Friedel–Crafts Cyclisations. Part III.[1a] Synthesis of Derivatives of 2(1*H*)-Quinolone (Carbostyril) by Aluminium Chloride-catalysed Cycloeliminations of Cinnamanilide and Related Compounds

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For the conversion of cinnamanilide into 2(1*H*)-quinolone (carbostyril) the use of 3 mol. equiv. of the catalyst, aluminium chloride, is desirable; the low yield of 2(1H)-quinolone obtained from 4-phenyl-3,4-dihydro-2(1*H*)-quinolone however, indicated that loss of the β-aryl group from cinnamanilide probably occurs virtually simultaneously with the cyclisation. Cyclisation was prevented by either a *p*-nitro- or a *p*-methoxy-group in the *N*-aryl nucleus, and also by an α-chloro-substituent in the cinnamoyl moiety. *p*-Chlorocinnamanilide was cyclised, however, to 4-phenyl-2(1*H*)-quinolone with loss of hydrogen chloride. The scope of the cycloelimination was indicated by the formation of 5,6,8-trichloro-2(1*H*)-quinolone from 2',4',5'-trichlorocinnamanilide. Although migration of a methyl group did not accompany the cyclisation of *o'*-methylcinnamanilide, cyclisation of 2',6'-dimethylcinnamanilide was permitted by shift of an *ortho*-methyl group to the adjacent *meta*-position.

PREVIOUS parts [1] have been concerned mainly with the influence of nuclear substituents on the polyphosphoric acid-catalysed isomerisation of cinnamanilide to 4-phenyl-3,4-dihydrocarbostyril [4-phenyl-3,4-dihydro-2(1*H*)-quinolone]. This paper deals with the mechanism of the related aluminium chloride-catalysed conversion of cinnamanilide into carbostyril [2(1*H*)-quinolone], and the scope of this cycloelimination as a synthesis of derivatives of 2(1*H*)-quinolone.

Whereas *N*-(ββ-dimethylacryloyl)-derivatives of aniline and *o*- and *p*-toluidine isomerised [2] to derivatives of 3,4-dihydro-2(1*H*)-quinoline (IIIa—c) when heated with 3 mol. equiv. of aluminium chloride at 100° for 1 h, similar treatment of cinnamoyl derivatives of *p*-toluidine and aniline gave [2] 6-methyl-2(1*H*)-quinolone (IIa) and 2(1*H*)-quinolone (IIb), respectively. Our investigations of the last-named reaction (Table 1) confirm that 3 mol. equiv. of aluminium chloride are required for the

TABLE 1

Cyclisation of cinnamanilide to 2(1*H*)-quinolone

$AlCl_3$ (mol per mol cinnamanilide)	1·2	2·0	2·0	3·0	3·0	3·0	3·0	3·0
Time (h)	1·0	1·0	1·0	0	0·25	1·0	1·0	1·0
Yield (%)	0	25	28 [a]	32	58	73—75 [b]	38 [a]	75

[a] In chlorobenzene. [b] The volatile product was benzene uncontaminated with chlorobenzene.

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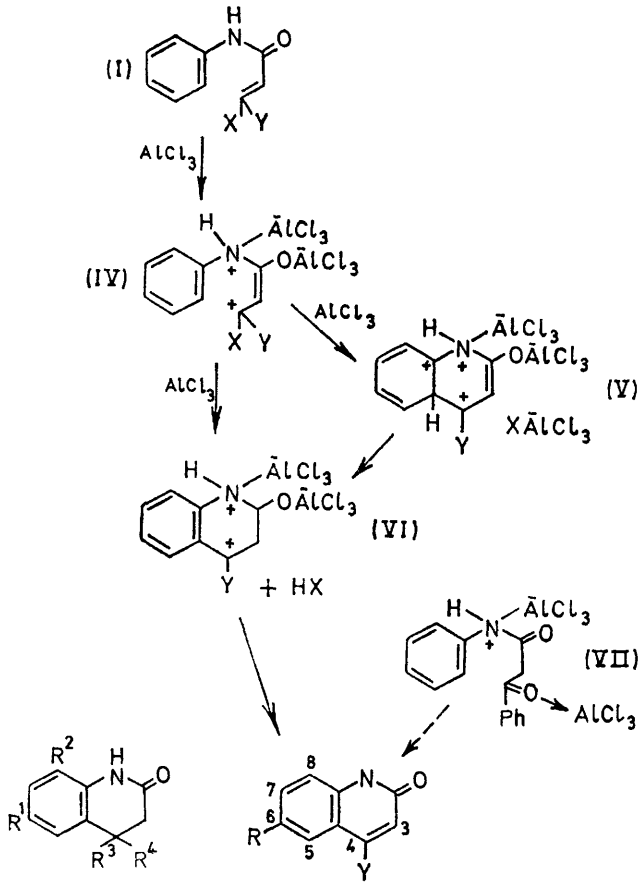
[1] (*a*) Part II, K. M. Johnston, *J. Heterocyclic Chem.*, 1969, **6**, 847; (*b*) Part I, K. M. Johnston, *Tetrahedron*, 1968, **24**, 5595.

