

REACTION OF HIPPURIC ACID WITH ANHYDRIDES OF DICARBOXYLIC ACIDS

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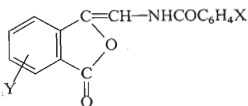
Hippuric acid reacts with phthalic anhydride, 3-nitrophthalic anhydride and 3,6-dithiacyclohex-1-ene-1,2-dicarboxylic acid anhydride under formation of 3-(benzamidomethylene)phthalides or their 4,7-dithia analogues, respectively, which are rearranged to 2-benzamido-1,3-indandiones or their 4,7-dithia analogues, respectively, on reaction with sodium methoxide in methanol.

Hippuric acid was used for the first time as a reaction component with an active methylene group in aldol condensation with aldehydes by Plöchl and Erlenmeyer¹⁻⁴. From that time many analogous reactions⁵ have been carried out with this acid. The reaction products of these syntheses are the derivatives of 2-phenyl-5-oxazolone. In addition to aldehydes phthalic anhydride and its substituted derivatives⁵⁻¹⁰ have also been used as the carbonyl component, mainly 3-nitrophthalic anhydride. The resulting product of these reactions were also derivatives of 2-phenyl-4-phthalidylidene-5-oxa-zolone. A constant reaction component in all instances was acetic anhydride. Potassium or sodium acetate were most often used as catalysts.

Since we wished to use hippuric acid for the synthesis of 1,3-indandione derivatives we looked for reaction conditions which would be suitable for the formation of 3-(benzamidomethylene)phthalides. We supposed that they could be rearranged to corresponding 1,3-indandione derivatives. The mechanism of the formation of benzylidene- or phthalidylideneoxazolones has not yet been investigated in spite of the fact that the authors of older papers^{5,6} supposed — basing their considerations on the low reactivity of hippuric acid — that at the first reaction stage cyclisation and dehydration took place under formation of unstable⁶ 2-phenyl-5-oxazolone, and that this then reacted with its active methylene group with the aldehyde or anhydride in the aldol condensation. When choosing the reaction conditions we started from the supposition that acetic anhydride was necessary for the cyclisation. As we wished the reaction to take place between phthalic anhydride and hippuric acid we carried it out without acetic anhydride under the conditions of Gabriel's modification of Perkin's synthesis, under which arylacetic acids also react with phthalic anhydride to corresponding arylmethylenephthalides¹¹. Potassium acetate was used as a catalyst

and the reaction was carried out at 220°C. Under these conditions 3-(benzamido-methylene)phthalide (*I*) was formed. This shows that hippuric acid or its anhydride, which can be formed, have a sufficiently reactive methylene group at temperatures about 220°C. The reactivity of hippuric acid or its anhydride with phthalic anhydride under the conditions of Gabriel's modification of Perkin's synthesis can be compared with the reactivity of phenoxyacetic acid¹², but the yields are higher in the case of hippuric acid. Under these conditions phthalic anhydride also reacts analogously with 4-nitrohippuric acid, under formation of *IV*. If 3-nitrophthalic anhydride is used as the carbonyl component under these conditions the reaction gives two positional isomers, *i.e.* 3-(benzamidomethylene)-4-nitrophthalide (*II*) and 3-(benzamidomethylene)-7-nitrophthalide (*III*), which we obtained by chromatographing the reaction mixture on silica gel. In a similar manner 3-nitrophthalic anhydride gives positional isomers on reaction with arylacetic acids¹³. From both isomers one single 1,3-indandione derivative, *IX* is formed on rearrangement with sodium methoxide, and therefore we did not further try to assign the structures to individual isomers. Analogously as phthalic anhydride 3,6-dithiacyclohex-1-ene-1,2-dicarboxylic acid anhydride also reacts under formation of 3-(benzamidomethylene)-5,6-dihydro-4,7-dithiaphthalide (*V*). In acetic anhydride 3,6-dithiacyclohex-1-ene-1,2-dicarboxylic acid anhydride reacts with hippuric acid under formation of 2-phenyl-4-(5,6-dihydro-4,7-dithiaphthalidylidene)-5-oxazolone (*VI*). The rearrangement of 3-(benzamidomethylene) phthalides *I–V* to 2-benzamido-1,3-indandiones *VII–X* under the effect of sodium methoxide in methanol takes place very easily even at 30°C, taking 10–20 minutes. When heated in aqueous alkaline medium phthalide *I* affords acid *XI*. When acting with formamide on *I* at 150°C the oxygen atom in the lactone ring is substituted by the NH group, giving rise to a phthalimidine derivative *XII* (Scheme 1).

