A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 8.[1] Conversion of Anilides into 3-Substituted Quinolines and into Quinoxalines [2]

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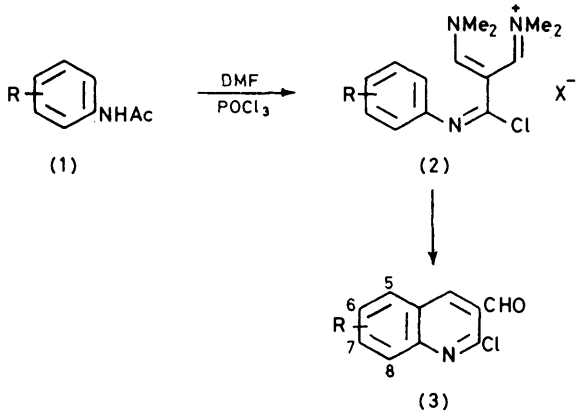
Anilides (4) ($ArNHCOCH_2R$) are readily converted into 2-chloro-3-R-quinolines (5) under Vilsmeier conditions and the 2-chloro-group may be removed with zinc and acetic acid yielding 3-substituted quinolines (7). When *N*-nitrosodialkylamines are used in place of dimethylformamide as the Vilsmeier agent, the anilides are converted into 2-chloroquinoxalines in low yields. Several by-products are formed and the mechanisms have been explored. Thus, the formation of ethyl *N*-arylcarbamate from the corresponding propionanilide is shown to involve an C→O alkyl migration related to a Wolff rearrangement, while *N*-arylformimidoyl dichloride (18), nitriles, and isocyanides are derived from C–C cleavage of the substituted side-chain. Variation of the acid chloride component of the Vilsmeier reagent or of the solvent was generally unproductive though use of phosphoryl bromide instead of the chloride caused conversion of anilides into bromoquinolines in low yields.

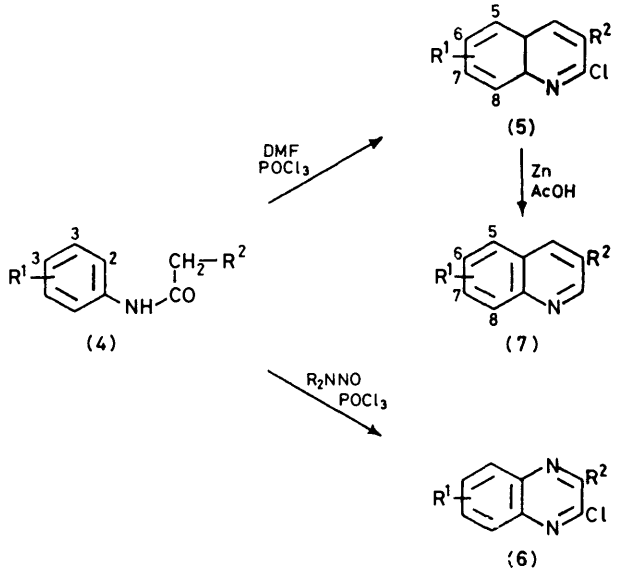
In Part 5 of this series [3] we elaborated the synthesis of 2-chloroquinoline-3-carbaldehydes (3) from acetanilides (1), showing that the key intermediates were the diformylated species (2) (Scheme 1). This reaction was extended to the acetamidothiophens.[1] We herein show that by use of higher anilides (4), specifically 3-substituted quinolines (5) may be synthesised (Scheme 2). Furthermore, by replacement of the dimethylformamide (DMF) by its aza-analogue, *N*-nitrosodimethylamine, a route to



Scheme 1

quinoxalines (6) is available (Scheme 2), although it is of limited synthetic value. Other potential variations have also been studied.

1 *Variation of the Acylanilide.*—Using the optimised conditions already described [3] a variety of 3-substituted quinolines (5) were synthesised from a series of anilides (4) (Table 1). Thus, 3-alkyl-, 3-chloroalkyl-, 3-methoxycarbonylalkyl-, 3-chloro-, and 3-aryl-quinolines were readily prepared. In general the only other product was a small amount of *NN*-dimethyl-*N'*-arylformamidine (8),[3] this being the major product when chloracetylanilides were reacted (*cf.* ref. 3). Interestingly when *N*-cyanoacetyl-*m*-toluidine (4; R^1 = 3-Me, R^2 = CN) was used, some of the hydrolysed intermediate (9) (26%) was isolated together with a low yield of the pyrimidine [probably (10)] (12%) presumably formed by *N*-formylation of the nitrile group followed by cyclisation and hydrolysis. Such formylations have been noted with other cyano-compounds prior to cyclisations occurring.[4] It is possible that the carbonyl and chloro-groups are interconverted in this product.



Scheme 2

The short reaction time required for efficient reaction reflects the greater ease of formylation of the higher acylanilides compared to acetanilide. Indeed, propionanilides were chosen as the preferred substrate for testing other variants of the reactants.