[2] J. Colonge and R. Chambard, *Bull. Soc. chim. France*, 1953, 982.

production of a good yield of 2(1*H*)-quinolone and showed that the yield is not improved by increasing the duration of the reaction or by addition of chlorobenzene. Indeed the presence of this useful Friedel–Crafts solvent hindered the isolation of the lactam. The low yield of benzene in the volatile products may be due to consumption of this



(III)

a; $R^1 = R^2 = H$, $R^3 = R^4 = Me$
b; $R^1 = H$, $R^2 =$ $R^3 = R^4 = Me$
c; $R^2 = H$, $R^1 =$ $R^3 = R^4 = Me$
d; $R^1 = R^2 = R^3 =$ H, $R^4 = Ph$

(II)

a; R = Me, Y = H
b; R = H, Y = H
c; R = H, Y = OH
d; R = H, Y = Ph

compound by aluminium chloride-catalysed polymerisation.[3] Previous workers [2] considered the cycloelimination to proceed through 4-phenyl-3,4-dihydro-2(1*H*)-quinolone (IIId), but the low yield of 2(1*H*)-quinolone we have obtained by heating this possible intermediate indicates that this is unlikely, and that another mechanism probably operates in which cyclisation and elimination are virtually concerted. The isolation of identical yields of 2(1*H*)-quinolone from cinnamanilide after 3 h and 1 h removed the possibility that the low yield from 4-phenyl-3,4-dihydro-2(1*H*)-quinolone was due to consumption of the product by another reaction.

Although aluminium chloride complexes preferentially with oxygen rather than with nitrogen in amides,[4] a second mole of metal halide could be complexed with nitrogen. Isomerisation of the complex of cinnamanilide with two moles of catalyst (IV) to a complex of the isomeric 4-phenyl-3,4-dihydro-2(1*H*)-quinolone involved loss of the αβ-unsaturated amide system and the formation of a saturated lactam (*cf.* the occurrence of this process in polyphosphoric acid [1]). The higher electrophilicity of aluminium chloride may provide an additional driving force for the retention of the αβ-unsaturated system, which can be achieved if a β-substituent is lost together with the hydrogen displaced by the intramolecular alkylation. We believe that the third mole of aluminium chloride assists the removal of the β-phenyl group and that the formation of 2(1*H*)-quinolone in the presence of only two moles of aluminium chloride may therefore be due to incomplete complex formation of the second mole of catalyst at the nitrogen atom. However, the much greater yield with three moles of catalyst may also be due in part to the solvent action of the third mole of catalyst as the reaction mixture is more mobile.

The failure of the elimination with the *N*-(ββ-dimethylacryloyl)-derivatives, and, as we have now shown, with crotonanilide, is due to the inability of a β-methyl group to supply electrons to the highly electrophilic metal halide. If this explanation is correct, the elimination should proceed more easily with other, more strongly electron-donating β-substituents in place of aryl. Indeed although Staskun has postulated [4] that the related aluminium chloride-catalysed conversion of benzoylacetanilide into 4-phenyl-2(1*H*)-quinolone (IId) proceeds *via* the intermediate (VII), this elimination of water can be conceived as arising through loss of the β-hydroxy-group in a complex of the enol form (IV; X = OH, Y = Ph). Additional support for this comes from the treatment of malondianilide with aluminium chloride and sodium chloride [5] where any enolic intermediate of type (IV; X = NHPh, Y = OH) would be expected to lose the more basic β-anilino-substituent to give 4-hydroxy-2(1*H*)-quinolone (IIc). A similar situation may hold in the sulphuric acid-catalysed conversion [6] of anilides of β-ethoxyacrylic acid into derivatives of 2(1*H*)-quinolone. In accordance with these views, we have found that β-chlorocinnamanilide (I; X = Cl, Y = Ph) when heated with aluminium chloride readily gives 4-phenyl-2(1*H*)-quinolone (IId) with the loss of hydrogen chloride in a Friedel–Crafts reaction presumably *via* the intermediates (V) and (VI). In polyphosphoric acid, a less electrophilic catalyst, benzene is lost [1] from cinnamanilide only at relatively high temperatures but the order established for the influence of *p*-substituents in facilitating loss of aryl nuclei (MeO > Me > H > Cl) shows that the elimination is assisted by the strong electron-donating properties of the β-aryl

