

Friedel-Crafts Cyclisations. II. (1)
Further Studies of Polyphosphoric Acid-catalysed Cyclisations of
N-Cinnamoyl Derivatives of Aromatic Amines.

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Further studies of the effects of substituents in the *N*-phenyl nucleus on the polyphosphoric acid-catalysed cyclisation of cinnamanilide to 4-phenyl-3,4-dihydrocarbostyryl have confirmed that the isomerisation is prevented by a nitro group and retarded by other substituents in the *ortho* position to the NH- group. Although a methyl group *ortho* to the only position at which cyclisation can occur was also shown to retard the reaction, *N*-cinnamoyl-2,4,5-trichloroaniline was cyclised in moderate yield after prolonged heating, but the 2,4-dibromo and 2,5-dimethoxy analogues were not isomerised.

Isomerisation of 2-cinnamidobiphenyl to 4,8-diphenyl-3,4-dihydrocarbostyryl was accompanied by cyclodehydration to 6-styrylphenanthridine. Five new derivatives of cinnamanilide and eight new derivatives of 4-phenyl-3,4-dihydrocarbostyryl are described.

In part I (1) of this series, the polyphosphoric acid-catalysed isomerisation of cinnamanilide to 4-phenyl-3,4-dihydrocarbostyryl (II, $R^1 = R^2 = R^3 = H$) was shown to be retarded by either a *o*-chloro or a *o*-methyl substituent in the *N*-aryl nucleus, and the failure of the cyclisation in the presence of a *p*-nitro group in this nucleus had been reported (2) previously. Further elucidation of the reaction has now been achieved by heating several more derivatives of cinnamanilide with polyphosphoric acid at 138°. Analytical data, melting points and yields of new derivatives of 4-phenyl-3,4-dihydrocarbostyryl thus prepared are given in Table I.

The formation of 4,8-diphenyl-3,4-dihydrocarbostyryl (II, $R^1 = Ph$, $R^2 = R^3 = H$) from 2-cinnamidobiphenyl (I, $R^1 = Ph$, $R^2 = R^3 = H$) was accompanied by the production of 6-styrylphenanthridine (IV). The latter may be considered to arise by cyclodehydration of the carbonium ion (IIIa), formed by protonation of the anilide, whereas the dihydrocarbostyryl derivative probably arises through the mesomeric ion (IIIb) as suggested (2) by Conley and Knopka. The isolation of a small yield of 6-styrylphenanthridine by heating 2-cinnamidobiphenyl with phosphorus oxychloride at 100° was reported by Ritchie (3), and Taylor and Kalenda (4) have shown that 2-formamidobiphenyl can be dehydrated to phenanthridine by treatment with polyphosphoric acid at 140-160°, provided that the mixture is stirred. 6-Methylphenanthridine has also been obtained (5,6) by cyclodehydration of 2-acetamidobiphenyl in refluxing phosphorus oxychloride. The almost quantitative recovery of *N*-cinnamoyl-*o*-ethyl-

aniline after refluxing with phosphorus oxychloride for 75 minutes now establishes that this reagent does not catalyse the isomerisation of a derivative of cinnamanilide to a derivative of 4-phenyl-3,4-dihydrocarbostyryl, and that the cyclodehydration cannot occur through a saturated β -carbon in the *ortho* substituent in the *N*-aryl nucleus.

