[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORIES OF THE U. S. VITAMIN AND PHARMACEUTICAL CORP.]

Indandione Anticoagulants

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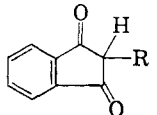
Received April 13, 1960

A series of 2-substituted indandiones has been synthesized and yielded compounds with considerable anticoagulant activity. High yields of arylindandiones from condensations of phthalide and the aromatic aldehyde have been obtained by employment of ethyl propionate as a solvent. The ultraviolet absorption spectra of selected compounds in this series have been reported.

An improved understanding of the coagulation process[1] and increased experience[2] have stimulated anticoagulant therapy[3] in thrombo-embolic disease. Recognition of enhanced blood coagulability[4] and increased sensitivity to alimentary lipemia[5] in atherosclerotics, and demonstration[6] that ACTH and cortisone treatment increase the incidence of thrombo-embolic manifestations, have broadened the therapeutic utility of anticoagulant drugs.

A search for more nearly ideal oral anticoagulants[7] has occupied many laboratories. Our explorations, recorded in this paper, involved indandiones of the type I.



I

R = aryl(R_1, phenyl and R_1, naphthyl)
R = long chain acyl (R_1 —CO—)

The category R = aryl was investigated as congeners of the clinically effective phenindione[8] (I, R = phenyl) and has been examined by others.[9]

The category R = long chain acyl, extended observations of shorter chain analogs,[10] diphenylacetyl,[11] and 2-halo-2-acyl derivatives of I[12] of other workers. The compounds in this category have been structurally envisioned as antimetabolites of vitamin K_1.

In addition to anticoagulant effects, compounds related to I have shown hypermetabolic activity,[14] parasiticidal effects,[15] rodenticidal,[16] analgesic,[17] antibacterial,[18] and bronchodilator[19] activity. Some of these properties have been evaluated.

For the synthesis[20] of I, R = aryl the appropriate aldehyde was condensed with phthalide under

(1) (a) F. D. Mann, *Ann. Rev. Physiol.*, **19**, 205 (1957); (b) C. L. Rose, *Research Today*, **15**, 23 (1959).

(2) (a) I. S. Wright, *Circulation*, **19**, 110 (1959); (b) R. E. Ensor and H. R. Peters, *J. Am. Med. Assoc.*, **169**, 914 (1959); (c) B. Manchester, *Ann. Internal Med.*, **47**, 1202 (1957); (d) J. H. Olwin and J. L. Koppel, *A. M. A. Arch. Internal Med.*, **100**, 842 (1957); (e) L. B. Ellis, H. L. Blumgart, D. E. Harken, H. S. Sise, and F. J. Stare, *Circulation*, **17**, 945 (1958); (f) W. B. Rawls and C. A. R. Connor, *Am. J. Cardiol.*, **4**, 470 (1959).

(3) (a) S. A. Carter, E. McDevitt, B. W. Gatje, and I. S. Wright, *Am. J. Med.*, **25**, 43 (1958); (b) W. G. Anlyan, G. D. DeLaughter, Jr., J. I. Fabrikant, J. W. Sullenberger, and W. T. Weaver, *J. Am. Med. Assoc.*, **168**, 725 (1958).

(4) J. F. Mustard, *Can. Med. Assoc. J.*, **79**, 554 (1958).

(5) J. F. Mustard, *Can. Med. Assoc. J.*, **79**, 736 (1958).

(6) G. Ungar, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 421.

(7) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 1520.

(8) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd Ed., The Macmillan Co., New York, N. Y., 1955, p. 1517.

(9) (a) G. Cavallini, E. Milla, E. Grumelli, and F. Ravenna, *Farmaco (Pavia), Ed. Sci.*, **10**, 710 (1955); (b) A. Banchetti, *Farmaco (Pavia), Ed. Sci.*, **10**, 742 (1955); (c) E. Gori and L. Molteni, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 223; (d) M. Furdík and P. Hrnčiar, *Chem. Zvesti*, **12**, 464 (1958); (e) M. Furdík, P. Hrnčiar, and E. Poláková, *Chem. Zvesti*, **12**, 642 (1958); (f) J. Moraux, *Therapie*, **11**, 104 (1956); (g) G. Pasero and G. Masini, *Arch. Maragliano*, **14**, 297 (1958); (h) N. Sperber, U. S. Patent **2,899,358** (Aug. 11, 1959); (i) D. Molho, French Patent **1,085,097** (Jan. 27, 1955) [*Chem. Abstr.* **53**, 3178 (1959)]; (j) G. Vanags and T. Dumpis, *Doklady Akad. Nauk, S.S.S.R.*, **125**, 549 (1959) [*Chem. Abstr.* **53**, 19991 (1959)]; (k) P. Hrnčiar, L. Krasnec, and M. Furdík, *Chem. Zvesti*, **10**, 12 (1956) [*Chem. Abstr.* **50**, 14674 (1956)]; (l) H. G. Krey, *Pharmazie*, **13**, 619 (1958).