[3] P. Kovacic, 'Friedel–Crafts and Related Reactions,' vol. IV, ed. G. A. Olah, Interscience, New York, 1965, p. 122.
[4] B. Staskun, *J. Org. Chem.*, 1964, **29**, 1153.
[5] E. Ziegler, R. Wolf, and T. Kappe, *Monatsh.*, 1965, **96**, 418.
[6] F. Effenberger and W. Hartmann, *Angew. Chem.*, 1964, **76**, 188.

group. Indeed with the strongly electron-releasing *p*-methoxy-group, care has to be taken if elimination is to be prevented even in this relatively mildly electrophilic reagent.

The recently reported [7] isomerisation of α-cyano-derivatives of cinnamanilide to 4-aryl-3-cyano-3,4-dihydro-derivatives of 2(1*H*)-quinolone when heated in a mixture of aluminium chloride and sodium chloride may be ascribed to the alternative conjugated system between the carbonyl and cyano-groups which reduces the tendency towards retention of the αβ-unsaturated

minium chloride, and inhibition of the cyclisation of the hydroxy-compound through the formation of an $O \rightarrow AlCl_3$ complex.

This method of cyclisation with three moles of aluminium chloride has been used to prepare a number of derivatives of 2(1*H*)-quinolone from the appropriate anilides. Yields of products of the various reactions are given in Table 2.

A recent report [9] that aluminium chloride-catalysed cyclisation of *N*-(*o*-tolyl)-β-chloropropionamide gives a mixture of 5- and 8-methyl-3,4-dihydro-2(1*H*)-quinolone

TABLE 2

Conversion of derivatives of cinnamanilide to derivatives of 2(1*H*)-quinolone and quinoline

Anilide	Derivative of 2(1*H*)-quinolone				Derivative of quinoline		
	M.p. (Lit. m.p.)		Yield (%)	M.p. (Lit. m.p.)		Yield (%)	M.p. (Lit. m.p.)
2′-Chloro-cinnamanilide	135—137° (137—138 [1b])	8-Chloro-	56	207—208° (210 [6])	2,8-Dichloro-	100	103—104° (101—103 [c])
3′-Chloro-	122—123 (125—126 [1b])	5-Chloro- / 7-Chloro-	90	296—297 (296—297 [f])	2,5-Dichloro- (40%) / 2,7-Dichloro- (60%)	100	
4′-Chloro-	185 (185—186 [1b])	6-Chloro- [a]	82	265—266 (262 [j])	2,6-Dichloro-	97	156—157 (156 [12])
2′,4′-Dichloro-	164—165 (162—164 [c])	6,8-Dichloro-	63	254—255 (255—256 [k])	2,6,8-Trichloro-	100	163—164·5 (165—166 [k])
2′,4′,5′-Trichloro-	180—181	5,6,8-Trichloro-	56	265—266			
4′-Bromo-	193—194 (191 [d])	6-Bromo-	55	268—269 (269—270 [l])	2-Chloro-6-bromo-	100	159—160 (157—158 [12])
2′-Methyl-	175 (175 [1b])	8-Methyl-	60	219—220 (221 [11])	2-Chloro-8-methyl-	100	56—57 (57—58 [c])
3′-Methyl-	110—112 (114 [e])	5-Methyl- / 7-Methyl-	50		2-Chloro-5-methyl- / 2-Chloro-7-methyl-	100	
2′,4′-Dimethyl-	180—181 (184 [1b])	6,8-Dimethyl-	60	201—202 (201—202 [m])			
2′,5′-Dimethyl-	190—191 (185 [f])	5,8-Dimethyl-	72	199·5—200·5			
2′,6′-Dimethyl-	190—191 (189—191 [g])	5,8-Dimethyl-	75	197—199			
β-Chloro-	127—129 (133 [13])	4-Phenyl-	85	257—258 (256—257 [4])			
4-Chloro-	180 (180 [1b])	Parent compd. [b]	24	196—197 (197 [2])			
Crotonanilide	112—113 (112·5—114·5 [h])	4-Methyl-3,4-dihydro-	15	96 (98 [n])			

