

A Synthesis of 1-Amino-2-pyridone Derivatives

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Reactions of acetylenic ketones (Ia-f) with methyl α -naphthylacetate in the presence of sodium methoxide gave the corresponding 6-aryl-3- α -naphthyl-4-phenyl-2-pyrones (IIa-f) which upon refluxing with hydrazine hydrate in ethanol gave the corresponding 1-amino-2-pyridone derivatives (VIa-f).

The structure of the products was established by chemical and spectroscopic evidence.

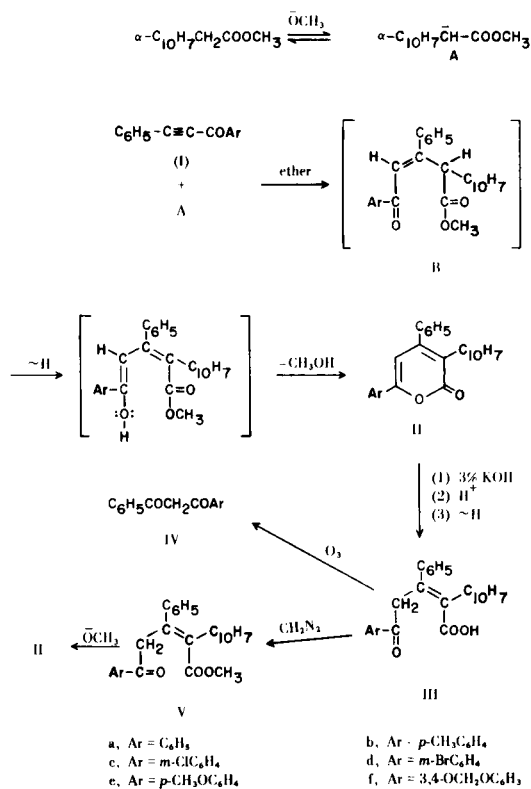
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The reaction of aroylphenylacetylenes with esters of phenylacetic (2), malonic (3-7), acetyl- and benzoylacetic (8,9) acids have been reported.

The present work was intended to study the structure and the properties of the products obtained from the reaction of aroylphenylacetylenes with methyl α -naphthylacetate.

When benzoyl- (Ia), *p*-toluyl- (Ib), *m*-chlorobenzoyl- (Ic), *m*-bromobenzoyl- (Id), *p*-methoxybenzoyl- (Ie) and 3,4-methylene-dioxybenzoyl- (If) phenylacetylenes were stirred with methyl α -naphthylacetate in the presence of a suspension of sodium methoxide in ether, they gave the corresponding 6-aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (II). The reaction seems to proceed by Michael addition of carbanion (A) (α -C₁₀H₇- \bar{C} H-COOCH₃) to the triple bond of the acetylenic ketone (I) followed by cyclisation of the intermediate (B) (cf. Scheme 1) (2-7).

Scheme 1



The structure of the above products (II) was established by chemical and spectral tools. Thus, compound II gave upon refluxing with 3% methanolic potassium hydroxide 4-methoxybenzoyl-2- α -naphthyl-3-phenylbut-2-enoic acid (IIIe). The structure of the keto-acid (IIIe) was established by ozonolysis to give *p*-methoxydibenzoylmethane (IVe). Further evidence for the structure of the acid (IIIe) is forthcoming from its spectral data. Thus, its nmr spectrum shows signals attributable to the different protons (Table I). The methylene group in the acid (IIIe) behaves as an AB system (JAB = 2 Hz; $\Delta \nu/J = 3.87$) (10). The behaviour of the methylene group as an AB system can be attributed either to the restriction of rotation of the COAr group by the weak hydrogen bonding between the OH and the carbonyl of the aroyl group or to the large anisotropy effect of the π -electron cloud of the naphthyl group. The fact, however, that the quartet also appears in the ester (Ve) (Table I) and is not coalesced to singlet when the nmr spectrum of this compound was measured in deuteriodimethylsulfoxide indicates that the AB system can be attributed to the anisotropy effect of the π -electron cloud of the naphthyl group. The ir spectrum shows band at 1690 cm⁻¹ (ν C=O) (2,9,11a). The electronic spectrum of this acid gave an absorption maximum at 277