(10) (a) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 492 (1942); (b) S. R. Heisey, J. P. Saunders, and K. C. Olson, *Proc. Soc. Exp. Biol. Med.*, **91**, 86 (1956), report undesirable cardiovascular side effects with I, R = isovaleryl, and R = pivalyl.

(11) R. D. Birkenmeyer and M. E. Speeter, U. S. Patent **2,827,489** (Mar. 18, 1958).

(12) K. C. Murdock, *J. Org. Chem.*, **24**, 845 (1959). The activity of these compounds which do not bear an enolizable hydrogen in the 2-position may well be rationalized as a case of "drug latentiation,"[13] with hydrolysis to acyl indandiones *in vivo*.

(13) N. J. Harper, *J. Med. Pharm. Chem.*, **1**, 467 (1959).

(14) U. Söderberg and C. A. Wachtmeister, *J. Pharmacol. Exp. Therap.*, **117**, 298 (1956).

(15) L. W. Hazleton and W. H. Dolben, U. S. Patent **2,884,357** (Apr. 28, 1959).

(16) (a) J. T. Correll, U. S. Patent **2,900,302** (Aug. 18, 1959); (b) D. G. Crabtree and W. H. Robinson, *Pest Control*, **21**, 22 (July 1953).

(17) M. Kubovic, M. Prazic, and D. Atanackovic, *Proc. Soc. Exp. Biol. Med.*, **90**, 660 (1955).

(18) E. Gori, *Thrombosis and Embolism. I. International Conf.*, Basel, 1954, p. 271.

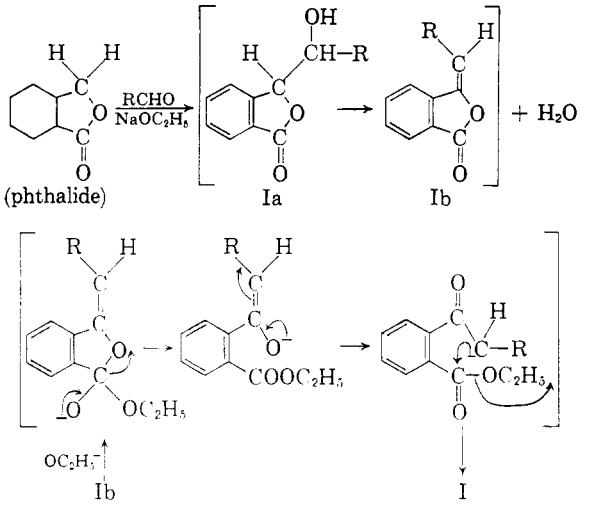
(19) H. Blumberg, H. B. Dayton, and S. M. Gordon, *Science*, **127**, 188 (1958).

(20) For an alternate synthetic route, see C. F. Koelsch, *J. Am. Chem. Soc.*, **58**, 1328 (1936). In our work, the procedure of W. Dieckmann, *Ber.*, **47**, 1439 (1914) was employed.

alkoxide catalysis to afford the required compound in moderate yield, as detailed in Scheme I.

SCHEME I

PREPARATION OF ARYLINDANDIONES



In the instance of I, R = α-naphthyl, the product was isolated in 34% yield under ethoxide catalysis as compared to 25% yield with *t*-butoxide catalysis. In addition, a compound fitting the analyses of Ia was isolated, which on treatment with ethoxide readily afforded I. The presumed intermediate Ib, α-naphthalphthalide was not isolated in the reaction, but *per se* on treatment with the ethoxide gives I.

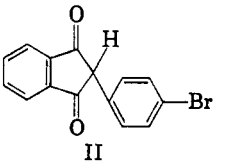
Critical to the noted yields was the formation of water (Scheme I, above) which severely restricted completion of the reaction as desired. This was overcome by employment of ethyl propionate (Method B) as the reaction solvent, along with an additional equivalent of sodium alkoxide.

The saponification of ethyl propionate served to remove the formed water of reaction and under these conditions, virtually quantitative yields of the arylindandiones were obtained. Using similar conditions, a variety of other dehydrating agents was ineffective.

The synthesis of I, R = acyl employed a modification of the procedure of Kilgore, *et al.*[10a] involving condensation of the appropriate methyl ketone with dimethyl phthalate under sodium methoxide catalysis (Method C).

The compounds prepared have been described in Table I.

