DERIVATIVES OF 2-(3'-COUMARINYL)-1,3-INDANDIONE

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The possibility of the direct preparation of 2-(3'-coumarinyl)-1,3-indandione and its derivatives by condensing phthalic and substituted phthalic anhydrides with 3-coumarinylacetic acid in acetic anhydride solution in the presence of triethylamine has been shown. The bromination and hydroxymethylation of 2-(3'coumarinyl)-1,3-indandione and its substituted derivatives have been performed.

Synthetic blood anticoagulants are derivatives of either 1,3-indandione (I) or of 4-hydroxycoumarin (II) [1,2] and, therefore, the biological activity of the recently-described [3] 2-(3'-coumarinyl)-1,3-indandione (III), containing structural fragments of both I and II, is causing interest.

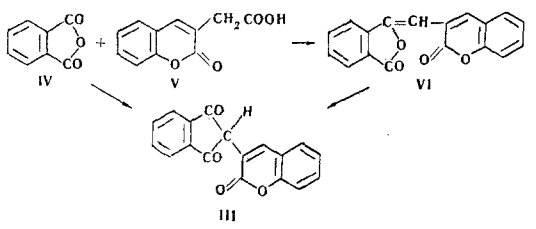
It has been shown [4,5] that the anticoagulant activity of the 2-aryl-1,3-indandiones disappears when substituents are introduced into the phthaloyl ring, but replacement of the active hydrogen either enhances or weakens the activity of the material, depending on the nature of the substituent.

In this paper we describe the synthesis and properties of 2-(3'-coumarinyl)-1,3-indandiones substituted in the phthaloyl ring and also their 2-bromo and 2-hydroxymethyl derivatives.

Compound III was synthesized by the rearrangement of 3-(3'-coumarinylmethylene)phthalide (VI), obtained from phthalic anhydride (IV) and 3-coumarinylacetic acid (V). In essence, this two-stage synthesis of III is completely analogous to the preparation of 2-aryl-1,3-indandiones from IV and arylacetic acids via arylidenephthalides as intermediates [6].

But, it is possible to obtain 2-aryl-1,3-indandiones from the same starting materials by a different—one-stage—method of synthesis [7–12] if the condensation is carried out in acetic anhydride solution in the presence of a large amount of triethylamine.

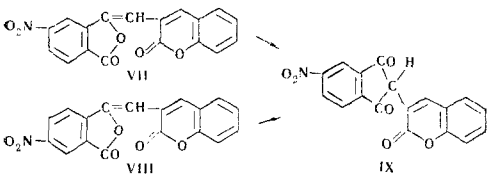
It has been found that under the conditions for the direct preparation of the 2-aryl-1,3-indandiones [7] the acid V behaves similarly to the aryl-acetic acids, and that if the condensation of IV with V is carried out in acetic anhydride solution at room temperature in the presence of a comparatively small amount of triethylamine, VI is formed. When the temperature is raised and in the presence of a larger amount of triethylamine, III is formed directly.



To identify the products that we obtained, in addition to their characteristic properties, we used the rearrangement of VI into III.

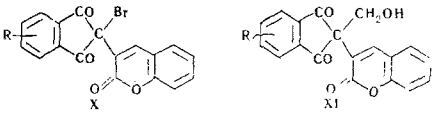
We have used condensation in acetic anhydride solution in the presence of a large amount of triethylamine also for the synthesis of previously undescribed derivatives of III having substituents in the phthloyl ring. For this purpose we used 3- and 4-substituted nitro-, halo-, and methylphthalic anhydrides and V.

