of liver toxicity is similar to that suggested for several other hepatotoxic halogenated hydrocarbons.²¹⁻²³ Studies are in progress to delineate the nature of chemically reactive metabolites of halothane.

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2-Cyano-1,3-dicarbonyl Compounds with Antiallergic Activity

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A number of 2-cyanoindan-1,3-diones and 3-cyano-4-hydroxycoumarins have been prepared and assessed for potential antiallergy activity as measured by their ability to inhibit passive cutaneous anaphylaxis in the rat, mediated by rat serum containing antigen specific IgE. The structural requirements for activity were similar not only for both series of compounds but also for the analogous 2-nitroindan-1,3-diones and 4-hydroxy-3-nitrocoumarins previously reported. The most active compounds were 2-cyano-5,6-diethylindan-1,3-dione (4e) and 3-cyano-6,7-diethyl-4hydroxycoumarin (11h).

As part of a program relating to 2-nitro-1,3-dicarbonyl compounds, some of which were found to be capable of inhibiting rat passive cutaneous anaphylaxis (PCA),¹⁻⁴ we have studied the effects of replacing the nitro function in both the 2-nitroindan-1,3-diones 1 and the 4-hydroxy-3-nitrocoumarins 2. The marked reduction or loss of activity observed on replacing the nitro group of 1 by such groups as hydrogen, alkyl, nitroso, acetyl, carboethoxy, halogen, phenyl, and sulfonic acid has been previously discussed,⁵ and we have noticed a similar effect with such substitution in 2.6 It was of some interest, therefore, to

find a high level of activity in the rat PCA test in both 2-cyanoindan-1,3-diones 4 and 3-cyano-4-hydroxycoumarins 11 (Belgian Patent 828690) in which the nitro moiety of 1 and 2, respectively, had been replaced by nitrile. We now report our results obtained with these two series of compounds.

Chemistry. (a) 2-Cyanoindan-1,3-diones. Two routes for the synthesis of 2-cyanoindandiones 4 have been employed: the base-induced rearrangement of 3-cyanomethylenephthalides 3 (method A)⁷ and the Claisen condensation of acetonitrile with phthalic esters 5 (method

Table I. 3-Cyanomethylenephthalides



Compd	R	Mp, $^{\circ}C^{a}$	Formula	Analyses	Yield, %	Method of synthesis ^b
3a	Н	178-180 ^c (AcOH)	C ₁₀ H ₅ NO ₂	C, H, N	25	C
3b	4-Me	147-170 (EtOH)	C, H, NO,	C, H, N	74	D
3c	5- or 6-Me	151-152 (AcOH)	C_1, H, NO_2	C, H, N	25	С
3d	5,6-Me,	165-181 (EtOH)	C, H, NO,	C, H, N	66	D
3e	5,6-Et,	159-168 (EtOH)	$C_{14}H_{13}NO_2$	C, H, N	47	D

^a Recrystallization solvent in parentheses. Melting points often wide range due to mixtures of geometric isomers. ^b See text and Experimental Section. ^c Lit.⁷ mp 195 °C.



B).⁸ These are exemplified in Scheme I.

The intermediate phthalates 5 are readily accessible by well-known routes, some of which we have previously discussed.¹ but access to the cyanomethylenephthalides 3 is less documented. Gudrinietsye⁷ has used the reaction of phthalic anhydride with cyanoacetic acid in pyridine to give the parent compound 3 (R = H, Scheme II, method)C) in low yield. The same reaction in our hands also gave a low yield of 3 as did a similar reaction with 4-methylphthalic anhydride. Under identical conditions 3methylphthalic, 4.5-dimethylphthalic, and naphthalic anhydrides failed to give any isolable quantity of 3. A better procedure based on the known⁹ ring contraction of 2-azidoquinones (Scheme II, method D) gave consistent yields of 3 over the range of substituents studied (see Table I). The light-sensitive 2-azidonaphthoquinones 7 were readily prepared from the corresponding halogenonaphthoquinones 6 by replacement of the halogen by azide ion according to the procedure of Fieser and Hartwell.¹⁰

Ring contraction of the azidoquinones 7 gave mixtures of the E and Z isomers of 3, usually with the thermodynamically more stable Z isomer predominating. These mixtures may be used without isomer separation since a single component is formed on rearrangement to 4.

Both methods A and B are suitable for the substituents studied although, in general, better yields were obtained using method A (see Table II).