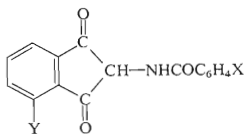
In addition to elemental analyses the structure was also confirmed by IR spectra. 3-(Benzamidomethylene)phthalides *I–IV* and their dithia analogue *V* have spectra differing from that of 2-phenyl-4-(phthalidylidene)-5-oxazolone in the 1600–1800 cm^{-1} region. A strong band of C=O stretching vibration of the phthalide system of substances *I–IV* is in the 1790–1795 cm^{-1} region. In the given region this band occurs also in the case of arylmethylenephthalides¹⁴. The band of the C=C bond protruding from the phthalide system is located in the 1700 cm^{-1} region, which is 10 cm^{-1} higher than for arylmethylenephthalides¹⁴. The dithiaphthalide *V* has its C=O stretching band of the dithiaphthalide grouping 30 cm^{-1} lower than in compounds *I–IV*. An analogous shift to lower values has also been observed in arylmethylene derivatives of dithiaphthalide^{15,16}. An analogous decrease in comparison with *I–IV* is also observed in the case of *V* for the stretching vibration of the C=C bond of the dithiaphthalide system. The band due to the C=O stretching vibration of the amide group of compounds *I–V* occurs in the 1656–1688 cm^{-1} region. A differing



I, X = H, Y = H

II, *III*, X = H, Y = 4(7)-NO₂

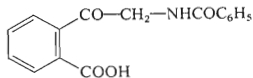
IV, X = NO₂, Y = H



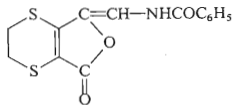
VII, X = H, Y = H

VIII, X = H, Y = 4-NO₂

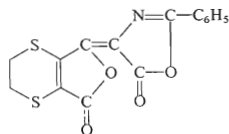
IX, X = 4-NO₂, Y = H



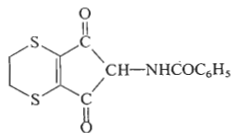
XI



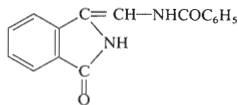
V



VI



X



XII

SCHEME 1

spectrum in the 1600–1800 cm⁻¹ region is also observed in 2-phenyl-4-(phthalidylidene)-5-oxazolones. The band of the C=O stretching vibration of the oxazolone grouping is 1800 cm⁻¹ (it can be determined from the spectrum of 2-phenyl-4-benzyl-5-oxazolone). In compounds *I–IV* this band is partly overlapped by the C=O stretching band of the phthalide grouping. In compound *V* the band of the C=O stretching vibration of the oxazolone grouping is at 1798 cm⁻¹ and the band of the C=O stretching vibration of the dithiaphthalide grouping is at 1755 cm⁻¹, and they can be well differentiated.

The prepared 2-benzamido-1,3-indandione (*VII*) displays two bands in the region above 1700 cm^{-1} , due to the symmetrical vibrations of the $\text{C}=\text{O}$ groups in the β -dicarbonyl grouping. The band at 1740 cm^{-1} is stronger, and that at 1781 cm^{-1} , belonging to the symmetrical vibration, is weaker. An analogous group of bands for the β -dicarbonyl grouping occurs also in the spectrum of compound *X*, but the positions of the bands are shifted by 25 cm^{-1} to lower values. Indandiones *VIII* and *IX* have different spectra in the $1600\text{--}1800\text{ cm}^{-1}$ region. Owing to the presence of the nitro group compounds *VIII* and *IX* do not exist as solids in the diketo form, but in enolanion arrangement (a similar arrangement is also observed in 2-phenyl-3-nitro-1,3-indandione¹⁴, for example). As the $\text{C}=\text{O}$ stretching vibration band of the amide group is at 1690 cm^{-1} , similarly as in compounds *VII* and *X*, the position of the bands of the β -dicarbonyl grouping is at 1610 and 1640 cm^{-1} .

EXPERIMENTAL

The infrared spectra of the substances *I*–*XII* were measured with a Specord spectrophotometer in nujol. The instrument was calibrated with a polystyrene foil.

3-(*X*-Benzamidomethylene)-4(7)-*Y*-phthalides *I*–*V*

Freshly remelted potassium acetate (0.005 mol) was added to remelted phthalic anhydride (3-nitrophthalic anhydride) (0.05 mol) at 190°C and the mixture was heated at 220°C . Hippuric acid (4-nitrohippuric acid) (0.01 mol) was then added in small doses under stirring over 50 minutes and the reaction was allowed to continue for 30 minutes. The still warm mixture was poured into 100 ml of water, 10 g of NaHCO_3 were added and the mixture was allowed to stand overnight. The separated product was crystallized from ethanol and then from toluene. Yield of *I* 45%, *II* and *III* 35%, *IV* 38%. When 3-nitrophthalic anhydride was used the crude product was chromatographed on silica gel, using benzene for elution. 3-(Benzamidomethylene)-5,6-dihydro-4,7-dithiaphthalide (*V*). Procedure as for *I*, but at 190°C , yield 38%.