The condensation of 3-nitro-, 3-chloro-, 4-chloro-, 3-bromo-, 4-bromo-, 3-iodo-, 4-iodo-, and 4-methylphthalic anhydrides with V, performed by the usual procedure for the synthesis given in the experimental part of this paper, furnished practically only one reaction product in each individual case—the corresponding derivative of III. But in the condensation of 4-nitrophthalic anhydride in acetic anhydride solution under the conditions giving the maximum yield of 2-(3'-coumarinyl)-5-nitro-1,3-indandione (IX), i.e., with the use of a threefold excess of triethylamine with respect to the condensation component, a yellow by product was formed in considerable amounts (17.9%), which, in contrast to the red 5-nitro derivative of III, did not dissolve in dilute solutions of alkalies but was converted into this derivative under the action of sodium methoxide. By analogy [8] and judging from the properties of this by-product, it corresponds to the structure of either 3-(3'-coumarinylmethylene)-5-nitrophthalide (VII) or 3-(3'-coumarinylmethylene)-6-nitrophthalide (VIII).



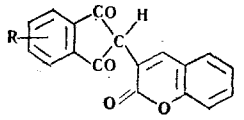
Some information is given in Table 1 on the synthesis, properties, and the results of elementary analysis of the III derivatives substituted in the phthaloyl ring synthesized.

By the bromination in glacial acetic acid of the III derivatives substituted in the phthaloyl ring, the colorless 2-bromo derivatives (X) were prepared.



The 2-hydroxymethyl derivatives (XI) could not be prepared from all the compounds III described. The 5-nitro-, 5-chloro-, 5-bromo-, and 5-iodo-2-(3-coumarinyl)-1,3-indandiones were recovered completely unchanged even after prolonged heating in an aqueous ethanolic solution of formaldehyde. The melting points and analytical results for the 2-bromo- and 2-hydroxymethyl derivatives of III are given in Table 2.

Table 1



R	Conditions of synthesis		Mp, °C	Color of the crystals	Empirical formula	Found, %			Calculated, %			Yield, %
	amount of triethylamine, mole	time of the reaction, min				C	H	halogen	C	H	halogen	
4-NO_2	0.03	15	215—216	Red	$C_{18}H_9NO_6$*	64.70	2.62		64.48	2.71		58.8
4-Cl	0.04	15	216—217	Orange-red	$C_{18}H_9ClO_4$	66.28	2.61	11.27	66.58	2.79	10.92	57.6
5-Cl	0.03	15	218—219	Orange-red	$C_{18}H_9ClO_4$	66.29	2.85	10.56	66.58	2.79	10.92	44.4
4-Br	0.03	30	186—188	Orange-red	$C_{18}H_9BrO_4$	58.19	2.60	21.98	58.56	2.46	21.65	66.7
5-Br	0.04	30	225—226	Orange-red	$C_{18}H_9BrO_4$	58.21	2.23	21.98	58.56	2.46	21.65	50.1
4-I	0.03	20	263—264	Red	$C_{18}H_9JO_4$	51.58	2.20	30.31	51.95	2.18	30.50	62.5
5-I	0.03	20	211—212	Red	$C_{18}H_9JO_4$	51.54	2.18	30.77	51.95	2.18	30.50	52.9
5-CH_3	0.05	20	200—201	Red	$C_{19}H_{12}O_4$	74.79	3.88	74.99	3.97			52.0

*Found, %: N 4.29. Calculated, %: N 4.18.

