

Synthesis of 3-Aryl-7-nitro-3,4-dihydroisocoumarins from 4-Nitrohomophthalic Acid

Roger D. Barry and Richard A. Balding

Department of Chemistry, Northern Michigan University, Marquette, Michigan 49855

Received July 31, 1972

4-Nitrohomophthalic acid reacts with aromatic aldehydes in the presence of piperidine to yield 3-aryl-7-nitro-3,4-dihydroisocoumarins. Under the same conditions, homophthalic acid yields stilbene- α ,2-dicarboxylic acids.

Esters of homophthalic acid undergo a Stobbe-type reaction with aromatic aldehydes yielding stilbene- α ,2-dicarboxylic acids II (1-5) and the acids can be cyclized to 3-aryl-3,4-dihydroisocoumarins (V). Homophthalic acid anhydride condenses with aromatic aldehydes to furnish 4-arylidenehomophthalic acid anhydrides (IV) (5,6) which rearrange in the presence of triphenylmethylsodium to 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids (7-10). Under Friedel-Crafts conditions, aromatic aldehydes and homophthalic acid or anhydride yield 3-aryliso-coumarins (11).

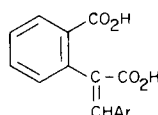
Homophthalic acid can react with aromatic aldehydes in the presence of piperidine to yield several products as outlined on Chart I. In order to evaluate the usefulness

of this reaction for synthesis of isocoumarins of type V, the major product isolatable from homophthalic acid and 4-nitrohomophthalic acid condensations with several substituted benzaldehydes was determined.

The major product from the reaction between homophthalic acid and substituted benzaldehydes was the stilbene- α ,2-dicarboxylic acids (II) (Table I). For the case of 4-nitrohomophthalic acid, good yields of 3-aryl-7-nitro-3,4-dihydroisocoumarins were obtained (Table II). Benzaldehyde and the three isomeric nitrobenzaldehydes yielded only trace amounts of solid products from reaction with either homophthalic acid or 4-nitrohomophthalic acid.

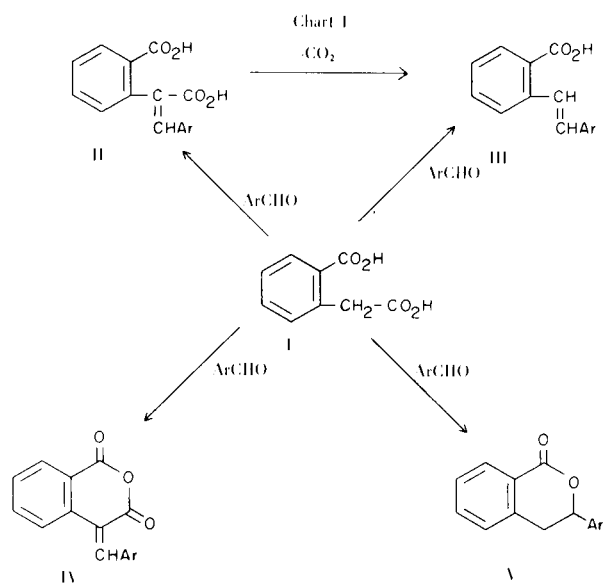
Proof of structure of the 3-aryl-7-nitro-3,4-dihydroiso-

TABLE I
Stilbene- α ,2-dicarboxylic Acids (a)