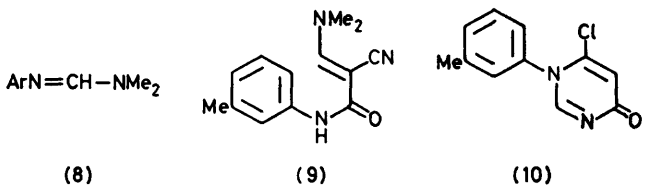


TABLE 1

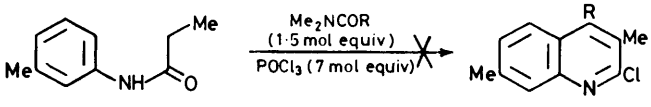
Yields of quinolines (5) from anilides (4) on treatment with DMF (1.5M) and $POCl_3$ (7M) at 75 °C and yields of quinolines (7) by reduction of (5) with Zn and acetic acid

Anilide (4)		Reaction time/	Quinolines (5) and (7)		(5)		(7)	
R^1	R^2	h	R^1	R^2	(%)	M.p./°C	(%)	M.p.(b.p.)/°C
H	Me	5	H	Me	62	84 [a]	75	(260 [c])
H	Bu^n	5	H	Bu^n	75	56—57		
H	Ph	5	H	Ph	42	53—54 [b]		
3-Me	Me	2	7-Me	Me	78	94—95	98	79—80 [d]
3-Me	Ph	2	7-Me	Ph	95	86—87	72	83—84
3-Me	Cl	2	7-Me	Cl	28	128.5—129.5	24	80
3-Me	CH_2CH_2Cl	2	7-Me	CH_2CH_2Cl	90	92—93		
3-Me	CN	2	7-Me	CN	13	187—188		
3-OMe	CH_2Cl	2	7-OMe	CH_2Cl	76	130		
3-OMe	CH_2CH_2Cl	2	7-OMe	CH_2CH_2Cl	76	90		
3-OMe	CH_2COOMe	2	7-OMe	CH_2COOMe	56	110		

[a] Lit., 84 °C (G. Ornstein, *Ber.*, 1907, **40**, 1088). [b] Lit., 55 °C (Soc. Anon. pour l'Ind. Chim. à Bâle, G. P. 547,082 (*Chem. Abstr.*, 1932, **26**, 3624). [c] Lit., 259.6 °C ('Handbook of Chemistry and Physics,' C.R.C. Press, Florida, 59th edition, 1978—1979, p. C-486) [d] Lit., 78.5 °C (W. P. Uterhmohlen, *J. Org. Chem.*, 1943, **8**, 544).

The ready reductive dechlorination of the 2-chloro-3-substituted quinolines (5) with zinc in warm acetic acid made this route of particular value for the synthesis of simple 3-substituted quinolines (7) (Table 1).

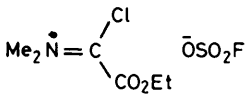
2 *Variation of the Vilsmeier Amide.*—In order to both improve yields and scope of the quinoline synthesis we have tested a variety of replacements for the DMF, but surprisingly, with little success. Thus, *N*-acetyl-*m*-toluidine gave only an oily product which contained 2-chloro-7-methylquinoline-3-carbaldehyde (3; R = 7-Me) on treatment with *N*-formylpyrrolidine in hot phosphoryl chloride for various periods. Various amides which we considered would give more electrophilic Vilsmeier reagents gave no 4-substituted quinolines at



R = CF_3, CCl_3, or CO_2Et

SCHEME 3

all (Scheme 3), the amide being recovered almost quantitatively. In case the iminium salt had not formed during these reactions we also utilised the recently reported highly reactive salt (11).[5] However, only ethyl *NN*-dimethyloxamate could be recovered (quantitatively)



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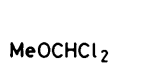

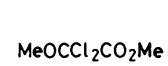

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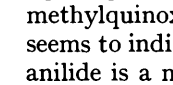
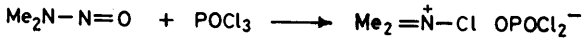


(13)

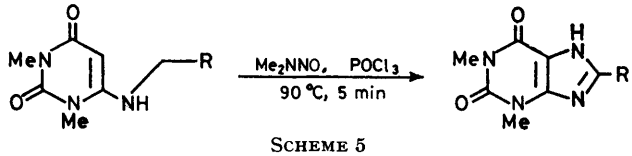
from the reaction mixture. The highly reactive Rieche reagents [6] (12) and (13) (covalent oxygen analogues of the Vilsmeier reagent) are known to bring about amide cyclisation in stannic chloride and phosphoryl chloride mixtures very efficiently.[7] However, under a variety of reaction conditions, no quinoline was obtained from 3'-methylacetanilide.