The anticoagulant effects noted show that considerable enhancement of activity of I, R = phenyl is obtained with R = *p*-halophenyl, and particularly with *p*-bromophenylindandione, II.[21] The acyl compound affording the highest anticoagulant activity was compound 33, which interestingly has a sixteen carbon chain attached to the



II

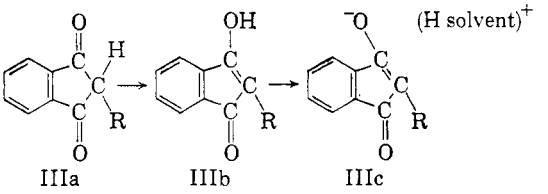
indandione nucleus, comparable to the sixteen carbon chain of the phytyl substituent in vitamin K_1.

The sodium salts of the acyl indandiones were only sparingly soluble in water, and it was established that conversion to *N*-methylglucamine salts of the enol form of such indandiones considerably enhanced water solubility. Thus, the water solubility of compound 32 was 0.1% as compared to 6.7% with compound 30.

A number of the compounds were evaluated for analgesic effect[22] (compounds 1, 15, 22, 24, 32, 35), and were inactive. Anti-bacterial studies showed complete inhibition of growth of B. *subtilis*, M. *flavus*, and S. *lutea* (compounds 27, 28, and 32) at 0.02 millimoles per liter, with no effect on E. *Coli*. Compound 33 required 2.0 millimoles per liter for similar inhibition whereas compound 34 was ineffective.

The ultraviolet absorption spectra of selected compounds of Table I have been reviewed in an effort to characterize the chromophores, and to assess whether any noted relationships between anticoagulant activity and the spectra could be found. The spectra are given in Table II.

Forms contributing to the noted pattern of absorption are:



Indandione (IIIa, R = H) has been established[23] to be in the diketo form IIIa. In this form it may be regarded as an *ortho*-substituted acetophenone[24] with stabilization in a conformation co-planar with the phenyl ring. The diffuse band in methanol at 253–259 mμ is intensified as discrete bands at about 240 and 257 mμ in sodium methoxide with formation of IIIb–c. The hyperchromic effect in isopropyl alcohol relative to methanol would suggest more enolization in the less polar solvent.[25] In aqueous alkali as well as phosphate buffer *p*H 7.5, the bands are more clearly resolved, and, hyperchromic relative to the main bands in organic

(21) This compound is currently under clinical trial under the name "Haldinone".

(22) The procedure for the analgesic test was that of C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).

(23) B. Eistert and W. Reiss, *Ber.*, **87**, 92 (1954).

(24) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(25) P. B. Russell, *J. Am. Chem. Soc.*, **74**, 2654 (1952).

TABLE I

INDANDIONES (SEE FORMULA I)