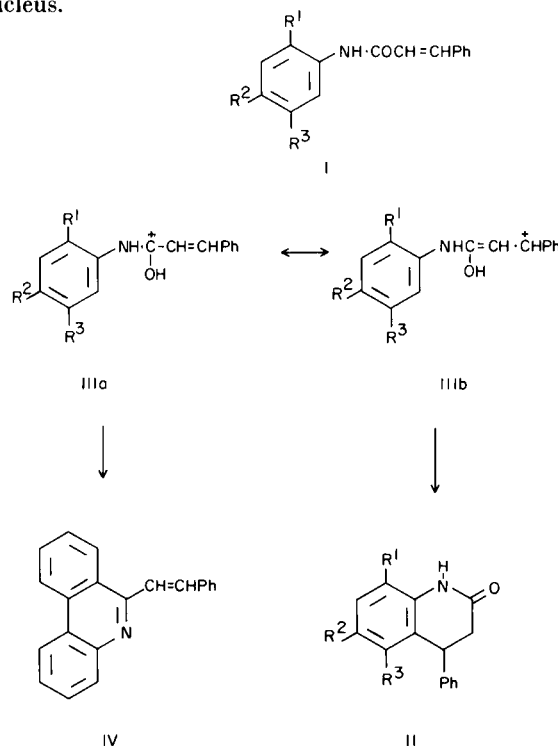


TABLE I
Formation of New Derivatives of 4-Phenyl-3,4-dihydrocarbostyryl from Cinnamanilides

Substituents in I & II		Time (min.)	Yield %	m.p.	Formula	R-3,4-Dihydrocarbostyryls				Calculated					
R ¹	R ²					R ³	Found C	H	N	Hal	M(Rast)	C	H	N	Hal
Br	H	H	13	128	C ₁₅ H ₁₂ BrNO	59.9	4.0	4.8	27.4	---	59.6	4.0	4.6	26.5	302
F	H	H	40	178	C ₁₅ H ₁₂ FNO	74.5	4.7	5.6	7.8	254	74.7	5.0	5.8	7.9	241
MeO	H	H	50	121	C ₁₆ H ₁₅ NO ₂	75.3	5.9	5.6	---	---	75.9	6.0	5.5	---	253
Et	H	H	52	118	C ₁₇ H ₁₇ NO	80.9	6.8	5.8	---	242	81.2	6.8	5.6	---	251
Me	H	Me	90	197	C ₁₇ H ₁₇ NO	80.8	6.7	5.3	---	234	84.2	5.7	4.7	---	299
Ph	H	H	57	199	C ₂₁ H ₁₇ NO	84.2	5.7	4.7	---	284	61.7	3.8	4.8	24.3	292
Cl	Cl	H	60	160	C ₁₅ H ₁₁ Cl ₂ NO	60.8	3.8	4.6	24.6	---	55.2	3.1	4.3	32.6	326.6
Cl	Cl	Cl	30	171	C ₁₅ H ₁₀ Cl ₃ NO	54.8	3.2	4.2	32.9	---	---	---	---	---	---

The yields of 8-ethyl-, 8-methoxy-, 8-bromo-, and 8-fluoro-4-phenyl-3,4-dihydro-carbostyryl (II, R¹ = X, R² = R³ = H), support the view (1) that steric retardation of the cyclisation by an *ortho* substituent in the *N*-aryl nucleus of cinnamanilide can be assisted by interaction of a -I effect (or perhaps even the direct effect) with the electron-releasing NH.CO- substituent, thus partially removing one of the activating influences on the electrophilic cyclisation. As expected (2) *N*-cinnamoyl-*o*-nitroaniline was recovered in good yield after heating with the acid at 138° for 1 hour.

Although the cyclisation of *N*-cinnamoyl-2,5-dimethylaniline (I, R¹ = R³ = Me, R² = H) was nearly quantitative after prolonged heating, the IR spectrum of the crude product after 10 minutes indicated that little of the lactam (II, R¹ = R³ = Me, R² = H) had been formed, and over 50% of the anilide was recovered. Comparison of the latter result with the good yield (1) of 6,8-dimethyl-4-phenyl-3,4-dihydrocarbostyryl (II, R¹ = R² = Me, R³ = H) from the 2,4-isomer of the anilide after 10 minutes at 125° shows that a small substituent in the *ortho* position to the only carbon atom at which cyclisation can occur causes considerable retardation of the isomerisation. The moderate yields of 6,8-dichloro-, and 5,6,8-trichloro-4-phenyl-3,4-dihydrocarbostyryl show that the deactivating influence of several halogen atoms can be overcome by increasing the duration of the reaction, but no cyclised product could be isolated after *N*-cinnamoyl-*p*-nitroaniline had been heated with polyphosphoric acid at 138° for 6 hours. The failure of the isomerisation in presence of nitro substituents can be attributed to protonation of an oxygen atom in the substituent, which would increase its electron-withdrawing properties. Protonation at oxygen may also contribute to the failure of *N*-cinnamoyl-2,5-dimethoxyaniline to cyclise. The failure of *N*-cinnamoyl-2,4-dibromoaniline to cyclise was expected in view of the very low yield from the 2-bromo- analogue.