Finally, we examined *N*-nitrosodimethylamine (the aza-analogue of dimethylformamide) and some of its higher homologues. In principle an aza-Vilsmeier reagent (Scheme 4) could be formed with phosphoryl



SCHEME 4

chloride. Indeed, some evidence for such a mixture behaving as a nitrosating agent and *in situ* heterocyclising medium (*e.g.* Scheme 5) exists.[8] In our case, the formation of quinoxalines would be expected. In



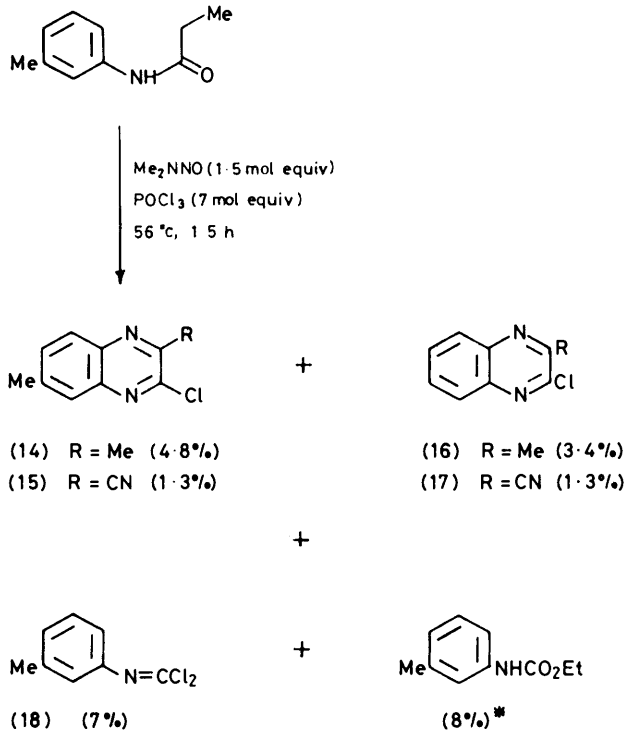
SCHEME 5

the event 3'-methylpropionanilide did give a mixture of quinoxalines, albeit in low yield (Scheme 6). This reaction throws up several interesting points. (a) Quinoxaline formation does occur most probably by way of initial side-chain substitution. However, unlike the Vilsmeier formylation conditions (which gives solely one regiospecific product, the 7-methylquinoline), almost equal quantities of both the 5- (14) and (15) and 7-methylquinoxalines (16) and (17) are produced. This seems to indicate that while the intermediate formylated anilide is a mildly reactive and bulky intermediate and thus highly selective (the Reactivity–Selectivity principle [9]), the corresponding aza-intermediate is considerably more reactive and probably less bulky. Certainly we found that the reaction was highly exothermic and needed to be conducted at lower temperatures than in the Vilsmeier case.

(b) The reagent accomplished conversion of the (active) methyl group of the quinoxaline into a cyano-function, a reaction which proceeded (inefficiently) with 2-methylquinoxaline but not with α-picoline or quinaldine. This

reaction seems again to point to a vigorous nitrosating agent.

(c) An interesting side-reaction resulting in the formation of the *N*-aryldichloroformimine (18) (and some



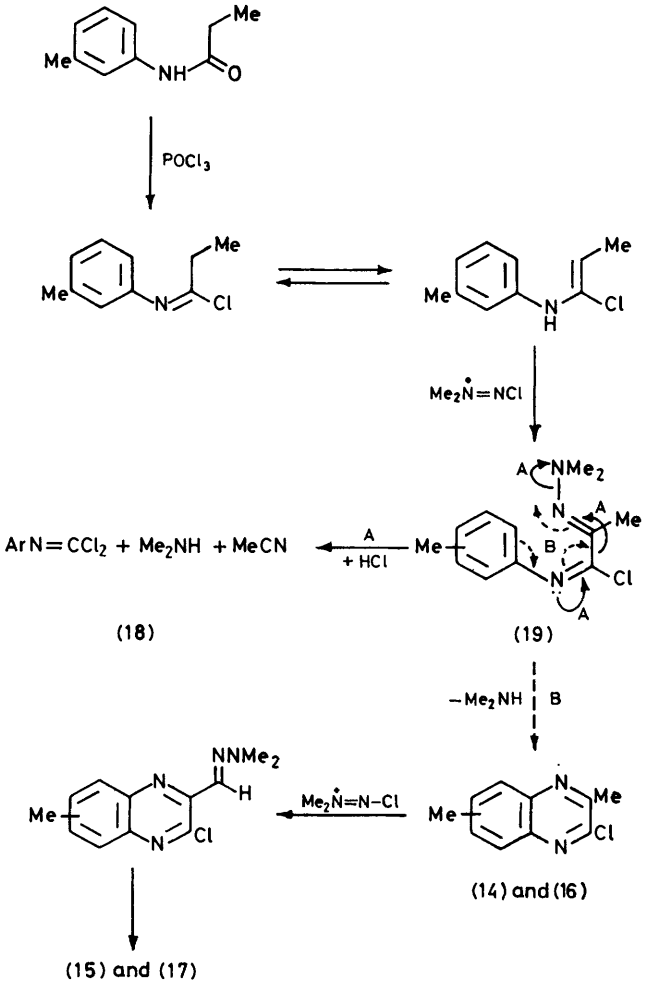
* Only formed when *N*-nitrosodi-isopropylamine was used.

SCHEME 6

isocyanide detected by its smell and i.r. absorption) also occurs. All these products can be envisaged to form from the same key type of intermediate (19) as outlined in Scheme 7.