(b) 3-Cyano-4-hydroxycoumarins. Salicylic acids 8, where not available commercially, were synthesized by the

Scheme I









Marassé procedure¹¹ and converted to their acetates 9 by standard methods (Scheme III). Reaction of 9 with thionyl chloride in benzene gave the acyl chlorides 10 which were condensed in their crude state with ethyl cyanoacetate using a modification of the procedure of Checchi¹² to give moderate yields of the cyanocoumarins 11 (see Table III).

Compounds of type 12 where the hydroxyl group of 11a was replaced by hydrogen, methyl, chloro, amino, ethylamino, and methoxyl were synthesized by literature procedures.¹²



12, X = H, Me, Cl, OMe, NH_2 , NHEt

Results and Discussion

2-Nitroindan-1,3-diones 1 and 4-hydroxy-3-nitrocoumarins 2 and some structurally similar compounds have



been shown to be potent inhibitors of rat passive cutaneous anaphylaxis.¹⁻⁴ Chemical modification of the 2-nitro-1,3-dicarbonyl moiety has, in general, resulted in greatly diminished activity suggesting that this or some similar unit might be significant to the biological effect of this group as a whole. Replacement of the nitro group of either 1 or 2 by the chemically similar nitrile group resulted in retention of the antiallergic activity of these series (Tables II and III).

Similar substitutions in the 2-cyanoindan-1,3-diones 4 and the 3-cyano-4-hydroxycoumarins 11 produced similar changes in activity in the rat PCA test. This similarity parallels that found within the nitro analogues 1 and $2^{1,3}$ Maximum activity was found in those compounds having alkyl groups at both C-5 and C-6 in 4 (4d and 4e) and at both C-6 and C-7 in 11 (11f-i). In addition, the fused benzenoid derivative 4f had a high level of activity. It is of interest that the aza derivatives 4i and 4j produced inhibition in the PCA test equivalent to that of the parent 4a, suggesting that in this series there is bioequivalence between the benzene and pyridine nuclei irrespective of the position of nitrogen occupation (cf. ref 4).

No compound was significantly more potent than disodium cromoglycate¹³ (Table II) although several showed a similar potency. Unlike disodium cromoglycate, some members of both classes were active by oral administration, compounds 4e and 11h being most effective in this respect each having an $ED_{50} \approx 60 \ \mu mol/kg$ when given 15–20 min prior to antigen challenge. This observation is in line with oral activity previously observed in the nitroindandiones 1.¹⁴

Replacement of the hydroxyl substituent of 11a by a wide variety of univalent groups including alkyl, halogen, methoxyl, and amino, as in 12, resulted in substantial loss of activity, further endorsing the apparent significance of the 1,3-dicarbonyl system as an essential structural feature.⁵

Experimental Section

Melting points were determined using a Buchi melting point apparatus and are recorded uncorrected. The structures of all compounds were confirmed by their IR and NMR spectra, the latter of which were determined as solutions in either CDCl₃ or Me₂SO-d₆. Where indicated by elemental symbols (Tables I-III) the results for these elements fall within $\pm 0.4\%$ of the calculated values.

Phthalic Acid Derivatives. Pyridine-3,4-dicarboxylic acid, 4-methylphthalic acid, and 4-chlorophthalic acid are commercially available. The anhydrides of phthalic, naphthalic, 3-methylphthalic, and pyridine-2,3-dicarboxylic acids may also be obtained commercially. Dimethyl esters of these acids or anhydrides where required were prepared by standard procedures. Dimethyl 3methoxyphthalate was prepared by the method of Birch and Hextall.¹⁵

2-Azido-5-methylnaphtho-1,4-quinone. To a solution of 2-bromo-5-methylnaphtho-1,4-quinone¹⁶ (13.54 g, 0.054 mol) in boiling EtOH (140 ml) was added a concentrated aqueous solution of NaN₃ (4.56 g, 0.07 mol) and the deep red solution kept at reflux for 2 min. On cooling in ice an orange solid separated which after filtration was washed with a little cold EtOH and then water and dried in vacuo over P₂O₅ in the absence of light to give 6.531 g (57%) of yellow material: mp 105 °C dec; ν_{max} (mull) 2150, 1665, 1650, 1610, 1565 cm⁻¹; τ (CDCl₃) 7.27 (3 H, s), 3.61 (1 H, s), 2.41 (1 H, m), 1.93 (1 H, t, J = 4.5 Hz).