All 8- substituted derivatives of 4-phenyl-3,4-dihydrocarbostyryl described now and previously (1) exhibit a sharp, fairly intense absorption near 3200 cm⁻¹ attributable to a stretching mode of a non-hydrogen bonded N-H group, as the most prominent feature in the region 2800-3500 cm⁻¹, whereas the IR spectra of compounds without a substituent in this position contain only a series of broad, overlapping absorptions in this region. These observations remove the remote possibility of migration of methyl groups from the 8-position, which was raised by its occurrence (7) in a related aluminum chloride-catalysed synthesis of 8-methyl-3,4-dihydrocarbostyryl.

EXPERIMENTAL

IR spectra were recorded in potassium chloride discs on a Perkin-Elmer Infracord spectrophotometer, and UV spectra were

measured on a Unicam SP 800 instrument.

N-Arylcinnamamides.

These compounds were obtained from aromatic amines as described (1).

2-Cinnamamidobiphenyl had m.p. 142° (lit. (3) 141°) and an absorption maximum at 283 μ (10^{-4} 2.46). Melting points of other known amides were *N*-(*o*-anisoyl)cinnamamide, 136-138° (lit. (8) 136-138°), *N*-2,5-dimethylphenylcinnamamide, 190-191° (lit. (9) 185°), *N*-*o*-nitrophenylcinnamamide, 126.5° (lit. (10) 123°), *N*-*p*-nitrophenylcinnamamide, 228° (lit. (10) 214-216°), and *N*-2,4-dichlorophenylcinnamamide, 162° (lit. (11) 162-164°).

N-*o*-Fluorophenylcinnamamide.

This compound had m.p. 118°.

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.7; H, 5.0; N, 5.8; F, 7.9; *M*, 241. Found: C, 74.2; H, 4.85; N, 6.25; F, 8.3; *M* (Rast), 308.

N-*o*-Ethylphenylcinnamamide.

This compound had m.p. 167°.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.2; H, 6.8; N, 5.6; *M*, 251. Found: C, 81.0; H, 6.9; N, 5.5; *M* (Rast), 235.

N-2,5-Dimethoxyphenylcinnamamide.

This compound had m.p. 116-117°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.05; H, 6.05; N, 4.95. Found: C, 71.8; H, 6.2; N, 5.05.

N-2,4-Dibromophenylcinnamamide.

This compound had m.p. 192°.

Anal. Calcd. for $C_{15}H_{11}Br_2NO$: C, 47.3; H, 2.9; Br, 41.95; N, 3.7; *M*, 381. Found: C, 47.65; H, 3.1; N, 3.9; Br, 41.75; *M* (Rast) 369.

N-2,4,5-Trichlorophenylcinnamamide.

This compound had m.p. 183° (12). All these amides had C=O absorption near 1660 cm^{-1} of about the same intensity as the C=C absorptions close to 1620 cm^{-1} , except the *o*- and *p*-nitro derivatives, which had rather stronger C=O absorptions at 1700 cm^{-1} (lit. 1690 cm^{-1}) and 1690 cm^{-1} (lit. 1675 cm^{-1}), respectively.

Reactions of *N*-Arylcinnamamides with Polyphosphoric Acid.

2-Cinnamamidobiphenyl.