Scheme 2

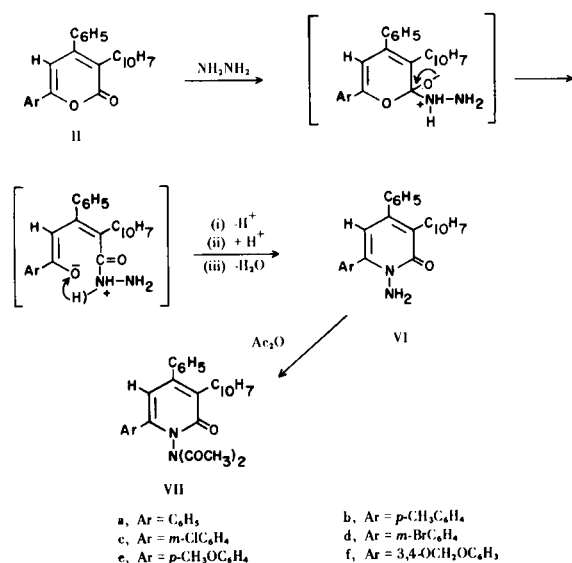


Table I

Infrared, Electronic and Nuclear Magnetic Resonance Spectral Data of 6-Aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (IIa-f)

Compound	Infrared Spectra (Potassium bromide)		Electronic Spectra (Ethanol)		Nmr Spectra (Deuteriochloroform)	
	cm ⁻¹	ν	λ max (nm)	ϵ max	δ	Assignment (No. of Protons)
IIa	1710 (s)	C=O	351	19,160	8.3-6.3 (m)	(17) ArH
	1625 (s)					
	1590 (m)					
	1570 (m)					
	1530 (s)					
IIb	1710 (s)	C=O	357	21,550	8.17-7.07 (m)	(16) ArH
	1625 (s)					
	1590 (m)					
	1580 (m)					
	1532 (s)					
IIc	1710 (s)	C=O	349	21,060	8.27-7.03 (m)	(16) ArH
	1625 (s)					
	1590 (m)					
	1560 (s)					
	1530 (s)					
II d	1710 (s)	C=O	348	17,090	8.2-7.0 (m)	(16) ArH
	1625 (s)					
	1590 (m)					
	1560 (s)					
	1530 (s)					
IIe	1700 (s)	C=O	372	22,540	8.27-6.90 (m)	(16) ArH
	1620 (s)					
	1600 (s)					
	1570 (s)					
	1530 (s)					
II f	1700 (s)	C=O	377	21,330	7.97-6.97 (m)	(15) ArH
	1620 (s)					
	1575 (s)					
	1530 (s)					
	1530 (s)					
IIIe (a)	3420-	O-H	277	23,540	8.4-7.22 (m)	(4) ArH
	2320 (bro.)					
	1690 (s)					
	1600 (s)					
	1600 (s)					
Ve	1728 (s)	C=O (COOCH ₃)	277	22,950	8.4-6.81 (m)	(16) ArH
	1681 (s)					
	1681 (s)					
	1603 (s)					
	1603 (s)					

(a) Carboxyl proton was not shown at a lower field as in the nmr spectrum of *p*-methoxybenzoic acid (2,15).

nm (2) (Table I). Methylation of IIIe with diazomethane gave the corresponding methyl ester which upon treatment with sodium methoxide in ether gave the corresponding 2-pyrone (IIe). The structure of the ester was established

from its chemical analysis and spectral data (Table I).