[a] Benzene (23%) was also isolated. [b] Chlorobenzene (5%) was also isolated. [c] H. W. Schultz and G. A. Wiese, *J. Amer. Pharm. Assoc. (Sci. Edn)*, 1959, **48**, 750. [d] A. H. Blatt, *J. Amer. Chem. Soc.*, 1931, **53**, 1133. [e] P. I. Ittyerah and K. C. Pandya, *J. Indian Chem. Soc.*, 1953, **30**, 717. [f] A. Philip and P. Ittyerah, *Indian J. Appl. Chem.*, 1963, **26**, 168. [g] G.P. 1,247,315/1967. [h] D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, 1958, **23**, 1149. [i] R. E. Lutz, G. Ashburn, and R. J. Rowlett, *J. Amer. Chem. Soc.*, 1946, **68**, 1322. [j] A. Einhorn and R. Lauch, *Annalen*, 1888, **243**, 342. [k] C. R. Saunders, C. E. Smith, jun., and J. D. Capps, *J. Amer. Chem. Soc.*, 1951, **73**, 5910. [l] E. Ochiai and T. Okamoto, *J. Pharm. Soc. Japan*, 1948, **68**, 88. [m] E. Spath, *Monatsh.*, 1919, **40**, 93. [n] F. Mayer, L. v. Zutphen, and H. Philipps, *Ber.*, 1927, **60***B*, 858. [o] G. Illuminati, P. Linda, and G. Marino, *Atti. Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1965, **38**, 389.

amide system. We attribute our failure to cyclise α-chlorocinnamanilide and *o*′-chloro-, *p*′-chloro-, and 2′,4′-dichloro-α-chlorocinnamanilide in aluminium chloride to the well-known vinyl halide conjugation which would cause the β-carbon atom to be negatively rather than positively polarised.

The failure of the cyclisation in *p*′-nitrocinnamanilide was expected in view of the well-known deactivating influence of nitro-groups in Friedel-Crafts reactions, and the isolation of *p*′-hydroxycinnamanilide as the only product from *p*′-methoxycinnamanilide is in accordance with the well-established cleavage [8] of ethers by alu-

raised the possibility that methyl migration could have occurred in the cyclisation of *o*′-methylcinnamanilide. The crude product from this cyclisation was therefore heated with phosphoryl chloride, but examination of the products by gas chromatography revealed the presence of only 2-chloro-8-methylquinoline. The yields of 5-and 7-substituted derivatives of 2(1*H*)-quinolone from *m*′-chloro- and *m*′-methyl-cinnamanilide were assessed by similar transformations of the crude products to derivatives of 2-chloroquinoline, and the other similar conversions confirmed the structures of the lactams (Table 2).

The structure of 5,8-dimethyl-2(1*H*)-quinolone is sup-

[7] E. Ziegler and T. Wimmer, *Monatsh.*, 1965, **96**, 1252.

[8] F. Johnson, 'Friedel–Crafts and Related Reactions,' vol. IV, ed. G. A. Olah, Interscience, New York, 1965, p. 5.

[9] T. Kametani and H. Nemoto, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 1910.

ported by the pair of doublets in the low field region of the n.m.r. spectrum (Table 3) attributable, from the coupling constant $J = 6{\cdot}3$ Hz, to two adjacent aromatic protons at positions 6- and 7-. This confirms the non-occurrence