Ar	Formula	Calculated			Found			Melting Point	Yield (%)
		C	H	Cl	C	H	Cl		
C ₆ H ₅	C ₁₆ H ₁₂ O ₄	71.63	4.51		71.86	4.68		210-211	45.0
2-CH ₃ C ₆ H ₄	C ₁₇ H ₁₄ O ₄	72.33	5.00		72.24	5.08		210-214	5.0
4-CH ₃ C ₆ H ₄	C ₁₇ H ₁₄ O ₄	72.33	5.00		72.22	5.08		224-225	31.0
3,4-CH ₂ O ₂ C ₆ H ₃	C ₁₇ H ₁₂ O ₆	65.38	3.87		65.43	4.02		236-237	17.8
2,5-(CH ₃ O) ₂ C ₆ H ₃	C ₁₈ H ₁₆ O ₆	65.85	4.91		65.62	4.80		212-214	27.1
3,4-(CH ₃ O) ₂ C ₆ H ₃	C ₁₈ H ₁₆ O ₆	65.85	4.91		65.90	4.96		196	17.5
2,4-Cl ₂ C ₆ H ₃	C ₁₆ H ₁₀ Cl ₂ O ₄	57.00	2.99	21.03	56.96	3.03	20.68	225-226	9.0
3,4-Cl ₂ C ₆ H ₃	C ₁₆ H ₁₀ Cl ₂ O ₄	57.00	2.99	21.03	56.89	3.08	21.09	207-212	53.0
3-ClC ₆ H ₄	C ₁₆ H ₁₁ ClO ₄	63.48	3.66	11.71	63.15	3.81	11.42	220-221	30.0

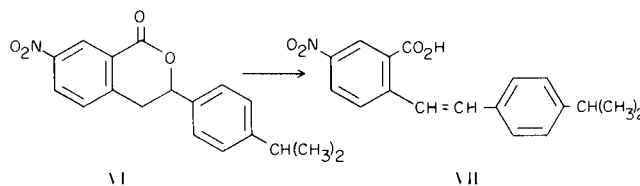
(a) All products were crystallized from acetone/hexane.



coumarins was based on elemental analysis (Table II), spectral analysis and chemical studies. The infrared carbonyl absorption (Table III) was in the region attributed to δ -lactones. The nmr spectra showed the chemical shifts for protons as expected for the isocoumarin structures (Table III), and the spin coupling for protons d, e, and f (Table III) further support the isocoumarin structures. The 3-aryl-7-nitro-3,4-dihydroisocoumarins were insoluble in warm or cold sodium bicarbonate but dissolved in 10% sodium hydroxide when heated. Acidifica-

tion of the sodium hydroxide solutions yielded the lactone starting compounds. These experiments further substantiate the presence of the isocoumarin ring system.

When 3-(4-isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (VI) was dissolved in aqueous base, then heated at 190° for 15 minutes, 4-nitro-4'-isopropylstilbene-2-carboxylic acid (VII) was produced, the expected product from dehydration.



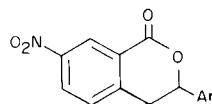
An explanation of the reason homophthalic acid yields stilbene- α ,2-dicarboxylic acids and 4-nitrohomophthalic acid yields 3-aryl-4-nitro-3,4-dihydroisocoumarins must await further investigation. The competition between lactonization-decarboxylation and dehydration-decarboxylation leading to lactones V and stilbenes II must be further studied.

EXPERIMENTAL

Melting points were determined on a Hershberg Melting Point Apparatus and are uncorrected. Elemental analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colorado.

TABLE II

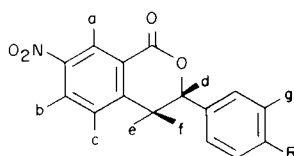
3-Aryl-7-nitro-3,4-dihydroisocoumarins (a)