No.[a]	R_1	M.P.[b]	Solvent[c]	Yield,[d] %	Method[e]	Formula	Analyses[f] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Activity[g]
	R = R_1-phenyl										
1[a1]	H	148–149	A	24	A						1+
2	NMG[h]	151–156	B	90		$C_{22}H_{27}NO_7$[h]	63.3	63.6	6.5	6.6	
3	4-F	116–117	A	17	A	$C_{15}H_9FO_2$	75.0	75.2	3.8	3.9	2+
4	2-Cl	183–184	C	20	A	$C_{15}H_9ClO_2$[i]	70.2	70.0	3.5	3.6	2+
5	3-Cl	153–155	A	30	A	$C_{15}H_9ClO_2$[i]	70.2	70.2	3.5	3.4	1+
6[a2]	4-Cl	142–144	B	15	A	$C_{15}H_9ClO_2$[i]	70.2	70.0	3.5	3.4	4+
7	2,4-diCl	143–145	B	13	A	$C_{15}H_8Cl_2O_2$	61.9	61.9	2.8	3.1	0
8[a3]	4-Br	142–146	B	74[j,k]	B	$C_{15}H_9BrO_2$	59.8	60.0	3.0	3.2	5+
9	NMG[h]	155–157	B	98		$C_{22}H_{26}BrNO_7$[l]	52.3	52.5	5.4	5.5	
10[a4]	4-I	143–144	D	89	B						
11[a5]	3,4-OCH_2O—	154–156	B	7	A	$C_{16}H_{10}O_4$	72.2	72.0	3.8	3.6	1+
12	3,4-diC_2H_5O—	155–157	A	24	A	$C_{19}H_{18}O_4$	73.5	73.8	5.9	6.0	3+
13	2-COOH	248–254	E	37	A	$C_{16}H_8O_4$	72.2	72.0	3.8	4.0	0
14	4-*i*-C_3H_7—	155–156	B	18	A	$C_{18}H_{16}O_2$	81.8	82.1	6.1	5.9	1+
	R = R_1-(α-naphthyl)										
15[a6]	H	217–218	F	83	B[m]	$C_{19}H_{12}O_2$	83.8	83.9	4.4	4.7	4+
16	NMG[h]	90–94	B			$C_{26}H_{29}NO_7$[n]	65.6	65.8	6.4	6.7	
17	2-CH_3	204–210	K		A	$C_{20}H_{14}O_2$	81.3	81.6	5.1	5.1	2+
18[a7]	4-Cl	199–201	A	4	A	$C_{19}H_{11}ClO_2$	74.4	74.0	3.6	3.6	2+
19[a8]	4-Br	203–204	G	11	A	$C_{19}H_{11}BrO_2$	65.0	65.3	3.2	3.3	3+
20[a9]	5-Br	151–153	B	20	A	$C_{19}H_{11}BrO_2$	65.0	65.3	3.2	3.0	2+
21[a10]	H[o]	173–174	A	28	A	$C_{19}H_{12}O_2$	83.8	83.9	4.4	4.5	0
	R = R_1-CO—										
22	C_3H_5—[p]	133–134	D	30	D	$C_{13}H_{10}O_3$	72.9	72.9	4.7	4.8	1+
23	CH_3COCH_2—	139–140	H	8	D	$C_{13}H_{10}O_4$	67.8	67.7	4.4	4.2	
24[a11]	*i*-C_4H_9—	68–69	B	15	D						0
25[a12]	*t*-C_4H_9—	109–115	A	19	D						
26	*n*-C_6H_{13}—[q]	258–262	I	33	C	$C_{16}H_{17}NaO_3$	68.6	68.0	6.1	6.2	
27	*n*-C_7H_{15}—[q]	266–267	I	12	C	$C_{17}H_{19}NaO_3$	69.4	69.7	6.5	7.0	4+
28	*n*-C_9H_{19}—[q]	172–175	I	13	C	$C_{19}H_{23}NaO_3$	70.8	70.7	7.2	7.1	4+
29	*n*-$C_{11}H_{23}$—	45–46	B			$C_{21}H_{28}O_3$	76.8	76.5	8.6	8.7	
30	NMG[h]	90–94	A	51		$C_{28}H_{45}NO_8$[r]	63.2	63.1	8.7	8.9	
31	DNP[s]	138–140	C	95		$C_{27}H_{32}N_4O_6$	63.7	63.9	6.3	6.4	
32	*n*-$C_{11}H_{23}$—[q]	208–209	J	26	C	$C_{21}H_{27}NaO_3$[t]	70.2	70.1	7.9	7.6	4+
33	*n*-$C_{15}H_{31}$—[q]	191–192	I	25	C	$C_{25}H_{35}NaO_3$	73.9	73.9	8.7	9.0	5+
34	*n*-$C_{17}H_{35}$—	59–61	B	22	C	$C_{27}H_{40}O_3$	78.6	78.7	9.8	9.8	5+
35	4-$CH_3C_6H_4$—	123–125	B	22	D	$C_{17}H_{12}O_3$	77.3	77.2	4.6	4.5	0
36	4-Cl—C_6H_4—	178–179	A	22	D	$C_{16}H_9ClO_3$[i]	67.5	67.6	3.2	3.4	3+
37	4-Br—C_6H_4—	174–176	C	28	D	$C_{16}H_9BrO_3$	58.4	58.9	2.8	2.6	0

[a] Compound previously reported:[a1] W. Dieckmann, *Ber.*, **47**, 1439 (1914), m.p. 146°;[a2] Ref. 9 (a), m.p. 145°,[a3] Ref. 9(a), m.p. 137–139°;[a4] Ref. 20, m.p. 145–146°;[a5] Ref. 9 (j), m.p. 159°;[a6] Ref. 9 (i), m.p. 216°;[a7] Ref. 9 (d), m.p. 212–213;[a8] Ref. 9 (d), m.p. 215–216°;[a9] Ref. 9 (k), no m.p. in abstract.[a10] Ref. 9 (i), m.p. 180°;[a11] Ref. 10 (a), m.p. 67–68°;[a12] Ref. 10 (a), m.p. 108.5–110.5°. [b] Melting points are not corrected. [c] Recrystallizing solvent: A = isopropyl alcohol, B = methanol C = ethanol, D = acetone-water, E = water–hydrochloric acid, F = methyl ethyl ketone, G = chloroform-hexane, H = acetone, I = water, J = methylal, K = acetic acid. [d] Yields are given for recrystallized products. [e] For method used, see Experimental. [f] Analyses are by Weiler and Strauss, Oxford, England. [g] The activity was established by subcutaneous injection (5 mg./kg.) of the compounds to guinea pigs. The compound was administered at 0,5 and 24 hr. and prothrombin time determined at 27 hr. The percentage depression from the normal prothrombin time of the animals was classified as 1+ (−10%); 2+ (10–19%); 3+ (20–29%); 4+ (30–39%); 5+ (over 40%). [h] *N*-methylglucamine salt of compound immediately above. [i] Acceptable halogen analyses also obtained, and omitted to save space. [j] Obtained in 38.4% yield by Method A. [k] See Experimental for different crystalline forms. [l] *Anal.* calcd. for 1/2 H_2O. Br, calcd./found: 15.8/15.7. [m] Obtained in 34% yield by Method A. [n] *Anal.* calcd. for 1/2 H_2O. N, calcd./found: 2.9/3.0. [o] β-Naphthyl rather than α-naphthyl. [p] C_3H_5— = cyclopropyl. [q] Compound isolated and characterized as sodium enolate. [r] *Anal.* calcd. for 1/2 H_2O. N, calcd./found: 2.6/2.7. [s] 2,4-Dinitrophenylhydrazone. [t] *Anal.* calcd. for 1/2 H_2O. Na, calcd./found: 6.6/6.5.