TABLE 3

N.m.r. spectra of some derivatives of 2(1*H*)-quinolone

2(1*H*)-Quinolone	Chemical shifts (τ)				
	N–H	3-H	4-H	5-H to 8-H	Methyl
Parent compound	−2·6s broad	2·27d $J_{3,4} = 9{\cdot}0$ Hz	3·35d	2·36—2·71m	
8-Chloro-	0·8s broad	2·34d $J_{3,4} = 8{\cdot}1$ Hz	3·34d	2·36—2·97m	
8-Methyl-	0·0s broad	2·24d $J_{3,4} = 9{\cdot}6$ Hz	3·36d	2·50—3·04m	7·46s
5,8-Dimethyl-		2·17d $J_{3,4} = 9{\cdot}0$ Hz	3·47d	2·91d $J_{6,7} = 6{\cdot}3$ 3·21d	7·54s
6,8-Dimethyl-	−0·2s broad	2·40d $J_{3,4} = 9{\cdot}3$ Hz	3·45d	2·92s	7·51s 7·65s

of methyl migration in the cyclisation of 2′,5′-dimethylcinnamanilide since the probable product of migration, 5,7-dimethyl-2(1*H*)-quinolone, has no adjacent aromatic protons. Indeed, examination of the spectrum of 6,8-dimethyl-2(1*H*)-quinolone which, similarly, has no adjacent aromatic protons, revealed only a singlet (τ 2·92) due to the protons at positions 5- and 7-.

The fact that the product of cyclisation of 2′,6′-dimethylcinnamanilide contains methyl groups in the 5- and 8-positions of the quinolone nucleus therefore indicates that migration of a methyl group to the adjacent position can occur if it is necessary to make the cyclisation possible.

Finally, this cycloelimination provides at least as convenient a synthesis of alkyl and halogeno-derivatives of 2(1*H*)-quinolone as some of the previously established methods (*e.g.* isomerisation of quinoline *N*-oxides [10,11]) and thus increases the synthetic usefulness of the conversion of derivatives of 2(1*H*)-quinolone into derivatives of 2-chloroquinoline.[12] The usefulness of an alternative method, namely by sulphuric acid-catalysed cyclisation of β-ethoxyacryl anilides, which proceeds smoothly,[6] is diminished by the relative non-accessibility of the starting inlides.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer No. 137 Infracord spectrophotometer in potassium chloride discs or on pure liquids, and n.m.r. spectra were measured in deuteriochloroform on a Varian HA60 instrument. The gas chromatograph was a Perkin-Elmer F11 instrument used at 190° with a 1 m column of silicone fluid MS550 and Bentone on Chromosorb W (80—100 mesh).

Cinnamanilides.—These compounds were obtained either by adding the appropriate amine to a solution of an acid chloride in benzene as previously described,[15] or by the Schotten–Baumann procedure, with the exception of β-chlorocinnamanilide, which was prepared by the reaction of phosphorus pentachloride with phenylpropiolanilide [13] (m.p. 125°, lit.,[13] m.p. 128°). Acid chlorides were prepared from the appropriate acids by Watson's method.[14] α-Chlorocinnamic acid was obtained as the mixture of stereoisomers by Sudborough and James's method,[15] and was converted into a mixture of stereoisomeric α-chlorocinnamanilides. *α,2′-Dichlorocinnamanilide* (Found: C, 61·3; H, 3·6; N, 5·1; Cl, 24·0. $C_{15}H_{11}Cl_2NO$ requires C, 61·7; H, 3·8; N, 4·8; Cl, 24·3%), had m.p. 108°; *α,4′-dichlorocinnamanilide* (Found: C, 61·3; H, 3·8; Cl, 24·4; N, 5·0. $C_{15}H_{11}Cl_2NO$ requires C, 61·7; H, 3·8; Cl, 24·3; N, 4·8%) had m.p. 130°; *α,2′,4′-trichlorocinnamanilide* (Found: C, 55·2; H, 3·1; Cl, 32·3; N, 4·4. $C_{15}H_{10}Cl_3NO$ requires C, 55·2; H, 3·1; Cl, 32·6; N, 4·3%) had m.p. 137—138°; and *2′,4′,5′-trichlorocinnamanilide* (Found: C, 54·9; H, 3·1; Cl, 32·8; N, 4·2. $C_{15}H_{10}Cl_3NO$ requires C, 55·2; H, 3·1; Cl, 32·6; N, 4·3%) had m.p. 181—182° (*cf.* Table 2, which also contains the m.p.s of known derivatives which were cyclised). *p′*-Nitrocinnamanilide had m.p. 228—229° (lit.,[16] 216°) and *p′*-methoxycinnamanilide had m.p. 153—154° (lit.,[17] 152—153°). All these amides had C=O absorptions in the i.r. spectrum at 1667—1640 cm^{-1}, of about the same intensity as the C=C absorptions at 1620 cm^{-1}.