Various potential nitrosating agents were studied in an endeavour to optimise this interesting reaction (Table 2). However, in all cases yields were low, amyl nitrite and sodium nitrite being totally ineffective, speaking against a simple action of ^{+}NO in this process. It is noteworthy that the bulkier agents $Pr^{i}_{2}NNO$ and Ph(Me)NNO give a higher ratio of the 7-methyl- (14) as opposed to the 5-methyl-quinoxaline (16), as would be expected. The formation of *N*-(3-methylphenyl)carbamate presents a puzzle, suggesting an ethyl group has migrated from C to O! A possible rationale is advanced in Scheme 8, involving a migration reminiscent of a Wolff rearrangement.

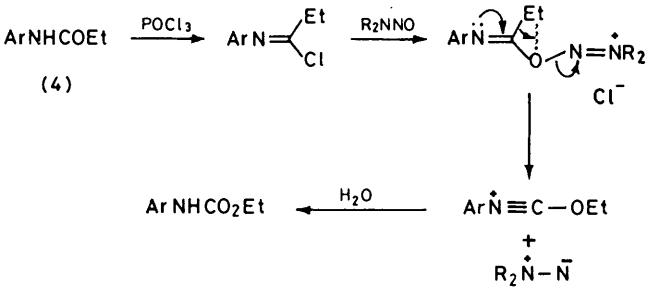
Further light was shed on the overall nitrosation process when we found that *N*-phenylacetyl-*m*-toluidine gave only a 7-methylquinoxaline (20) together with a nitrosated intermediate (21), benzonitrile, the imidoyl chloride (18), and an isocyanide, probably *m*-tolyl isocyanide (Scheme 9). Mild reducing reagents are known to convert such imidoyl chlorides into isocyanides.[10]



SCHEME 7

The isolation of benzonitrile tends to support the mechanism proposed in Scheme 7, while the lack of a 5-methylquinoxaline again confirms our views expressed above. Finally, we subjected 3′,5′-dimethoxypropionalide to the nitrosating conditions, as a highly reactive substrate with only one potential quinoxaline substitution pattern possible (Scheme 10). The expected products (22) and (23) were again formed but still in low yield.

3 *Variation of the Reaction Solvent.*—Our earlier studies [1,3] had suggested $POCl_3$ was the most effective



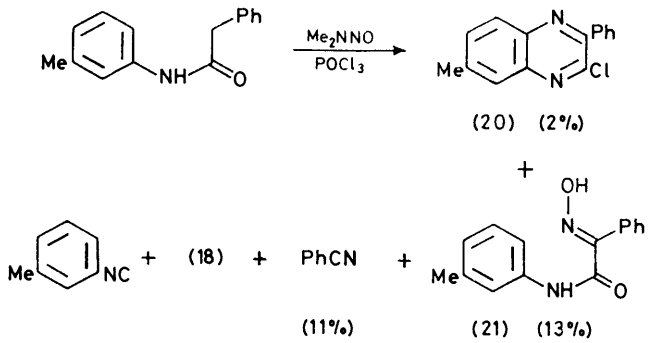
SCHEME 8

TABLE 2

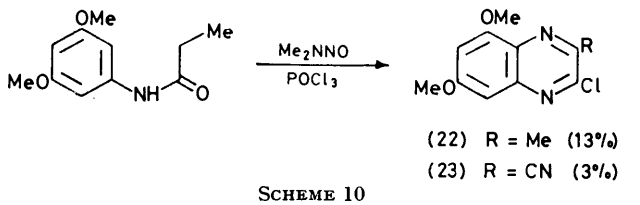
Action of various nitrosating agents (1.5 mol equiv.) and $POCl_3$ (7 mol equiv.) on 3′-methylpropionanilide (4) at 56 °C

	Products (%)					
	3-Methylquinoxaline		3-Cyanoquinoxaline		ArN=Cl$_2$	
Agent	(14)	(16)	(15)	(17)	(18)	Others
Me_2NNO	4.8	3.4	1.3	1.3	7	
Pr^i_2NNO	4.0	0.8	1.3	1.3		(4) (34%)
						3-$MeC_6H_4NHCO_2Et$ (8%)
Ph(Me)NNO	7.8	3.0	0	0	1.4	
p-$Me_2NC_6H_4NO$	0	0	0	0	0	
$NaNO_2$	0	0	0	0	0	
$C_5H_{11}ONO$	0	0	0	0	0	(4) (43%)

solvent for general purposes. However, several other alternatives were considered. Thus with dimethylformamide as solvent (a commonly used medium) only low quinoline yields ensued together with the formation of