The stereochemical configuration of the acid (IIIe) and its ester (Ve) was confirmed from the following results:

(i) The formation of the acid (IIIe) from the corre-

Table II

Infrared Electronic and Nuclear Magnetic Resonance Spectral Data of 1-Amino-6-aryl-3- α -naphthyl-4-phenyl-2-pyridones (VIa-f)

Compound	Infrared Spectra (Potassium bromide)		Electronic Spectra (Ethanol)		Nmr Spectra (Deuteriochloroform)	
	cm ⁻¹	ν	λ max (nm)	ϵ max	δ	Assignment (No. of Protons)
VIa	3300 (m)]	NH ₂	340	14,150	8.23-6.9 (m)	(18) ArH
	3200 (m)]		257-245	22,340	6.03 (bro.)	(2) NH ₂
	3060 (m)	C-H				
	1630 (s)	C=O				
	1570 (s)] 1490 (s)]	C=C				
VIb	3300 (m)]	NH ₂	340	15,480	8.0-7.0 (m)	(17) ArH
	3200 (m)]		260-242 (sh)	23,990	6.43 (s)	(1) =CH
	3060 (s)	C-H			5.43 (bro.)	(2) NH ₂
	1630 (s)	C=O			2.47 (s)	(3) C ₆ H ₄ -CH ₃
	1570 (s)] 1500 (s)]	C=C				
VIc	3300 (m)]	NH ₂	339	13,290	8.0-7.0 (m)	(17) ArH
	3200 (m)]		257-246 (sh)	22,280	6.43 (s)	(1) =CH
	3060 (m)	C-H			5.33 (bro.)	(2) NH ₂
	1630 (s)	C=O				
	1580 (s)] 1480 (s)]	C=C				
VIId	3300 (m)]	NH ₂	340	18,270	8.0-7.0 (m)	(17) ArH
	3200 (m)]		268-246 (sh)	25,390	6.43 (s)	(1) =CH
	3060 (m)	C-H			5.10 (bro.)	(2) NH ₂
	1630 (s)	C=O				
	1570 (s)] 1470 (s)]	C=C				
VIe	3250 (bro.)	NH ₂	343	17,440	8.1-6.77 (m)	(17) ArH
	3060 (m)		253-245 (sh)	24,130	6.43 (s)	(1) =CH
	1630 (s)	C=O			5.40 (bro.)	(2) NH ₂
	1600 (s)] 1560 (s)] 1500 (s)]	C=C			3.9 (s)	(3) C ₆ H ₄ -O-CH ₃
	VIIf	3240 (m)]	-NH ₂	344	19,460	7.97-6.43 (m)
3160 (m)]		253-247 (sh)		22,840	6.07 (s)	(2) OCH ₂ O
3040 (m)		C-H			5.43 (s)	(2) NH ₂
1620 (s)		C=O				
1590 (m)] 1490 (m)]		C=C				
VIIf	1750 (s)]	C=O of acetate	335	16,290	7.87-7.31	(15) ArH
	1728 (m)]		298-294 (sh)	11,210	6.43 (s)	(1) =CH
	1636 (s)	C=O of Pyridone ring	244	25,130	6.04 (s)	(2) OCH ₂ O
	1605 (m)] 1584 (m)]	C=C			2.66 (s)	(6) COCH ₃

sponding 2-pyrone (IIe) and the conversion of the ester (Vc) to the starting pyrone (IIe) indicate that the phenyl and the ester or carboxy groups are *trans* to each other.

(ii) The nmr spectrum of the acid (IIIe) shows two

signals at δ 7.13 (s, 5, C₆H₅) and δ 6.96 (s, 7, C₁₀H₇) (Table I), indicating the *cis*-configuration of the phenyl and naphthyl groups (2,9).

The structure of the 2-pyrones (IIa-f) was further

supported by their reaction with hydrazine hydrate to give the corresponding 1-aminopyridones (VI) (cf. Scheme 2). The action of acetic anhydride on VI_f gave the corresponding *N*-diacetyl derivative (VII_f) (2). The structure of the acetyl derivative was confirmed by its ir, uv and nmr spectra (cf. Table II). Further evidence for the structure of the compounds (VIa-f) is forthcoming from their spectral data (Table II). Thus, their ir spectra show two sharp bands in the region 3300-3160 cm⁻¹ (ν NH₂) (2,11a,12) in addition to a strong band appeared in the region 1630-1620 cm⁻¹ attributable to the ν C=O of the pyridone ring (2). The nmr spectra show a broad signal exchanged with deuterium oxide (2H, NH₂) (2) (cf. Table II). The electronic spectra of these compounds are identical which reflects their structural analogy. They show absorption maxima in the range 344-399 nm and are very similar to those of 1-amino-2-pyridones derivatives (2).

