values correspond to the pH values at the half-neutralization point in these titrations. Ir spectra were determined in KBr pellets. Analyses were carried out by the Physical Measurements Laboratory of Chas. Pfizer & Co., Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(16) This compound, prepared by reduction of the corresponding nitro compound, has been reported[5] to melt at 198–200°.

methylphthalic anhydride (Eastman Organic Chemicals), 6.2 g (0.030 mole) of *m*-trifluoromethylphenylacetic acid (Pierce Chemical Co.), and 100 mg of anhydrous NaOAc was heated under N_2 (using an electric heating mantle connected to a pyrometer) at 290° for 3 hr. The resulting soft solid was triturated with 75 ml of 10% $NaHCO_3$, and the insolubles were quickly filtered and dried under vacuum over P_2O_5. A combination of the resulting dry solid with 50 ml of MeOH and 2.2 g (0.045 mole) of $NaOCH_3$ in 50 ml of MeOH produced an immediate red solution. After refluxing for 0.5 hr and evaporation to dryness, the residue was taken up in H_2O and acidified with excess 6 *N* HCl. The resultant red precipitate was filtered, 4.0 g, and recrystallized from EtOH to yield 1.9 g (21%) of **40**.

5-Bromo-2-(2-naphthyl)-1,3-indandione (49).—Preparation of 4-bromophthalic acid was accomplished by either the method of Stephens[17] (7% yield, mp 165° dec) or by the oxidation of 4-bromo-*o*-xylene with permanganate[18] (20% yield, mp 116° dec).

Refluxing a solution of 3.7 g (0.015 mole) of 4-bromophthalic acid for 2 hr with 50 ml of Ac_2O containing 1 drop of H_2SO_4 followed by evaporation to dryness produced 4-bromophthalic anhydride. To the crude anhydride was added 2.8 g (0.015 mole) of 2-naphthylacetic acid and 50 mg of anhydrous NaOAc. Heating the solid mixture under N_2 at 275° for 2 hr (electric mantle, pyrometer), followed by cooling, produced a brown solid which was rapidly triturated with 10% $NaHCO_3$ and dried under vacuum. The thoroughly dried crude solid was rearranged in 100 ml of refluxing MeOH containing 2.1 g (0.039 mole) of $NaOCH_3$. After 1 hr the reaction was evaporated to dryness, dissolved in H_2O, and extracted repeatedly with Et_2O and the aqueous layer was acidified with 6 *N* HCl acid. The crude red precipitate was immediately recrystallized from EtOH to yield 2.5 g (47%) of **49**.

2-(4-Chlorophenyl)-5-methyl-1,3-indandione (46).—A solution of 4.9 g (0.030 mole) of 4-methylphthalic anhydride, 5.1 g (0.030 mole) of *p*-chlorophenylacetic acid, 109 g (1.07 moles) of Ac_2O, and 91 g (0.09 mole) of Et_3N was heated on the steam bath for 0.5 hr. The dark brown reaction was then poured onto 200 g of ice containing 90 ml of concentrated HCl. The resulting gum was separated and dissolved in 400 ml of 5% NaOH, washed several times with Et_2O, and acidified with concentrated HCl to produce a red solid **46**, 0.57 g (7%).

Yields of 5-methyl-2-aryl-1,3-indandiones made from 5-methylphthalic anhydride and arylacetic acids by the method described above for **40** were superior to yields obtained by the method used for **46** (Table II).

4-Nitro-2-phenyl-1,3-indandione (54).—A solution of 9.65 g (0.05 mole) of 3-nitrophthalic anhydride, 6.8 g (0.05 mole) of phenylacetic acid, 182 g (1.8 moles) of Ac_2O, and 15.2 g (0.15 mole) of Et_3N was warmed on the steam bath for 15 min. After cooling, the reaction was poured onto a mixture of ice and concentrated HCl. The resulting gummy solid was separated and dissolved in aqueous NaOH and washed repeatedly with Et_2O and the cooled aqueous layer was acidified with 6 *N* HCl. Continued stirring at 0° finally produced a granular solid, 4.7 g (35%).