2-Bromo-6,7-dimethylnaphtho-1,4-quinone. A stirred solution of 6,7-dimethylnaphtho-1,4-quinone¹⁷ (20 g, 0.107 mol) in glacial AcOH (250 ml) was treated dropwise with a solution of Br₂ (17.2 g, 5.5 ml, 0.107 mol) in glacial AcOH (10 ml) at 15 °C and left to stir at this temperature for 2 h. Anhydrous NaOAc (20 g) was added and the mixture stirred at room temperature for 30 min and then at 100 °C for an additional 1.5 h. The cooled mixture was poured into water (2.5 l.) and the precipitated

Act in rat PCA test

Table III. 3-Cyano-4-hydroxycoumarins



Compd	\mathbf{R}_{ι}	\mathbf{R}_{2}	\mathbf{R}_{3}	R₄	Mp, $^{\circ}C^{a}$	Formula	Analyses	Yield, %	$\frac{\text{ED}_{50}, \mu \text{mol/kg sc}}{\text{at } T \max^{b,c}}$
11a	Н	Н	Н	Н	267-269 dec ^{d,e}	C ₁₀ H ₅ NO ₃	C, H, N	79	39.1 (19-81.8, 100, 30)
11b	Н	Me	Н	Н	238 - 241	$C_{11}H_7NO_3$	C, H, N	45	497 (f, 6)
11c	Н	Н	Me	Н	261-264	$C_{11}H_7NO_30.25H_2O$	C, H, N	59	52.4(14-199, 82, 18)
11d	Н	Н	Н	Me	211 - 214	$C_{11}H_7NO_3H_2O$	C, H, N	51	32.8(11-90, 85, 17)
11e	Н	Н	\mathbf{Et}	Н	211-215	$C_{12}H_9NO_3$	C, H, N	72	23.8(2-80, 87, 12)
11f	Η	Me	Me	Η	262 - 264	$C_{12}H_{9}NO_{3}H_{2}O$	C, H, N	56	$15.2 \ (8-29, 127, 12)$
11g	Н	\mathbf{Et}	Me	Н	224 - 226	$C_{13}H_{11}NO_3$	C, H; N^g	52	10.1 (3-37, 79, 18)
11ĥ	Η	\mathbf{Et}	\mathbf{Et}	Н	198-200 ^h	$C_{14}H_{13}NO_3$	C, H, N	55	7.6(2-32.7, 57, 24)
11i	Н	Tet	ra-	Н	265 - 267	$C_{14}H_{11}NO_3$	C, H, N	61	16.4 (6-48, 82, 30)
		methy	lene						
11j	Η	H	Me	Me	255-256 ⁱ	$C_{1,2}H_{0,NO_{3}}H_{0,O_{3}}$	C, H, N	64	26.2(10-71, 85, 24)
11k	Η	Bu	ta-	Н	297-299	C ₁₄ H ₇ NO ₃	C, H, N	64	211(f, 6)
		dieny	lene						
111	Η	OMe	Н	Н	249 – $253 ext{ dec}^d$	$C_{11}H_7NO_4 \cdot 0.25H_3O$	C, H, N	57	28.2(6-119, 83, 24)
11m	Н	Н	OEt	Η	224-225	$C_{12}H_9NO_4H_2O$	C, H, N	54	15.1 (8-26, 83, 24)

^a Recrystallized from EtOH-dilute HCl unless specified otherwise. ^b Figures in parentheses are 95% confidence limits, slope of inhibition/log dose line, number of animals used. ^c T max is the time between sc administration of the drug and challenge to give maximum activity and was 10 min in each case. ^d Recrystallized from H₂O-dilute HCl. ^e Lit.¹² mp 242 [°]C dec. ^f Insufficient data to calculate confidence limits. ^g N: found, 5.68; required, 6.11. ^h Recrystallized from EtOH-dilute HCl and then from CHCl₃-petroleum ether. ⁱ Recrystallized from EtOH-petroleum ether.

bromide filtered off, washed well with water, and recrystallized (EtOH–AcOH–H₂O) to give 26.05 g (92%) of yellow material of mp 155–157 °C. A further recrystallization (EtOH–CHCl₃) afforded yellow plates: mp 156–159 °C; ν_{max} (mull) 1680, 1665, 1600 cm⁻¹; τ (CDCl₃) 7.60 (6 H, s), 2.60 (1 H, s), 2.22 (1 H, s), 2.14 (1 H, s). Anal. (C₁₂H₉BrO₂) C, H, Br.