Spectroscopic data of 6-aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (IIa-f) give further evidence for the assigned structure. Thus, the ir spectra of these compounds (cf.

Table I) show absorption in the region 1710-1700 cm⁻¹ attributable to the carbonyl stretching frequency of the 2-pyrone (2,13,14). The two bands which appeared in the range 1630-1620 cm⁻¹ and at 1530 cm⁻¹ are due to the stretching frequency of the double bonds in the 2-pyrone system (2). The electronic spectra of the 2-pyrone derivatives (IIa-f) (Table I) gives a further evidence for the proposed structure and show good resemblance to the spectra of substituted 2-pyrones (2,13,14). The nmr spectra of these compounds (IIa-f) are reported in Table I.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were measured on a Perkin-Elmer 577 Grating Infrared Spectrophotometer (potassium bromide). Nmr spectra were measured on a JEOL JNM-PMX60 spectrometer using TMS as internal standard. Electronic spectra were measured on a Beckman spectrophotometer ACTA MVI (ethanol). The purity of the analytical samples was checked by tlc (silica gel). Microanalyses were determined by Alfred Bernhardt, West Germany. All evaporations were performed on rotary evaporators *in vacuo*.

Table III

6-Aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (IIa-f)

Compound	Yield (%)	M.p. (°C)	Formula	Analysis (%)							
				Calcd.			Found				
				C	H	Br	Cl	C	H	Br	Cl
IIa	86	180-181 (a)	C ₂₇ H ₁₈ O ₂	86.61	4.85	-	-	86.51	4.93	-	-
IIb	82	178-179 (a)	C ₂₈ H ₂₀ O ₂	86.57	5.19	-	-	86.31	5.28	-	-
IIc	86	182-183 (a)	C ₂₇ H ₁₇ ClO ₂	79.31	4.19	-	8.67	79.58	4.24	-	8.37
IId	90	184-185 (a)	C ₂₇ H ₁₇ BrO ₂	71.54	3.78	17.63	-	71.89	3.63	17.95	-
IIe (d)	92	256-257 (b)	C ₂₈ H ₂₀ O ₃	83.15	4.98	-	-	83.01	5.18	-	-
II _f	92	207-208 (c)	C ₂₈ H ₁₈ O ₄	80.37	4.34	-	-	80.61	4.22	-	-

(a) Crystallized from methanol. (b) Crystallized from benzene-methanol. (c) Crystallized from ethanol. (d) Calcd. for OCH₃: 7.69. Found: 7.97.

Table IV

1-Amino-5-aryl-3- α -naphthyl-2-pyridones (VIa-f)

Compound	Yield (%)	M.p. (°C)	Formula	Analysis (%)							
				Calcd.			Found				
				C	H	N	Br/Cl	C	H	N	Br/Cl
VIa	77	261-262 (a)	C ₂₇ H ₂₀ N ₂ O	83.48	5.19	7.21	-	83.51	5.11	7.55	-
VIb	80	220-221 (b)	C ₂₈ H ₂₂ N ₂ O	83.56	5.51	6.96	-	83.71	5.43	7.22	-
							<u>Cl</u>				<u>Cl</u>
VIc	74	256-257 (c)	C ₂₇ H ₁₉ ClN ₂ O	76.68	4.53	6.62	8.39	76.71	4.55	6.77	8.61
							<u>Br</u>				<u>Br</u>
VId	76	279-280 (a)	C ₂₇ H ₁₉ BrN ₂ O	69.39	4.10	5.99	17.10	69.13	4.32	6.21	17.42
VIe	77	207-208 (d)	C ₂₈ H ₂₂ O ₂ N ₂	80.36	5.30	6.69	-	80.44	5.37	6.82	-
VI _f	72	235-236 (a)	C ₂₈ H ₂₀ N ₂ O ₃	77.76	4.66	6.48	-	77.75	4.80	6.60	-

(a) Crystallized from benzene. (b) Crystallized from benzene-cyclohexane. (c) Crystallized from dioxane-water. (d) Crystallized from methanol.