solvents, suggestive of initial formation of IIId followed by formation of IIIb[26] in aqueous systems. When the R substituent is varied as phenyl, and substituted phenyl, a variety of new bands at longer wave lengths are obtained, not noted in III, R = H, or the analogous 1,2-diketo-3-phenylhydrindene,[27] indicative of interaction between the R

(26) A. Schönberg, A. Mustafa, and W. Asker, *J. Am. Chem. Soc.*, **73**, 2876 (1951).

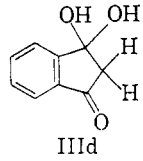
(27) C. F. Koelsch and H. Hochman, *J. Org. Chem.*, **3**, 503 (1939).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA[a]

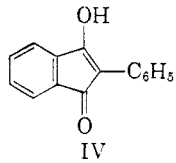
No.,[b] Solvent[c]		No.,[b] Solvent[c]	
b_1-A	253–259,[d] 10.6	6-C	273, 20.0; 310, 2.8; 322, 3.4; 336, 2.8; 354, 1.2
b_1-B	257, 28.0		
b_1-C	248, 9.9	6-D	280, 29.0; 325, 8.8; 338, 10.3; 355, 7.2
b_1-D	249, 11.9		
b_1-E	245, 10.2	6-E	291, 10.7; 347, 11.9; 361, 9.7
b_1-F	246, 32.6; 255, 30.6	6-F	285, 31.2; 331, 13.1
b_1-G	246, 25.4; 254, 24.2	6-G	286, 29.2; 330, 12.2
1-A	277, 17.8; 287, 15.8; 335, 6.2	10-A	250, 11.5; 292, 32.7; 339, 24.4; 354, 19.5
1-B	286, 35.8; 333, 14.9	10-B	250, 11.1; 292, 32.3; 339, 24.4; 353, 19.8
4-A	252, 17.8; 319, 4.3; 333, 3.5		
4-B	253, 21.2; 275, 16.9; 319, 6.3; 333, 5.0	15-A	260, 30.0
4-C	247, 12.5	15-B	252, 28.6
4-D	248, 14.5; 323, 2.5	22-A	236, 18.8; 286, 31.8; 312, 16.0; 323, 14.6
4-E	246–254,[d] 11.2		
4-F	251, 24.1; 317, 3.7	22-B	244, 17.6; 272, 27.2; 281, 44.4; 301, 12.4; 311, 18.7; 323, 19.7
4-G	251, 23.7; 300–318,[d] 3.5		
5-A	289, 31.1; 335, 17.9; 349, 14.4	25-A	238, 15.7; 285, 26.8; 312, 9.7; 322, 8.3
5-B	289, 32.2; 335, 18.5; 349, 15.3		
6-A	251, 10.7; 289, 32.8; 337, 19.0; 351, 14.9	25-B	245, 19.6; 271, 25.4; 280, 36.4; 310, 15.9; 323, 15.8
6-B	250, 10.7; 289, 33.3; 337, 18.9; 350, 15.4	29-A	246, 11.1; 274, 19.9; 282, 30.2; 310, 11.8; 322, 12.5
		29-B	244, 20.4; 282, 38.8; 310, 18.4; 322, 18.7
36-A	293, 14.5; 331, 17.4	36-E	300, 13.2; 335, 19.6
36-B	288, 14.1; 328, 16.2	36-F	291, 17.0; 330, 15.4
36-C	300, 17.3; 335, 22.4	36-G	291, 16.3; 330, 15.1
36-D	303, 16.6; 338, 23.6		

[a] The spectra were determined in a Beckman recording spectrophotometer, model DK. The data for the main absorption bands are reported as λ_{max} mμ, $\epsilon \times 10^{-3}$. [b] Numbers correspond to compound numbers in Table I; b_1 indandione, m.p. 129–131°. [c] The solvents were varied as follows: A = methanol; B = 0.1*N* sodium methoxide in methanol; C = methanol containing 1% acetic acid; D = isopropyl alcohol; E = acetonitrile containing 1% methanol; F = 0.1*N* sodium hydroxide and in the case of compounds 10 and 15, contains 1% methanol; G = 0.1*M* phosphate buffer, *p*H 7.5, containing 1% methanol. The spectra of compounds 5, 10 and 15 were established in solvents C-G and have not been reproduced to save space. [d] Shoulder, ε calculated at center of range.