2-Azido-6,7-dimethylnaphtho-1,4-quinone. A concentrated aqueous solution of NaN₃ (4.4 g, 0.068 mol) was added in one portion to a suspension of 2-bromo-6,7-dimethylnaphtho-1,4-quinone (13.8 g, 0.052 mol) in refluxing EtOH (130 ml) and the resulting red solution maintained at reflux for a further 2 min. After cooling in ice the precipitated orange solid was filtered, washed with EtOH and then water, and recrystallized from EtOH to give 8.98 g (76%) of orange azide: mp 116–119 °C dec; ν_{max} (mull) 2100, 1660, 1656, 1595, 1290 cm⁻¹; τ (CDCl₃) 7.61 (6 H, s), 3.65 (1 H, s), 2.23 (1 H, s), 2.21 (1 H, s).

3-(3,4-Diethylbenzoyl)propanoic Acid. Powdered anhydrous AlCl₃ (180 g, 1.35 mol) was slowly added with stirring to dry PhNO₂ (300 ml) and the mixture cooled to 20 °C. Finely ground succinic anhydride (59 g, 0.60 mol) was added portionwise and after cooling to 5 °C 1,2-diethylbenzene (80 g, 0.6 mol, commercially available) was added dropwise over 1 h with the internal temperature maintained below 10 °C by external cooling. After a further 1-2 h at 5 °C the mixture was stirred for 2 h at room temperature and then poured onto crushed ice (700 g) containing concentrated HCl (150 ml). An oily solid separated in the organic phase which rapidly crystallized after steam distillation of the nitrobenzene followed by cooling. Filtration gave an off-white solid which recrystallized from benzene-petroleum ether (bp 60-80 °C), after decolorizing with charcoal, to give 105.72 g (79%) of white solid: mp 102–105 °C; ν_{max} (mull) 2700 (br), 1690, 1675, 1603 cm⁻¹; τ (CDCl₃) 8.76 (6 H, t, J = 7.0 Hz), 7.27 (4 H, quartet, J = 7.0 Hz), 7.20 (2 H, t, J = 5.5 Hz), 6.68 (2 H, t, J = 5.5 Hz), 2.74 (1 H, d, J = 8.5 Hz), 2.23 (1 H, dd, J = 8.5, 2 Hz), 2.18 (1 H, s), one low-field exchangeable proton. Anal. $(C_{14}H_{18}O_3)$ C, Η.

4-(3,4-Diethylphenyl)butanoic Acid. A solution of 3-(3,-4-diethylbenzoyl)propanoic acid (69 g, 0.295 mol) in glacial AcOH (450 ml) was hydrogenated at 50 psi and 70 °C for 5 h over 10% palladinized charcoal (5.6 g). After filtration the solvent was removed in vacuo to give a colorless oil which distilled to give 59.00 g (91%) of material: bp 143–147 °C (0.7 mm); ν_{max} (film) 2800, 1710 cm⁻¹; τ (CDCl₃) 8.82 (6 H, t, J = 8 Hz), 8.00 (2 H, complex m), 7.75 (2 H, t), 7.48 (2 H, t), 7.37 (4 H, quartet, J = 8 Hz), 3.01 (3 H, m), one sharp low-field exchangeable proton. Anal. ($C_{14}H_{20}O_3$) C, H.

6,7-Diethyl-1-tetralone. 4-(3,4-Diethylphenyl)butanoic acid (59 g, 0.27 mol) was added to 85% polyphosphoric acid (450 g) at 70 °C and the mixture stirred for 40 min at ~80 °C. After cooling the mixture was poured into ice-water (1 l.) and the oily product extracted into Et₂O. The Et₂O phase was washed throughly with water, saturated aqueous NaHCO₃ solution, and then water and dried (MgSO₄). Evaporation gave an oil which distilled to give 48.30 g (89%) of colorless liquid: bp 118–122 °C (0.7 mm); ν_{max} (film) 1680, 1605 cm⁻¹; τ (CDCl₃) 8.78 (6 H, t, J = 7.5 Hz), 7.84 (2 H, m), 7.38 (2 H, t), 7.31 (4 H, quartet, J = 7.5 Hz), 7.06 (2 H, t), 2.94 (1 H, s), 2.14 (1 H, s). Anal. (C₁₄H₁₈O) C, H.