Table 2

2-Bromo- and 2-Hydroxymethyl Derivatives of 2-(3'-Coumarinyl)-1,3-indandiones

Compound	Mp, °C	Empirical formula	Found, %				Calculated, %			
			C	H	N	halogen	C	H	N	halogen
2-Bromo-2(3'-coumarinyl)-1,3-indandione	234—235	$C_{18}H_9BrO_4$	58.22	2.44		21.71	58.56	2.46		21.65
2-Bromo-2-(3'-coumarinyl)-4-nitro-1,3-indandione	271—272	$C_{18}H_8NBrO_6$	52.59	2.06	3.26	19.60	52.20	1.95	3.38	19.29
2-Bromo-2-(3'-coumarinyl)-5-nitro-1,3-indandione	214—215	$C_{18}H_8NBrO_6$	52.43	2.09	3.44	19.51	52.20	1.95	3.38	19.29
2-Bromo-4-chloro-3-(3'-coumarinyl)-1,3-indandione	268—270	$C_{18}H_8ClBrO_4$	53.17	2.07		28.90	53.56	2.00		28.58
2-Bromo-5-chloro-2-(3'-coumarinyl)-1,3-indandione	247—249	$C_{18}H_8ClBrO_4$				28.09	53.56	2.00		28.58
2,4-Dibromo-2-(3'-coumarinyl)-1,3-indandione	214—216	$C_{18}H_8Br_2O_4$	47.85	2.14		36.33	48.25	1.80		35.67
2,5-Dibromo-2-(3'-coumarinyl)-1,3-indandione	235—236	$C_{18}H_8Br_2O_4$	47.98	1.69		36.20	48.25	1.80		35.67
2-Bromo-2-(3'-coumarinyl)-4-iodo-1,3-indandione	263—264	$C_{18}H_8BrJO_4$				41.90	43.67	1.63		41.77
2-Bromo-2-(3'-coumarinyl)-5-iodo-1,3-indandione	215—217	$C_{18}H_8BrJO_4$	43.21	1.79		40.96	43.67	1.63		41.77
2-Bromo-2-(3'-coumarinyl)-5-methyl-1,3-indandione	230—231	$C_{19}H_{11}BrO_4$	59.21	2.68		21.04	59.55	2.89		20.85
2-(3'-Coumarinyl)-2-hydroxymethyl-1,3-indandione	207—208 (decomp)	$C_{19}H_{12}O_5$	71.22	3.66			71.25	3.78		
2-(3'-Coumarinyl)-2-hydroxymethyl-4-nitro-1,3-indandione	215—216 (decomp.)	$C_{19}H_{11}NO_7$	62.61	3.20	4.01		62.47	3.04	3.83	
4-Chloro-2-(3'-coumarinyl)-2-hydroxymethyl-1,3-indandione	216—217 (decomp.)	$C_{19}H_{11}ClO_5$	64.06	2.80		10.28	64.33	3.13		9.99
4-Bromo-2-(3'-coumarinyl)-2-hydroxymethyl-1,3-indandione	220—222 (decomp.)	$C_{19}H_{11}BrO_5$	56.98	2.82		19.89	57.17	2.78		20.04
2-(3'-Coumarinyl)-2-hydroxymethyl-4-iodo-1,3-indandione	226—228 (decomp.)	$C_{19}H_{11}JO_5$	50.98	2.62		28.84	51.15	2.48		28.44
2-(3'-Coumarinyl)-2-hydroxymethyl-5-methyl-1,3-indandione	199—200 (decomp.)	$C_{20}H_{14}O_5$	71.80	4.27			71.85	4.22		

EXPERIMENTAL

2-(3'-Coumarinyl)-1,2-indandione (III). A mixture of 1.48 g (0.01 mole) of IV, 2.04 g (0.01 mole) of V, and 10.2 g (0.1 mole) of acetic anhydride was heated in the boiling water bath until the solid substances had dissolved completely. To the solution was slowly added 5.05 g (0.05 mole) of triethylamine, and heating was continued for 40 min. The dark red solution was poured onto a mixture of 100 g of ice and 75 ml of concentrated HCl. An orange oil separated which rapidly solidified. The precipitate was filtered off and while still wet was suspended in a 1% solution of caustic soda. After some time, the small amount of insoluble matter was filtered off, and the filtrate was acidified with hydrochloric acid. A red-orange precipitate deposited. Yield 1.7 g (58.6%). Mp 203–208° C. After two recrystallizations from glacial acetic acid, the III had mp 207–208° C. According to the literature [3], mp 199–200° C. Found, %: C 74.26; H 3.57. Calculated for $C_{18}H_{10}O_4$, %: C 74.48; H 3.47.

3-(3'-Coumarinylmethylene)phthalide (VI). A solution of 1.48 g (0.01 mole) of IV and 2.04 g (0.01 mole) of V in 10.2 g (0.1 mole) of acetic anhydride was treated with 2.02 g (0.02 mole) of triethylamine, and the mixture was left at room temperature for a day. Then it was poured onto a mixture of 100 g of ice and 60 ml of HCl. A yellow precipitate deposited which was filtered off, washed with 2% sodium carbonate solution, and dried. Yield 1.44 g (49.7%); mp 270–272° C. After crystallization from glacial acetic acid, yellow crystals with mp 272–274° C were obtained. According to the literature [3], mp 274° C. Found, %: C 74.65; H 3.36. Calculated for $C_{18}H_{10}O_4$, %: C 74.48; H 3.47.