2-(*m*-Tolyl)-2,3-dihydrobenz[*f*]indene-1,3-dione (59).—The required anhydride was produced from 4.3 g (0.02 mole) of 2,3-naphthalene dicarboxylic acid, 50 ml of Ac_2O and two drops of concentrated H_2SO_4. After refluxing for 2 hr and evaporation to dryness, the resulting solid was stored over P_2O_5 under vacuum. A thorough mixture of this solid, 3.0 g (0.02 mole) of *m*-tolylacetic acid, and 100 mg of NaOAc was heated under N_2 at 270°. After 3 hr of heating the reaction was allowed to cool and solidify. To this solid was added 20 ml of MeOH and a solution of 3.3 g (0.06 mole) of $NaOCH_3$ in 50 ml of MeOH. After refluxing 1 hr and evaporating to dryness, the residue was dissolved in 250 ml of H_2O and washed repeatedly with Et_2O. The cooled aqueous phase was acidified with 6 *N* HCl and yielded an orange solid. Recrystallization from 1 l. of boiling Me_2CO yielded in several crops 2.2 g (39%) of **59**.

5-Trifluoromethyl-2-phenyl-1,3-indandione (64).—The required anhydride was prepared from 4.7 g (0.02 mole) of 4-trifluoromethylphthalic acid,[19] 50 ml of Ac_2O, and 1 small drop of concentrated H_2SO_4. After refluxing for 4 hr, evaporation to dryness produced a dark solid which was stored over P_2O_5.

A combination of the above residue, 2.7 g (0.020 mole) of phenylacetic acid, and 200 mg of anhydrous NaOAc was heated to 270° as above. After cooling, the residue was subjected to high vacuum for approximately 15 min. After dissolving the solid in 50 ml of MeOH, a solution of 4.3 g (0.080 mole) of $NaOCH_3$ in 30 ml of MeOH was added. The resulting dark red solution was refluxed 1 hr, cooled, evaporated to dryness, dissolved in 150 ml of H_2O, and acidified with 6 *N* HCl to produce a red solid which was recrystallized from EtOH; yield of **64**, 1.8 g (31%).

2-(3-Trifluoromethylphenyl)-5-trifluoromethyl-1,3-indandione (65).—The anhydride of 4-trifluoromethylphthalic acid was prepared as described for **64** above. To the crude anhydride residue was added 8.2 g (0.040 mole) of *m*-trifluoromethylphenylacetic acid (Pierce Chemical Co.) and 400 mg of anhydrous NaOAc. After heating at 265° for 2 hr, the residue was subjected to high vacuum for approximately 15 min. This residue was then combined with 25 ml of MeOH and a solution of 8.7 g (0.16 mole) of $NaOCH_3$ and 100 ml of MeOH. After refluxing for 0.75 hr and evaporation to dryness, the residue was dissolved in 300 ml of H_2O and extracted three times with 200-ml portions of Et_2O. In this case, however, the Et_2O layers extracted considerable dark material. Acidification of the aqueous layer produced only a small amount of black oil. Evaporation of the *ether layers* produced a solid which was dissolved in H_2O and strongly acidified to precipitate a red solid (**65**), 7.1 g (50%). Apparently, the influence of two lipophilic trifluoromethyl substituents causes the sodium salt of **65** to extract out of aqueous base into ether.

4-Amino-2-phenyl-1,3-indandione (71).—A solution of 3.0 g (0.011 mole) of 4-nitro-2-phenyl-1,3-indandione (**54**) in 150 ml of absolute EtOH was stirred by bubbling in dry N_2. After addition of 2.3 g (0.045 mole) of hydrazine hydrate a small portion of fresh Raney nickel catalyst was added. After 20 min at room temperature a second portion of catalyst was added. After 1 hr excess catalyst was added and mixture was heated to boiling and filtered while hot. Acidification with 6 *N* HCl and addition of H_2O precipitated a yellow solid which was recrystallized from EtOH to yield 1.5 g (55%) of **71**.

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