6-Aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (IIa-f).

General Procedure.

Methyl α -naphthylacetate (0.015 mole) and the aroylphenylacetylene (I) (2,16) (0.015 mole) were added successively to a suspension of sodium methoxide (0.015 mole) in dry ether (50 ml.). The reaction mixture was kept at room temperature for 2 days with occasional stirring, then poured into a dilute sulphuric acid (10%, 50 ml.) and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution, dried, evaporated and the residue crystallized from a suitable solvent to give 6-aryl-3- α -naphthyl-4-phenyl-2H-pyran-2-ones (II) as yellow crystals. The results are reported in Table III.

The sodium bicarbonate solution was worked up as usual to give α -naphthylacetic acid m.p. and mixed m.p. 131-132°.

4-Methoxybenzoyl-2- α -naphthyl-3-phenylbut-2-enoic Acid (IIIe).

A mixture of the pyrone (IIe) (10 g.) and 3% methanolic potassium hydroxide (40 ml.) was refluxed on a boiling water bath for one hour. The acid separated from the reaction mixture was crystallized from cyclohexane as colorless needles, m.p. 133-134°, yield = 72%.

Anal. Calcd. for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25; OCH_3 , 7.35. Found: C, 79.83; H, 5.37; OCH_3 , 7.73.

The structure of the acid (IIIe) was established by ozonolysis, and by esterification followed by cyclisation.

(a) Ozonolysis of IIIe.

The chloroform solution of the acid (IIIe) [(1.0 g.) in 10 ml. of solvent] was subjected to ozonolysis at 0° (1 hour) and the ozonide was decomposed with zinc/dilute acetic acid mixture. Evaporation of the solvent after washing with sodium bicarbonate solution gave a colorless solid (0.5 g.) which proved to be *p*-methoxydibenzoylmethane, m.p. and mixed m.p. 94-95° (cyclohexane).

(b) Esterification of IIIe.

This was performed by treating the acid (IIIe) with an ethereal solution of diazomethane. The residual oil gave methyl 4-methoxybenzoyl-2- α -naphthyl-3-phenylbut-2-enoate (Ve) as colorless needles (cyclohexane) m.p. 83-84°, yield = 91%.

Anal. Calcd. for $C_{29}H_{24}O_4$: C, 79.80; H, 5.54. Found: C, 80.11; H, 5.63.

The solution of the ester (Ve) (1.0 g.) in dry ether was treated with suspension of sodium methoxide (0.2 g.) and then left for 12 hours at room temperature. The reaction mixture was worked up as usual to give 6-*p*-methoxyphenyl-3- α -naphthyl-4-phenyl-2H-pyran-2-one (IIe) as yellow needles, m.p. and mixed m.p. 256-

257°.

1-Amino-6-aryl-3- α -naphthyl-2-pyridones (VIa-f).

General Procedure.

A solution of the pyrone (II) (2.0 g.) in ethanol (20 ml.) was refluxed with hydrazine hydrate (3 ml., 99% w/w) on a boiling water bath for 5 hours. The reaction mixture was diluted with water and the precipitated solid was crystallized from a suitable solvent to give the corresponding 1-amino-2-pyridone derivatives (VI) as colorless leaflets. The results are reported in Table IV.

Acetylation of 1-amino-6-(3',4'-methylenedioxyphenyl)-3- α -naphthyl-2-pyridone (VI_f) with acetic anhydride gave the corresponding 1,1-diacetylamino derivative (VIII_f) as colorless needles, m.p. 211-212°, yield = 81%.

Anal. Calcd. for $C_{32}H_{24}N_2O_5$: C, 74.41; H, 4.68; N, 5.42. Found: C, 74.53; H, 4.73; N, 5.22.

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