Rearrangement of the phthalide VI into III. A mixture of 0.7 g of VI and sodium methoxide (from 0.2 g of metallic sodium in 20 ml of absolute methanol) was heated in the boiling water bath for 40 min, cooled, filtered, poured into 50 ml of water, and acidified with dilute hydrochloric acid. An orange precipitate (0.5 g) deposited, and after crystallization from glacial acetic acid the substance had mp 207–208° C and gave no depression of the melting point with authentic III.

2-(3'-Coumarinyl)-5-nitro-1,3-indandione (IX). A mixture of 1.93 g (0.01 mole) of 4-nitrophthalic anhydride and 2.04 g (0.01 mole) of V was dissolved in 30.6 g (0.3 mole) of acetic anhydride by heating in the water bath, and then 5.0 g (0.05 mole) of triethylamine was added and the reaction mixture was heated for another 15 min. After cooling, the precipitate formed was filtered off (substance A) and the filtrate was decomposed by being poured onto 100 g of ice and 75 ml of concentrated HCl. Red crystals of compound IX separated out, and these were filtered out and dissolved in 1% caustic soda solution. The solution was filtered, and the filtrate was acidified with hydrochloric acid to give 1.6 g (47.8%) of a product which, after recrystallization from dioxane, had mp 268–269° C. Found, %: C 64.47; H 2.86; Calculated for $C_{18}H_9NO_6$, %: C 64.48; H 2.71; N 4.18.

3-(3'-Coumarinylmethylene)-5- (or -6-)nitrophthalide (VII, VIII). The yellow substance obtained above was washed and dried. Yield 0.6 g (17.9%); After recrystallization from glacial acetic acid, mp 308–310° C. Found, %: C 64.48; H 2.93; N 4.16; 4.31. Calculated for $C_{18}H_9NO_6$, %: C 64.48; H 2.71; N 4.18.

Rearrangement of the phthalide VII (VIII) into IX. A 0.4 g amount (0.001 mole) of the VII (VIII) obtained as described above was heated in a solution of sodium methoxide from 0.2 g of metallic sodium and 20 ml of absolute methanol for 40 min, after which the solution was filtered and the filtrate was diluted with 50 ml of water and acidified with dilute hydrochloric acid. This gave 0.14 g (35%) of red crystals which, after recrystallization from dioxane, had mp 268–269° C. The substance gave no depression of the melting point with an authentic sample of compound IX.

Preparation of derivatives of 2-(3'-coumarinyl)-1,3-indandione substituted in the phthaloyl ring. The appropriate derivative of IV (0.01 mole) and V (0.01 mole) was condensed in solution in 20 ml (0.2 mole) of acetic anhydride in the presence of triethylamine, as in the preparation of III (see Table 1). The products were recrystallized from glacial acetic acid.

2-Bromo derivatives of the 2-(3'-coumarinyl)-1,3-indandiones (X). With heating, 0.05 mole of the appropriate III was dissolved in glacial acetic acid, an excess of a solution of bromine in glacial acetic acid was added, and the reaction mixture was left overnight at room temperature. The precipitate that deposited was filtered off and recrystallized from glacial acetic acid. Compound X consisted of colorless or slightly yellowish crystals soluble in dioxane and ethanol (Table 2).

The 2-hydroxymethyl derivatives of the 2-(3'-coumarinyl)-1,3-indandiones (XI). To a solution of 0.003 mole of one of compounds III in 60–100 ml of methanol was added 20 ml of formalin (35%), and the mixture was heated in the water bath for 1 hr. The colorless solution was diluted with water, and the resulting precipitate (71–80%) was recrystallized from glacial acetic acid. A colorless product soluble in ethanol, dioxane, and acetone was obtained (Table 2).

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