Cyclisation of Cinnamanilides to Derivatives of 2(1H)-*Quinolone.*—Colonge and Chambard's [2] conditions (intimate mixture of the cinnamanilide with 3 mol. equiv. of aluminium chloride melted over a flame, then kept at 100° for 1 h) were used in all experiments except those in which the effects of concentration of aluminium chloride and period of heating on the cyclisation of cinnamanilide (Table 1) were studied. Some reactions were conducted under a stream of nitrogen which was subsequently passed through a trap at −80°. The identities of the condensates were demonstrated by comparison of their i.r. spectra and refractive indices with those of authentic specimens.

2(1*H*)-Quinolone, m.p. 196—197°, undepressed on admixture with a commercial specimen, was recrystallised from water, and its derivatives from ethanol, except those which contained halogens. These were purified either by recrystallisation from glacial acetic acid, or better, by sublimation under reduced pressure. M.p.s and yields of *5,6,8-trichloro-2(1H)-quinolone* (Found: C, 43·4; H, 1·7; Cl, 42·6; N, 5·6. $C_9H_4Cl_3NO$ requires C, 43·5; H, 1·6; Cl, 42·8; N, 5·6%) and *5,8-dimethyl-2(1H)-quinolone* (Found: C, 76·1; H, 6·3; N, 8·0. $C_{11}H_{11}NO$ requires C, 76·3; H, 6·4; N, 8·1%) and of known derivatives which were cyclised thus are given in Table 2. Similarly treated *p′*-nitrocinnamanilide gave a dark intractable mass, but extraction of the product from *p′*-methoxycinnamanilide with sodium hydroxide gave *p′*-hydroxycinnamanilide (5%), m.p. 213—214° (lit.,[18] 216°), undepressed on admixture with an authentic specimen.[18] All the lactams thus prepared had C=O absorptions near 1667 cm^{-1} in the i.r. spectrum much stronger than the C=C absorptions at 1620 cm^{-1}. N.m.r. spectra of some of these derivatives are given in Table 3.

[10] F. Montanari and L. Pentimalli, *Gazzetta*, 1953, **83**, 273.
[11] O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, 1965, **19**, 1120.
[12] P. Linda and G. Marino, *Ricerca sci.*, 1964, *A***7**(2), 309.
[13] J. v. Braun and H. Ostermayer, *Ber.*, 1937, **70***B*, 1002.
[14] E. R. Watson, *J. Chem. Soc.*, 1904, 1319.
[15] J. J. Sudborough and T. C. James, *J. Chem. Soc.*, 1906, **89**, 105.
[16] M. Yamaguchi, *Nippon Kagaku Zasshi*, 1957, **78**, 1236.
[17] K. v. Auwers and M. Seyfried, *Annalen*, 1930, **484**, 178.
[18] F.P. 1,404,586/1965.

Reaction of 4-Phenyl-3,4-dihydro-2(1H)-quinolone with Aluminium Chloride.—An intimate mixture of the lactam (1·12 g, 0·005 mol) and aluminium chloride (2·0 g, 0·015 mol) was heated at 100° for 1 h. Recrystallisation of the product formed after hydrolysis gave 2(1*H*)-quinolone (0·25 g, 34·5%), m.p. and mixed m.p. 196°.

Conversion of Lactams into Derivatives of 2-Chloroquinoline.—A modification of Linda and Marino's procedure [12] was used. A solution of 2(1*H*)-quinolone in a large excess of phosphoryl chloride was refluxed for 0·5 h; hydrolysis with water gave 2-chloroquinoline, m.p. 37° (lit.,[19] 37—38°) in 95% yield. Pure lactams gave the bases as white precipitates, which were readily recrystallised from ethanol. Crude products from aluminium chloride-catalysed cyclisations of cinnamanilides gave brown precipitates, which were extracted with dichloromethane. The dried ($MgSO_4$) extracts were evaporated almost to dryness, then poured through a column of alumina (Brockmann Activity No. 1). The pure bases were eluted with benzene. Mixtures were analysed by gas chromatography. M.p.s and yields of the products are given in Table 2.

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