2-Phenyl-4-(5,6-dihydro-4,7-dithiaphthalidylidene)-5-oxazolone (*VI*)

A mixture of 0.01 mol of hippuric acid, 0.01 mol of 3,6-dithiacyclohex-1-ene-1,2-dicarboxylic acid anhydride, 0.005 mol freshly melted potassium acetate and 10 ml of acetic anhydride was heated at 80°C for one hour. After cooling the precipitate formed was filtered off, boiled two to three times with water and the crude product was crystallized from dimethylformamide. Yield 60% of *VI*.

2-(4-*X*-Benzamido)-4-*Y*-1,3-indandiones *VII*–*X*

Compounds *I*–*V* (1 g) were added at 30°C into 50 ml of a 1% sodium methoxide solution in methanol and the mixture was allowed to react for 10–15 minutes under stirring. After cooling the solution was acidified with 10% hydrochloric acid. The red precipitate was crystallized from ethanol. Yield 60%. 2-(Benzamido)-5,6-dihydro-4,7-dithia-1,3-indandione (*X*), yield 6%,

2-Benzamidoacetylbenzoic Acid (XI)

Compound *I* (0.01 mol) was refluxed with 50 ml of 3% sodium hydroxide for 2 hours. The solution was decolorized with charcoal (filtration) and acidified to pH 2 with 1M hydrochloric acid. The precipitated crude product was crystallized from 70% ethanol. Yield 89%.

TABLE I
Analytical Data of the Substances Prepared

Substance	Formula (m.w.)	M.p., °C (Kofler)	Calculated/Found			$\nu(\text{C}=\text{O})^a$ cm^{-1}	$\nu(\text{C}=\text{O})$ (amide)
			% C	% H	% N		
<i>I</i>	$\text{C}_{16}\text{H}_{11}\text{NO}_3$ (265.3)	206–208	72.44	4.17	5.27	1 787	1 678
			72.32	3.86	5.03		
<i>II–III</i>	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_5$ (310.3)	253.5	61.94	3.25	9.03	1 788	1 664
			62.08	3.43	8.84		
	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_5$ (310.3)	266.0	61.94	3.25	0.03	1 790	1 656
			62.11	3.40	8.98		
<i>IV</i>	$\text{C}_{16}\text{H}_{10}\text{N}_3\text{O}_5$ (310.3)	302.5	61.94	3.25	9.03	1 785	1 685
			62.16	3.30	8.90		
<i>V</i>	$\text{C}_{14}\text{H}_9\text{NO}_3\text{S}_2$ (303.4)	227.0	55.43	2.98	4.61	1 750	1 670
			55.62	3.12	4.59		
<i>VI</i>	$\text{C}_{15}\text{H}_7\text{NO}_4\text{S}_2$ (329.4)	267–268	54.70	2.14	4.25	1 798 ^b	1 672
			54.70	2.34	4.43		
<i>VII</i>	$\text{C}_{16}\text{H}_{11}\text{NO}_3$ (265.3)	200–202	72.44	4.17	5.27	1 740	1 680
			72.61	4.23	4.92		
<i>VIII</i>	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_5$ (310.3)	194–195	61.94	3.25	9.03	1 612	1 690
			62.28	3.02	9.39		
<i>IX</i>	$\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_5$ (310.3)	242–244	61.94	3.25	0.03	1 610	1 700
			61.78	3.21	9.17		
<i>X</i>	$\text{C}_{14}\text{H}_9\text{NO}_4\text{S}_2$ (303.4)	105–108	55.43	2.98	4.61	1 740	1 680
			55.51	3.31	4.55		
<i>XI</i>	$\text{C}_{16}\text{H}_{13}\text{NO}_4$ (283.3)	165.0	67.84	4.64	4.94	1 710	1 655
			67.73	4.66	4.94		
<i>XII</i>	$\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ (264.3)	304–305	72.72	4.58	10.60	1 705	1 670
			72.36	4.48	10.62		

^a *I–VI* $\nu(\text{CO})$ for the phthalidic grouping, *VII–IX* for the indandione grouping; ^b $\nu(\text{CO})$ for the azlactone grouping.

3-(Benzamidomethylene)phthalimidine (XII)

3-(Benzamidomethylene)phthalide (1 g) was heated at 150°C in 50 ml of formamide for 30 minutes. The mixture was poured into ice and the precipitated substance crystallized from ethanol. Yield 85%. The m.p. and the analytical data are given in Table I.

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