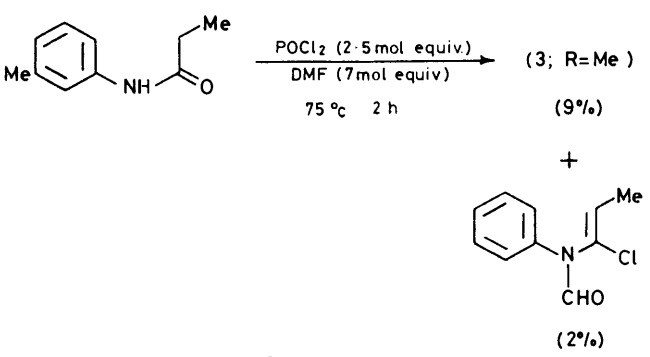
SCHEME 9



SCHEME 10

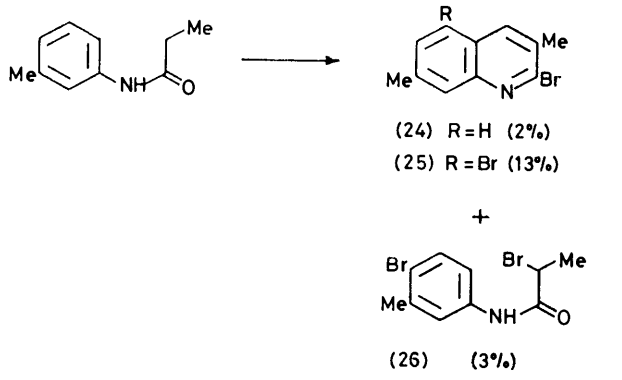
a curious by-product derived by *N*-formylation (Scheme 11).

Since in $POCl_3$ the quinoline yield is 78% we did not pursue this further. Use of thionyl chloride in place of



SCHEME 11

phosphoryl chloride proved totally ineffective, only unidentified gummy products being formed. However, with a view to forming bromoquinolines we examined phosphoryl bromide, a rather expensive, fuming solid, b.p. 193 °C. Because of the insolubility of the bromo-Vilsmeier reagent in $POBr_3$ we had to conduct these reactions at high temperatures (*ca.* 150 °C) to give a homogeneous medium.



SCHEME 12

Although quinoline formation was observed, the yield was low and was accompanied by electrophilic bromination both of the quinoline and of the anilide (Scheme 12).

EXPERIMENTAL

General conditions and methods are as outlined in Part 5.

The Anilides.—(*a*) Propionanilide (m.p. 104—105 °C, lit.,[11] 105 °C), 3′-methylpropionanilide (m.p. 79—81 °C, lit.,[11] 81 °C), and *3′,5′-dimethoxypropionanilide* (m.p. 97.5—98.5 °C) as white plates from aqueous ethanol (Found: C, 63.1; H, 7.2; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%) were prepared by heating the appropriate aniline (0.2 mol) with propionic anhydride (27 ml, 0.21 mol) and propionic acid (10 ml) under reflux for 1 min. The cooled reaction mixture was diluted with water (100 ml), made alkaline (40% aqueous sodium hydroxide), and stirred for 0.5 h. The solid product was filtered off, washed, and dried.

(*b*) The remaining anilides were made using acid chlorides in the following typical way. To freshly distilled *m*-toluidine (10.0 g, 10.1 ml, 93 mmol) in dry ether (50 ml) at 0 °C was added dropwise with stirring 4-chlorobutyryl chloride (6.58 g, 5.3 ml, 47 mmol) and the mixture was stirred for 5 min and filtered. The solid was washed well with ether and the combined filtrate washed successively with water, aqueous sodium carbonate (10%), water, aqueous hydrochloric acid (1M), and water, and then dried ($MgSO_4$). Evaporation gave N-(*4-chlorobutyryl*)-m-*toluidine* (9.6 g, 97%) as a white solid pure enough for further use. Re-

crystallisation from aqueous ethanol gave white plates, m.p. 72—73 °C (Found: C, 62.2; H, 6.6; N, 6.7. $C_{11}H_{14}ClNO$ requires C, 62.4; H, 6.7; N, 6.6%). In a similar manner the following anilides were obtained: *N*-(n-hexanoyl)aniline, m.p. 93—94 °C (lit.,[12] 92 °C); *N*-(phenylacetyl)-aniline, m.p. 115—116 °C (lit.,[12] 177—118 °C); *N*-(phenylacetyl)-*m*-toluidine, m.p. 89.5—90.5° (lit.,[13] 75 °C) (Found: C, 80.0; H, 6.7; N, 6.4. Calc. for $C_{15}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2%); *N*-(chloroacetyl)-*m*-toluidine, m.p. 93—95 °C (lit.,[14] 90—91 °C); *N*-(cyanoacetyl)-*m*-toluidine, m.p. 136—138 °C (lit.,[15] 138 °C); N-(3-*chloropropionyl*)-m-*methoxyaniline*, m.p. 95 °C (Found: C, 56.6; H, 5.85; N, 6.4. $C_{10}H_{12}ClNO_2$ requires C, 56.2; H, 5.6; N, 6.6%); *N*-(4-*chlorobutyryl*)-m-*methoxyaniline*, m.p. 50—54 °C (Found: C, 58.6; H, 6.5; N, 6.1. $C_{11}H_{14}ClNO_2$ requires C, 58.1; H, 6.15; N, 6.15%); *methyl* N-(m-*methoxyphenyl*)-*succinamate*, m.p. 107—108 °C (Found: C, 60.9; H, 6.1; N, 5.9. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.3; N, 5.9%).

Other Reagents.—(a) *Acylating agents.* Methyl dichloromethyl ether (12),[6] methyl dichloro(methoxy)acetate (13),[16] *NN*-dimethyltrichloroacetamide,[17] *NN*-dimethyltrifluoroacetamide,[18] ethyl *NN*-dimethyloxamate,[19] and ethyl *NN*-dimethyliminochloroacetate fluorosulphonate [5] were all prepared by reported methods.