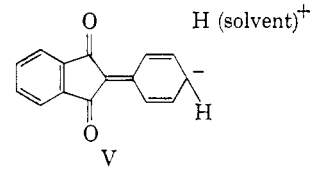
IIId

substituent and the indandione nucleus. In these structures, the *trans*-stilbene absorption characteristics are to be noted (IV).[28] The existence of a



IV

preponderance of the molecules in the enol form with I, R = *m*- or *p*-halophenyl, is reflected in the virtual identity of the spectra of these compounds in sodium methoxide and methanol. By contrast, I, R = phenyl, manifests considerable hyperchromic effect when going from methanol to sodium methoxide. An important solvating influence is also indicated in the relative hypochromicity of the spectra of the halophenyl compounds in such solvents as acetonitrile and isopropyl alcohol. Contribution of forms such as V[29] in methanol would be indicated.



V

In 1% acetic acid the longer bands disappear or diminish considerably.[30]

Of interest, and by contrast to I, R = H, the compounds, I, R = *m*- or *p*-halophenyl, are considerably less hyperchromic in aqueous alkali, relative to the spectra obtained in sodium methoxide.

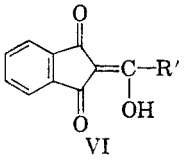
With I, R = *o*-chlorophenyl, and to some extent, R = α-naphthyl the influence of steric factors is manifest, with absorption at the longer wave lengths disappearing or being substantially diminished from steric inhibition of coplanarity of the hindered R group and the indandione system.

(28) (a) G. Berti, *Gazz. chim. ital.*, **86**, 655 (1956); (b) H. Jaffé and M. Orchin, *J. Chem. Soc.*, 1078 (1960).

(29) (a) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **82**, 1180 (1960); (b) J. E. Banfield, *J. Org. Chem.*, **25**, 300 (1960).

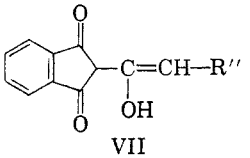
(30) L. F. Fieser and M. Fieser, *Organic Chemistry*, D. C. Heath and Co., Boston, Mass., 1944, p. 831.

With the 2-acyl indandiones studied, another allowable enolizable form[31] is VI.



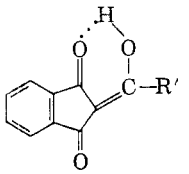
VI

The spectral characteristics of compounds in which R′ contains a methylene group *alpha* to the acyl carbonyl group (compounds 22, 29), do not permit assessment (compounds 25, 36) of the contribution to the spectra from forms such as VII.

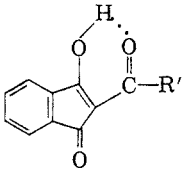


VII

The bathochromic effect with the acyl compounds relative to I, R = H, support the important contribution of forms of type VI, which parallel the V structures. Enhancement of the extinction coefficient in sodium methoxide, relative to methanol, without substantial effect on the locus of the main absorption bands would indicate that the acylated compounds are largely in the enolic form of the type corresponding to IIIb, or VI in the solvent systems inspected. Compound 36 is not vulnerable to quenching of the spectra in 1% acetic acid, and in fact, the spectra in this solvent, as well as in isopropyl alcohol are bathochromic and hyperchromic relative to those noted in methanol, which would be accountable for by chelated forms as VIIIa and VIIIb, also realizable with the other acyl derivatives.



VIIIa



VIIIb

Similar structures have been assigned for β-diketones[32-34] in other studies. It is of interest that with the diaroylmethanes[32] the extinction coefficients of the enolate ion were hypochromic relative to the ε values for the diketones *per se* in ethanol.

There is no correlation with anticoagulant activity in that virtually any of the spectral characteristics noted above are shared by compounds which are physiologically very active, or substantially inactive.

(31) J. Schieber and G. Hopfer, *Ber.*, **53**, 697 (1920).

(32) (a) G. S. Hammond, W. G. Bordius, and G. A. Guter, *J. Am. Chem. Soc.*, **81**, 4621 (1959); (b) G. A. Guter and G. S. Hammond, *J. Am. Chem. Soc.*, **81**, 4686 (1959).