6,7-Diethyl-2-hydroxynaphtho-1,4-quinone. A 1 M solution of KO-t-Bu in dry t-BuOH (2 l.) was saturated with O_2 and 6,7-diethyl-1-tetralone (48 g, 0.24 mol) added. The mixture was stirred at ambient temperature (exothermic reaction, $\sim 50-55$ °C) for 1 h during which time 2 equiv of O_2 was absorbed. The deep red solution was cooled and acidified with concentrated HCl and the bulk of the t-BuOH removed in vacuo. The residue was partitioned between water and CHCl₃ and the organic phase extracted with aqueous NaHCO3 solution. Acidification of the extract afforded 34.60 g (63%) of the naphthoquinone as an orange-yellow solid. Recrystallization from EtOH-H₂O after decolorization with charcoal gave yellow material: mp 105-109 °C; ν_{max} (mull) 3200, 1665, (sh), 1640, 1590 cm⁻¹; τ (CDCl₃) 8.72 (6 H, t, J = 7.5 Hz), 7.20 (4 H, quartet, J = 7.5 Hz), 3.71 (1 H, 1000 Hz)s), 2.10 (2 H, s), one exchangeable proton. Anal. $(C_{14}H_{14})$ O₃•0.5H₂O) C, H.

2-Chloro-6,7-diethylnaphtho-1,4-quinone. A solution of 6,7-diethyl-2-hydroxynaphtho-1,4-quinone (22 g, 0.096 mol) in SOCl₂ (250 ml) was heated at reflux for 12 h and the solvent removed in vacuo. Repeated evaporation with anhydrous PhH gave an orange solid which recrystallized from EtOH after decolorization with charcoal to give 18.04 g (76%) of golden crystals: mp 90–92 °C; ν_{max} (mull) 1675, 1660, 1590 cm⁻¹; τ (CDCl₃) 8.70 (6 H, t, J = 7.5 Hz), 7.21 (4 H, quartet, J = 7.5 Hz), 2.90 (1 H, s), 2.18 (1 H, s), 2.08 (1 H, s). Anal. (C₁₄H₁₃ClO₂) C, H, Cl.

2-Azido-6,7-diethylnaphtho-1,4-quinone. A concentrated aqueous solution of NaN₃ (6.15 g, 0.095 mol) was rapidly added to a stirred, refluxing solution of 2-chloro-6,7-diethylnaphtho-

1,4-quinone (18.0 g, 0.073 mol) in EtOH (180 ml). After a further 2 min at reflux the red solution was cooled and the precipitated orange azide filtered off and washed with cold EtOH and then water to give after drying 13.87 g (75%) of material of mp 73–76 °C dec. Recrystallization from EtOH raised the melting point to 74–76 °C dec: $\nu_{\rm max}$ (mull) 2110 cm⁻¹; τ (Me₂SO) 8.72 (6 H, t, J = 7.5 Hz), 7.20 (4 H, quartet, J = 7.5 Hz), 3.63 (1 H, s), 2.14 (1 H, s), 2.12 (1 H, s). Anal. (C₁₄H₁₃N₃O) C, H, N.

3-Cyanomethylenephthalides (Table I). Method C. General Procedure for Condensation of Cyanoacetic Acid with Phthalic Anhydrides. Powered phthalic anhydride or its 4-methyl homologue (0.1 mol) and cyanoacetic acid (0.11 mol) were dissolved in dry pyridine (12 ml) and the mixture was stirred at 60-70 °C for 6 h. After cooling overnight the mixture was brought to pH 3 with 5 N HCl and the precipitated solid filtered off and washed well with water. Recrystallization from glacial AcOH afforded the cyanomethylenephthalides **3a** or **3c**, respectively.

Method D. General Procedure for Ring Contraction of 2-Azidoquinones. The azidoquinone 7 (0.01 mol) was added in small portions to cold (0-5 °C) vigorously stirred concentrated H_2SO_4 (40 ml) over 1-1.5 h and the resulting red solution stirred at this temperature for a further 15 min until no more nitrogen was evolved. The mixture was cautiously poured onto ice-water (400 ml) with stirring and the pink precipitate filtered off, washed well with water, and dried. Recrystallization from EtOH in the presence of charcoal gave a near colorless product consisting of E and Z isomers. Yields were in the order of 50-70%.

2-Cyanoindan-1,3-diones (Table II). Method A. General Procedure. The cyanomethylenephthalide 3 (0.01 mol) was added in one portion to a solution of NaOMe (from 0.23 g, 0.01 mol of Na) in MeOH (10 ml) and the red solution heated at reflux for 20 min. After cooling the mixture was diluted with 5 N HCI (50 ml) and the precipitated indandione filtered off. Extraction of the residue with boiling water (3×300 ml) gave a yellow extract from which the product 4 crystallized either on cooling or on dilution with one-third its volume of concentrated HCl.