(b) *The nitroso-compounds.* *NN*-Dimethyl- and *NN*-di-isopropyl-nitrosamine were prepared according to a reported procedure.[20]

The Quinolines (5).—To dimethylformamide (5.80 ml, 0.075 mol) at 0 °C was added phosphoryl chloride (32.2 ml, 0.35 mol) dropwise with stirring. To this solution was added the anilide (4) (0.05 mol) and after 5 min the mixture was heated at 75 °C for the appropriate time (Table 1). On pouring the reaction mixture into ice–water the quinoline (5) precipitated to give the products recorded in Table 1. Their further properties are recorded in Table 3. From *N*-(cyanoacetyl)-*m*-toluidine an oily solid precipitated on pouring into water. This was extracted with chloroform, the extracts were dried and evaporated, and the residue (10.91 g) was chromatographed on alumina. Elution with toluene gave 2-*chloro*-3-*cyano*-7-*methylquinoline* (see Tables 1 and 3). Further elution with chloroform–toluene (1 : 9 v/v) gave 6-*chloro*-1-(m-*tolyl*)-4-*pyrimidone* (10) (0.95 g, 12%) as white needles from ethanol, m.p. 138—139 °C (Found: C, 59.8; H, 4.1; N, 12.7. $C_{11}H_9ClN_2O$ requires C, 59.9; H, 4.1; N, 12.7%); $\nu_{max.}$ (Nujol) 1 690 (CO), 1 580, 1 520, 1 060, 840, 780, and 690 cm^{-1} (*m*-C_6H_4); δ ($CDCl_3$) 2.40 (s, Me), 6.57 (s, H-5), 7.0—7.4 (m, C_6H_4), and 8.05 (s, H-2); *m/e* 222 (13%, M^+) and 220 (40, M^+), 118 (100, $MeC_6H_4N{=}CH^+$), 91 (70, $C_7H_7^+$), and 65 (26, C_5H_5). Further elution with chloroform–toluene (1 : 4 v/v) gave 2-*cyano*-3-*dimethylamino*-N-(m-*tolyl*)*acrylamide* (9) (3.03 g, 26%) as cream crystals from ethanol, m.p. 181—182 °C (Found: C, 68.2; H, 6.5; N, 18.3. $C_{13}H_{15}N_3O$ requires C, 68.1; H, 6.6; N, 18.3%); $\nu_{max.}$ (Nujol) 3 310 (NH), 2 190 (CN), 1 665 (amide I), 1 605 (C=C), 1 530 (amide II), 1300, 1215, 700, and 690 cm^{-1} (*m*-C_6H_4); δ ($CDCl_3$) 2.32 (s, Me), 3.19 (s), 3.34 (s, Me_2N), 6.90 (d, Ar-H-6), 7.1—7.4 (m, 3 × ArH), 7.60br (NH), and 7.86 (s, H-3); *m/e* 229 (M^+), 123 (100%, *m*-C_7H_8N), 95, 80, and 68. Further elution with ethyl acetate gave the starting material (1.58 g, 18%).

TABLE 3

Further properties of the quinolines (5) and (7)

Compound			Found (%)				Required (%)			
	R^1	R^2	C	H	N	Formua	C	H	N	δ ($CDCl_3$); *J* (Hz)
(5)	H	Me								2.40s (Me), 7.3—7.7 (m, H-5,-6,-7), 7.78 (s, H-4), 7.95 (dd, H-8)
(5)	H	Bu^n	71.1	6.5	6.4	$C_{13}H_{14}ClN$	71.1	6.4	6.4	0.96 (t, Me), 1.2—1.9 (m, CH_2CH_2), 2.83 (t, CH_2), 7.2—7.8 (m, H-5, -6,-7), 7.88 (s, H-4), 7.98br (d, H-8)
(5)	7-Me	Me	69.9	5.2	7.3	$C_{11}H_{10}ClN$	68.9	5.3	7.3	2.42 (s) and 2.49 (s) (2 Me), 7.28 (dd, H-6), 7.55 (d, H-5), 7.71 (s, H-8), 7.80 (s, H-4); $J_{5,6}$ 9
(5)	7-Me	Ph	75.5	5.0	5.6	$C_{16}H_{12}ClN$	75.7	4.8	5.5	2.52 (s, Me), 7.34 (dd, H-6), 7.43 (s, Ph), 7.66 (d, H-5), 7.81 (s, H-8), 7.98 (s, H-4); $J_{5,6}$ 9
(5)	7-Me	Cl	56.6	3.25	6.6	$C_{10}H_7Cl_2N$	56.6	3.3	6.6	2.61 (s, Me), 7.35 (dd, H-6), 7.57 (d, H-5), 7.70 (s, H-8), 8.07 (s, H-4)
(5)	7-Me	CH_2CH_2Cl	60.2	4.6	6.0	$C_{12}H_{11}Cl_2N$	60.0	4.6	5.8	2.51 (s, Me), 3.27 (t, $ArCH_2$), 3.84 (t, CH_2Cl), 7.35 (dd, H-6), 7.65 (d, H-5), 7.76 (s, H-8), 7.96 (H-4); $J_{5,6}$ 8.5
(5)	7-Me	CN	65.2	3.6	13.9	$C_{11}H_7ClN_2$	65.2	3.5	13.8	2.60 (s, Me), 7.51 (d, H-6), 7.79 (s, H-8), 7.81 (d, H-5), 8.54 (s, H-4); $J_{5,6}$ 8
(5)	7-OMe	CH_2Cl	54.6	3.9	5.7	$C_{11}H_9Cl_2NO$	54.55	3.7	5.6	
(5)	7-OMe	CH_2CH_2Cl	56.3	4.2	5.5	$C_{12}H_{11}Cl_2NO$	56.25	4.3	5.25	
(5)	7-OMe	CH_2COOMe	58.8	4.5	5.3	$C_{13}H_{12}ClNO_3$	58.8	4.7	5.3	
(7)	7-Me	Ph	87.5	6.0	6.3	$C_{16}H_{13}N$	87.6	6.0	6.4	2.54 (s, Me), 7.2—7.8 (m, 7 × ArH), 7.93 (s, H-8), 8.20 (d, H-4), 9.13 (d, H-2); $J_{2,4}$ 2.5
(7)	7-Me	Me								2.36 (s, Me), 2.46 (s, Me), 7.24 (d, H-6), 7.53 (d, H-5), 7.71 (s, H-8), 7.85 (s, H-4), 8.70 (s, H-2)
(7)	7-Me	Cl *								2.49 (s, Me), 7.31 (d, H-6), 7.53 (d, H-5), 7.80 (s, H-8), 7.95 (d, H-4), 8.71 (d, H-2)