(33) L. G. Van Uitert and W. C. Fernelius, *J. Am. Chem. Soc.*, **76**, 375 (1954), and previous papers in this series.

(34) A. Brandström, *Arkiv. för Kemi*, **7**, 81 (1954).

EXPERIMENTAL[35]

2-(p-Bromophenyl)indandione-1,3 (Compound 8). Method A. A mixture of 13.9 g. (0.075 mole) of *p*-bromobenzaldehyde, 10 g. (0.075 mole) of phthalide, and 5.5 g. (0.08 mole) of sodium ethoxide in 80 ml. of ethanol was heated under reflux for 1.5 hr. Water (80 ml.) was added, the alcohol removed, and the residue diluted with 500 ml. of ice water and washed with two 80-ml. portions of ether. After acidifying with hydrochloric acid the product was extracted into 100 ml. of ether, and then re-extracted with aqueous sodium bicarbonate, which was acidified with hydrochloric acid to *p*H 2. After 20 hr. the product was separated, dried, and recrystallized (methanol), 8.7 g. (38.4%) of dark red crystals, m.p. 142–146°, with the red color fading at 132°.

On recrystallization from four parts of acetic acid the white form (86%) of the product was obtained, m.p. 143–148°. On recrystallization of the white form from methanol, it reverted to the dark red crystals. The white form and red form on admixture melted 142–146° C.[36]

2-(α-Naphthyl)indandione-1,3 (Compound 15). In a manner similar to the above, and using α-naphthaldehyde, a 34.2% yield of the yellow product was obtained.

The mother liquor (from aqueous acidification and recrystallization) on concentration gave 40% of a white by-product, formulated as compound Ia (Scheme I), 3-[(α-naphthyl)hydroxymethyl]phthalide which melted 178–179° (ethanol).

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 78.4; H, 4.9.

This product, on solution in methanol and treatment with sodium methoxide, gave compound 15 in 53% yield.

The product dissolves in hot aqueous sodium hydroxide, and is recovered unchanged upon acidification.

Compound 15 is obtained in 25% yield (m.p. 213–216°) when potassium *t*-butoxide is substituted for sodium ethoxide.

α-Naphthalphthalide was prepared in 36% yield, m.p. 184–184.5°[37] (methyl ethyl ketone) following the procedure of Weiss, using α-naphthyl acetic acid and phthalic anhydride.[38] On admixture with compound Ia, the m.p. was 148–156°.

2-[(α-Naphthyl)acetyl]o-benzoic acid was prepared from α-naphthalphthalide, following the procedure of Arcus and Marks[39] in 75% yield, m.p. 195–196° (ethanol). The mixed m.p. with compound Ia was 158–165°.

Anal. Calcd. for $C_{19}H_{14}O_3$: C, 78.6; H, 4.9. Found: C, 79.1; H, 4.9.

2-(α-Naphthyl)indandione-1,3. Method B.[40] A mixture of 156 g. (1 mole) of α-naphthaldehyde, 134 g. (1 mole) of phthalide, and 580 ml. of ethyl propionate was rendered anhydrous by distillation of 100 ml. of ethyl propionate from the reaction mixture (ethyl propionate–water azeotrope, b.p. 81.2°). Sodium methoxide (3 moles) in 700 ml. of methanol was added rapidly to the refluxing mixture which was maintained at about 66–68° over 4 hr. by occasional

(35) Typical procedures for the preparations given in the table are indicated.

(36) See Ref. 9 (1) for similar observations with 2-(*p*-chlorophenyl)indandione-1,3. It is of interest that compounds 4 and 7 which have an *o*-chlorophenyl substituent are obtained as colorless crystals, as is phenylindandione.

(37) E. D. Bergmann, *J. Org. Chem.*, **21**, 461 (1956) reports m.p. 179°.

(38) R. Weiss, *Org. Syntheses*, **Coll. Vol. II**, 61 (1943).

(39) C. L. Arcus and R. E. Marks, *J. Chem. Soc.*, 1627 (1956).

(40) A more fully detailed exploration of this method is in progress.

distillation of solvent. After removal of the volatile material the residue was dissolved in 5.5 l. of water, washed with ether, filtered, and acidified to *p*H 2, whereupon the product separated, 262 g. (96.5%), m.p. 207–211°. On recrystallization (9 parts methyl ethyl ketone) there was obtained 217 g. (83%), m.p. 217–218°.