(a) The amide (3.0 g.) was heated with commercial (B.D.H.) polyphosphoric acid (40.0 g.) for 20 minutes at 138° in an apparatus similar to that described by Fitton and Smalley (13) with ethylbenzene as the heating bath liquid. After the products had been added to ice-water (400 ml.) and the mixture kept overnight, the yellow precipitate was boiled with ethanol (50 ml.) for 10 minutes. The insoluble portion, a bright yellow powder, had m.p. ca. 240° dec.

Anal. Calcd. for $C_{21}H_{18}NPO_4$: N, 3.7; P, 8.15. Found: N, 3.95; P, 10.1.

The above compound on digestion with 20% aqueous sodium hydroxide solution (40 ml.) at 90° for 1 hour gave 6-styrylphenanthridine (0.66 g.), m.p. 133° (lit. (3,6) 133°).

Anal. Calcd. for $C_{21}H_{15}N$: N, 5.0. Found: N, 5.25. UV absorption maxima at 249 and 330 μ , 10^{-4} 2.50 and 1.27, respectively (lit. (6) 249 and 330, 10^{-4} 3.83 and 1.58 in methanol). After the ethanolic extracts had been partially evaporated, dilution with water gave crystals (1.1 g.), m.p. 191-192°, which, after several recrystallisations from ethanol-water, gave 4,8-diphenyl-3,4-dihydrocarbostyryl, ν (C=O) 1695 cm^{-1} . The UV

spectrum contained shoulders at 235 and 260 μ , 10^{-1} 2.07 and 1.12, respectively.

(b) After the amide (0.20 g.) had been heated with polyphosphoric acid (10 g.) as in (a), the products were poured in water (100 ml.), made alkaline with ammonia solution, then extracted with chloroform (3 x 25 ml.). The combined extracts were dried (magnesium sulfate), then evaporated. The UV spectrum of the residue, dissolved in absolute ethanol (250 ml.) showed that it contained 2-cinnamamidobiphenyl (21%), 6-styrylphenanthridine (23%) and 4,8-diphenyl-3,4-dihydrocarbostyryl (57%).

Other *N*-Arylcinnamamides.

The previously described (1) method was modified as in (a). Commercial polyphosphoric acid (B.D.H.), ca. 40 g. per 0.01 mole of amide, gave equally good results as the mixture of phosphorus pentoxide and orthophosphoric acid used in Part I (1). The products were poured into water, then recrystallization of the precipitates from ethanol-water readily gave derivatives of 4-phenyl-3,4-dihydrocarbostyryl (Table I), except for the 8-methoxy derivative. Although the IR spectrum of this crude product was closely similar to that of the pure compound, a good yield of pure crystals was only obtained after washing with sodium hydroxide solution, then distillation under reduced pressure, b.p. 200-204°/1 mm.

N-Cinnamoyl-*o*-nitroaniline.

This compound was recovered in 85% yield after heating with the catalyst for 1 hour at 138°, but after the *p*-nitro isomer had been similarly heated for 6 hours, only a small quantity (ca. 15%) of this anilide was isolated as the sole product with m.p. below 350°.

The IR spectrum of the crude product (0.4 g.) from *N*-cinnamoyl-2,4-dibromoaniline (1.0 g.) and the catalyst (25 g.) at 138° for 1 hour indicated that it contained some unchanged amide but no lactam, and only a small quantity of tarry material was isolated after the same mixture had been heated for 3 hours. The products from *N*-cinnamoyl-2,5-dimethoxyaniline and the catalyst at 138° for 30 minutes were washed with sodium hydroxide solution, but 50% of the amide was recovered and no lactam could be detected. After the same reactants had been heated at 138° for 1.5 hours, only tarry products were obtained.

The Attempted Reaction of *N*-*o*-Ethylphenylcinnamamide with Phosphorus Oxychloride.

The amide (1.3 g.) was refluxed with freshly distilled phosphorus oxychloride (20 g.) for 75 minutes. Although a yellow solution formed quickly, when the products were poured into water and made alkaline, the starting material (1.2 g.) was precipitated.

Acknowledgment.

Mr. R. L. Williams is thanked for the UV spectra and Mr. A. Hossain for technical assistance.

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Received August 14, 1969

London, England