* Found: M^+, 177.0345. $C_{10}H_8{}^{35}ClN$ requires *M* 177.0345.

Reduction of the Chloroquinolines (5) *to Quinolines* (7).—The chloroquinoline (5) (0.5 g) in acetic acid (10 ml) and water (0.85 ml) was heated to 75 °C, zinc (0.4 g) was added, and the stirred mixture was maintained at 75 °C for 1 h. Water (50 ml) was added, and the mixture was made alkaline with aqueous sodium hydroxide (40% w/v) and extracted with ether. The dried ($MgSO_4$) extract was evaporated and the residue distilled (Kugelrohr) under high vaccum to give the products in Tables 1 and 3.

Reaction of Anilides with N-*Nitroso-compounds in* $POCl_3$. *General Method.*—To the stirred nitrosamine (27.6 mmol) at 0 °C was added dropwise phosphoryl chloride (19.77 g, 11.8 ml, 12.9 mmol) followed by addition of the anilide (18.4 mmol). The mixture was then heated to 56 °C (refluxing acetone in an outer jacket) for 1—1.5 h following an exothermic reaction. The mixture was cooled, poured into ice–water (200 ml), stirred for 0.5 h, and extracted with chloroform. The organic phase was dried ($MgSO_4$) and evaporated and the residue chromatographed on alumina. Basification of the above aqueous mother-liquor gave tarry material that was discarded. The products are recorded in Table 2 and below.