Ar	Formula	Calculated			Found			Melting Point	Yield (%)
		C	H	N	C	H	N		
2-CH ₃ C ₆ H ₄	C ₁₆ H ₁₃ NO ₄	67.84	4.63	4.95	67.97	4.78	5.10	171-172	29.0
3-CH ₃ C ₆ H ₄	C ₁₆ H ₁₃ NO ₄	67.84	4.63	4.95	67.92	4.78	5.02	134-135	36.7
4-CH ₃ C ₆ H ₄	C ₁₆ H ₁₃ NO ₄	67.84	4.63	4.95	67.79	4.46	4.86	177-178	76.1
4-(CH ₃) ₂ CHC ₆ H ₄	C ₁₈ H ₁₇ NO ₄	69.44	5.50	4.50	69.33	5.52	5.02	149-150	43.4
2-ClC ₆ H ₄	C ₁₅ H ₁₀ ClNO ₄	59.32	3.32	4.61	59.57	3.26	4.66	190-191	60.3
4-ClC ₆ H ₄	C ₁₅ H ₁₀ ClNO ₄	59.32	3.32	4.61	59.56	3.54	5.14	181-182	69.2
2-CH ₃ OC ₆ H ₄	C ₁₆ H ₁₃ NO ₅	64.21	4.38	4.68	64.17	4.48	5.01	169-170	47.5
3,4-(CH ₃ O) ₂ C ₆ H ₃	C ₁₇ H ₁₅ NO ₆	62.00	4.59	4.25	62.20	4.75	4.52	173-174	25.5
3,4-CH ₂ O ₂ C ₆ H ₃	C ₁₆ H ₁₁ NO ₆	61.34	3.54	4.47	61.48	3.64	4.19	179-180	56.3
2,6-Cl ₂ C ₆ H ₃	C ₁₅ H ₉ Cl ₂ NO ₄	53.28	2.68	4.14	53.32	2.80	4.03	208-209	49.7

(a) All products were crystallized from acetone/hexane.

TABLE III
Spectral Data (a)



	Infrared Lactone Carbonyl (cm^{-1})	Chemical Shift Values (τ)							
		a	b	c	d	e	f	g	h
2-CH ₃	1730	---	2.60	1.65 Jd,e 8.9	4.60 Jd,f 5.9	6.65	6.70	2.72	7.66
4-CH ₃	1715	1.08	2.55	1.65 Jd,e 8.9	4.40 Jd,f 5.8	6.63	6.68	2.70	7.63
4-(CH ₃) ₂ CH	1725	1.02	2.50	1.65 Jd,e 9.4	4.43 Jd,f 6.0	6.62	6.68	2.68	8.75
2-CH ₃ O	1715	1.13	3.30	2.45 Jd,e 8.5	4.08 Jd,f 6.8	6.67	6.71	2.80	6.15
3,4-(CH ₃ O) ₂	1720	1.16	2.50	1.60 Jd,e 9.5	4.45 Jd,f 5.3	6.00	6.62	3.10	6.12
3,4-CH ₂ O ₂	1715	---	2.77	1.65 Jd,e 9.3	4.50 Jd,f 5.5	6.61	6.65	3.15	4.08
2,6-Cl ₂	1710	---	2.95	2.48 Jd,e 8.5	4.67 Jd,f 6.5	6.58 Je,f 1.8	7.42	3.75	---

(a) The other isocoumarins listed in Table II were insoluble in deuteriochloroform and no nmr spectrum was obtained.

Condensation of Homophthalic Acids with Aromatic Aldehydes.

In a typical reaction, 0.020 mole homophthalic acid, 0.021 mole aldehyde and 4 drops of piperidine were heated at 180° in a bath for 30 minutes. The temperature of the mixture was permitted to drop to 110°, then an equal volume of methanol was added carefully. Crystals separated and were collected and recrystallized as detailed in Tables I and II.

Dehydration of 3-(4-Isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (VI).

A mixture of 25 ml. of 80% ethanol, 0.18 g. of potassium hydroxide and 1.05 g. (0.0035 mole) 3-(4-isopropylphenyl)-7-nitro-3,4-dihydroisocoumarin (VI) was refluxed until solution was complete. Heating was continued until all of the solvent had evaporated, then the bath temperature was raised to 190° and kept at 190° for 15 minutes. The reaction mass was cooled to room temperature, approximately 100 ml. of water was added and the mixture was acidified to Congo Red indicator using dilute hydrochloric acid. Yellow crystals of 4-nitro-4'-isopropylstilbene-2-carboxylic acid (VII) were collected and recrystallized from methanol, m.p. 219-220°, 0.51 g., 48.6% yield.

Anal. Calcd. for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.73; H, 5.60; N, 4.48.

Acknowledgement.

The authors wish to express their appreciation to Dr. Jerome A. Roth for advice in interpreting certain of the nmr spectra.

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