Sodium(2-lauroyl)indandione-1,3 (Compound 32). Method C. To a suspension of 54 g. (1 mole) of sodium methoxide in 1200 ml. of benzene was added 198 g. (1 mole) of methyl undecyl ketone and 194 g. (1 mole) of dimethyl phthalate; the mixture was heated under reflux for 24 hr. with stirring. The benzene was removed, the residue suspended in a mixture of 1500 ml. of water and 200 ml. of ether, and while vigorously stirred, acidified with hydrochloric acid to *p*H 3. On extraction of the ethereal phase with 2.5 l. of 2% sodium hydroxide, the sparingly soluble sodium enolate precipitated, was separated, dried (100°), and recrystallized (methylal) to give 93.1 g. (25.9%), m.p. 208–209°.

A suspension of 30 g. (0.084 mole) of the above product in 250 ml. of water and 250 ml. of ether was acidified to *p*H 3 with hydrochloric acid. The ethereal layer was dried (magnesium sulfate), the ether removed, and the residue on recrystallization (methanol) gave 24.8 g., (88%) of 2-lauroylindandione-1,3, m.p. 45–46° (compound 29).

N-Methylglucamine salt of 2-lauroylindandione-1,3, (Compound 30). The mixture of 8 g. (0.024 mole) of 2-lauroylindandione-1,3 and 4.76 g. (0.024 mole) of *N*-methylglucamine in 15 ml. of methanol dissolved after 60 min. heating on the steam bath. The methanol was removed and the residue recrystallized (isopropyl alcohol) to give 6.5 g. (51%) of product, m.p. 90–94°.

2-(Cyclopropylketo)indandione-1,3 (Compound 22). Method D. A solution of 5.75 g. (0.25 mole) of sodium in methanol was prepared and the methanol removed. Benzene (150 ml.) was added and residual methanol removed by azeotropic distillation. After addition of 21 g. (0.25 mole) of methyl cyclopropyl ketone and 48.5 g. (0.25 mole) of dimethyl phthalate in 125 ml. of benzene, the reaction mixture was heated under reflux for 6 hr. with stirring. After steam distillation, the nonvolatile residue was diluted with one l. of water, filtered, and the product precipitated by acidification with hydrochloric acid to *p*H 3. Recrystallization (acetone-water) gave 16 g. (30%) of product, m.p. 132–134°.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological screening of the compounds, M. Blitz and R. Levinton for the antibacterial results, and D. Farkas for the ultraviolet absorption data.

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[CONTRIBUTION FROM PLASTICS LABORATORY AND RESEARCH CENTER, MINNEAPOLIS-HONEYWELL REGULATOR CO.]

Reaction of Aniline with 3-Phenoxy-1,2-epoxypropane

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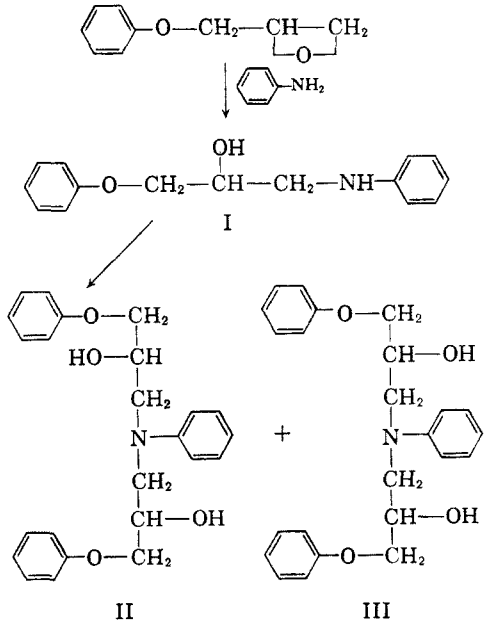
Received December 21, 1959

The products from the reaction of aniline and 3-phenoxy-1,2-epoxypropane have been characterized. One compound was shown to be a secondary amine and the other two to be the *dl* and *meso* forms of a tertiary amine. The structures were proved by independent synthesis.

In order to study the reaction between polyfunctional epoxides and polyfunctional aromatic amines in the formation of resins, a study was made of the model reaction between 3-phenoxy-1,2-epoxypropane and aniline. Fourneau[3] reported one compound from this reaction to which he assigned the structure I; however he reported no evidence for his assignment.

From the direct reaction of 3-phenoxy-1,2-epoxypropane and aniline, the authors have obtained three crystalline products, I, II, and III. Compound I proved to be a secondary amine, while II and III, not previously reported, were higher molecular weight tertiary amines. By the reaction of I with a second mole of 3-phenoxy-1,2-epoxypropane, II and III were formed, indicating that the original model reaction involved two steps.

The infrared spectrum of I indicated it to be a secondary aminoalcohol in conformance with Fourneau's assignment, and the spectra of II and III, which were identical, indicated that they were tertiary aminoalcohols, hence must be related as the *dl* and *meso* forms. The structures of I,



I

II III

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(3) E. Fourneau, *J. Pharm. Chem.*, 1, 99 (1910).