Method B. General Procedure. A solution of the phthalic ester 5 (0.1 mol) in dry MeCN (10.3 g, 0.25 mol) was treated with NaOMe (10.8 g, 0.2 mol) and the mixture stirred for 6 h on a steam bath, a further quantity of MeCN (10 ml) being added after 30 min. The cooled yellow mass was diluted with dry Et_2O (50 ml) and the solid filtered off and washed well with dry Et_2O . This sodium salt was taken up in water and acidified with concentrated HCl to give the yellow cyanoindandione. Recrystallization from water, with or without the addition of HCl, gave pure 4.

Salicylic Acids. The salicyclic acids 8 which were not commercially available were prepared by the Marasse procedure as described by Baine et al.¹¹

Two new compounds were prepared by this method: 5ethyl-2-hydroxy-4-methylbenzoic acid [mp 152.5-154 °C (EtOH-H₂O). Anal. ($C_{10}H_{12}O_3$) C, H] and 4,5-diethyl-2hydroxybenzoic acid [mp 126-128.5 °C (EtOH-H₂O). Anal. ($C_{11}H_{14}O_3$) C, H].

2-Acetoxybenzoic Acids. General Procedure. A mixture of the salicylic acid 8 (0.1 mol), Ac_2O (80 ml), and glacial AcOH (80 ml) was heated under reflux for 1.5 h, cooled, poured into water, and allowed to stand overnight. Filtration and recrystallization of the solid gave the 2-acetoxybenzoic acid 9.

Five new compounds were prepared by this method: 2-acetoxy-5-methoxybenzoic acid [mp 156–158 °C (EtOH). Anal. ($C_{10}H_{10}O_5$) C, H]; 2-acetoxy-4-ethoxybenzoic acid [mp 122–124 °C (PhH). Anal. ($C_{11}H_{12}O_5$) C, H]; 2-acetoxy-4-ethylbenzoic acid [mp 84–87 °C [PhH–petroleum ether (40–60 °C)]. Anal. ($C_{11}H_{12}O_4$) C, H]; 2-acetoxy-5-ethyl-4-methylbenzoic acid [mp 132–134 °C (PhH). Anal. ($C_{12}H_{14}O_4$) C, H]; and 2-acetoxy-4,5-diethylbenzoic acid [mp 127–129 °C (PhH). Anal. ($C_{13}H_{16}O_4$) C, H].

2-Acetoxybenzoyl Chlorides. General Procedure. A mixture of the 2-acetoxybenzoic acid 9 (0.05 mol) and $SOCl_2 (20 \text{ mol})$

ml) in dry PhH (100 ml) was heated under reflux for 6 h, cooled, and evaporated to dryness to give the 2-acetoxybenzoyl chloride 10 which, due to instability to moisture, was used rapidly without further purification.

3-Cyano-4-hydroxycoumarins (Table III). These products were prepared by a modification of the procedure of Checchi, Vettori, and Vincieri.¹²

General Procedure. The 2-acetoxybenzoyl chloride 10 (0.048 mol) in dry Et_2O (75 ml) was added slowly to a stirred, refluxing suspension of the sodium salt of ethyl cyanoacetate [prepared from ethyl cyanoacetate (0.132 mol) and a 60% dispersion of NaH in mineral oil (0.125 mol)] in dry Et_2O (275 ml). After a further 18 h at reflux, the cooled mixture was poured into water (500 ml) containing 2 N NaOH solution (30 ml). The aqueous phase was separated, washed with Et_2O (three times), acidified with cold concentrated HCl, and filtered. Recrystallization of the solid gave the 3-cyano-4-hydroxycoumarin 11.

Passive Cutaneous Anaphylaxis. Serum containing heat-labile homocytotropic antibody was raised in rats to crystallized ovalbumin by the method of Mota¹⁸ using Bordettela pertussis vaccine as adjuvant.

Passive cutaneous anaphylaxis (PCA) was carried out by a method based on that of Ovary and Bier¹⁹ as modified by Goose and Blaire²⁰ and is described in detail in ref 14.

All compounds were tested as their sodium salts, either as solutions in pH 7.2 buffer or as suspension in 1% methylcellulose, depending on their solubility.

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