(a) *Products from* N-*propionyl*-m-*toluidine*. Elution with light petroleum gave in appropriate cases the imidoyl chloride (18) as a foul-smelling, colourless, mobile, lachrymatory liquid [b.p. 68 °C at 0.1 mmHg (lit.,[21] 130 °C at 10 mmHg); $\nu_{max.}$ (liquid film) 1 640 (C=N), 1 600, 1 580, 905, 880, and 690 cm^{-1}; δ ($CDCl_3$) 2.33 (s, Me), 6.79br (s, 2 H), 7.00 (d, 1 H), and 7.10—7.35 (m, 1 H)], followed by 2-*chloro*-3,5-*dimethylquinoxaline* (16) [pale yellow needles from light petroleum, m.p. 74.5—75.5 °C (Found: C, 62.4; H, 4.5; N, 14.7. $C_{10}H_9ClN_2$ requires C, 62.35; H, 4.7; N, 14.5%); $\nu_{max.}$ (Nujol) 1 570, 1 305, 1 285, 1 000, and 770 cm^{-1} (*o*-C_6H_4); δ ($CDCl_3$) 2.68 (s, 5-Me), 2.77 (s, 3-Me), 7.4—7.8 (m, 3 H)]. Further elution with the same solvent gave 2-*chloro*-3,7-*dimethylquinoxaline* (14) as white needles from toluene–light petroleum (1 : 1 v/v), m.p. 90—91 °C (Found: C, 62.5; H, 4.7; N, 14.7. $C_{10}H_9ClN_2$ requires C, 62.35; H, 4.7; N, 14.5%). $\nu_{max.}$ (Nujol) 1 300, 1 040, and 830 cm^{-1}; δ ($CDCl_3$) 2.49 (s, 7-Me), 2.71 (s, 3-Me), 7.44 (dd, H-6), 7.60 (s, H-8), and 7.77 (d, H-5) ($J_{5,6}$ 9, $J_{6,8}$ 2 Hz), followed by an oily solid which was further purified by preparative t.l.c. (20 × 20 cm × 1 mm) using silica gel type G. Elution first with light petroleum and then with toluene gave a major band which was extracted (CH_2Cl_2) and recrystallised from toluene to give 2-*chloro*-3-*cyano*-5-*methylquinoxaline* (17) as white needles, m.p. 137.5—138.5 °C, $\nu_{max.}$ (Nujol) (no CN), 1 600, 1 285, 1 010, 820, and 790 cm^{-1}; δ ($CDCl_3$) 2.80 (s, Me), 7.7—8.1 (m, 3 H); *m/e* 205 (33%, M^+), 203 (100, M^+) (^{35}Cl) (Found: M^+, 203.0242. $C_{10}H_6ClN_3$ requires *M*, 203.0250), 168 (10), 152 (10), 141 (14), 116 (17), and 89 (21%). Further elution of the column with toluene gave a solid further purified by preparative t.l.c. as above by elution with toluene. 2-*Chloro*-3-*cyano*-7-*methylquinoxaline* (15) was obtained as the main band {as pale yellow crystals from toluene, m.p. 198—199 °C (Found: C, 58.8; H, 3.1; N, 20.7 $C_{10}H_6ClN_3$ requires C, 58.99; H, 3.0; N, 20.6%); $\nu_{max.}$ (Nujol) (no CN), 1 620, 1 520, 1 290, 1 205, and 1 050 cm^{-1}; δ ([$^2H_6$]DMSO) (at 90 °C) 2.56 (s, Me), 7.78 (dd, H-6), 7.84 (s, H-8), and 8.04 (d, H-5)}. Finally, elution with chloroform gave ethyl *N*-(*m*-tolyl)carbamate as an oil [$\nu_{max.}$ (liquid film) 3 320 (NH), 2 990, 2 930, 1 710, (CO), 1 605d, 1 540, 1 230, 1 065, 770, and 690 cm^{-1} (*m*-C_6H_4); δ ($CDCl_3$) 1.25 (t, Me), 2.30 (s, ArMe), 4.20 (q, CH_2), and 6.8—7.4 (5 H)], identical with an authentic sample prepared by the action of ethyl chloroformate on *m*-toluidine according to the above method of making anilides from acid chlorides.

(b) *From N-(phenylacetyl)*-m-*toluidine*. (i) After a 1 h reaction period, elution with light petroleum gave benzonitrile (11%), identical with an authentic sample (i.r. spectrum). Further elution with light petroleum–toluene (9 : 1 v/v) gave 2-*chloro*-7-*methyl*-2-*phenylquinoxaline* (20) (2%) as white needles from light petroleum–toluene, m.p. 158—159 °C, (Found: C, 70.7; H, 4.5; N, 11.1. $C_{15}H_{11}ClN_2$ requires C, 70.7; H, 4.35; N, 11.0%); $\nu_{max.}$ (Nujol) 1 320, 1 260, 1 090, and 685 cm^{-1}; δ ($CDCl_3$) 2.60 (s, Me), 7.4–7.7 (m, 4 H), 7.7—7.95 (m, 3 H), and 8.04 (d, H-5) ($J_{5,6}$ 9 Hz); *m/e* 256 (M^+, 27%), 254 (M^+, 80), 219 (M − Cl, 100), and 89 (30%). With light petroleum–toluene (4 : 1 v/v) a red gum was eluted followed by N-(α-*oximinophenylacetyl*)-m-*toluidine* (21) (13%) as white needles from toluene, m.p. 171—172 °C (Found: C, 71.0; H, 5.6; N, 11.15. $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.0%); $\nu_{max.}$ (Nujol) 3 260 (NH), 1 660 (amide I), 1 590, and 1 520 cm^{-1} (amide II); δ ($CDCl_3$) 2.37 (s, Me), 6.9—7.8 (m, 9 H), 9.38br (NH and OH, exchanged with D_2O + CF_3CO_2D); *m/e* 254 (M^+, 70%), 135 (*m*-C_7H_5NO, 70), 134 (*m*-C_7H_6NO, 100), 121 (*m*-C_8H_7NO, 15), 120 (*m*-C_8H_8NO, 15), 107 (60), 93 (48), 91 (33), 77 (19), 65 (22), and 51 (11). Further elution with chloroform gave a red gum followed by some starting material (14%).

(ii) After a 4 h reaction period and the usual work-up, elution with light petroleum gave a mixture of a little *m*-tolyl isocyanide and much *m*-tolylimidoyl dichloride (18) (0.59 g), $\nu_{max.}$ (liquid film) 2 125 (NC), 1 640, 1 600, 1 580, 905, 880, and 690 cm^{-1}, followed by a mixture of the same isocyanide and benzonitrile (0.24 g, *ca.* 3 : 2), $\nu_{max.}$ (liquid film) 2 225, 2 125, 1 660, 1 600, 1 490, 1 445, 760, and 685 cm^{-1}. This was followed by pure benzonitrile (0.30 g, 16%). Elution with light petroleum–toluene (9 : 1 v/v) gave 2-chloro-7-methyl-3-phenylquinoxaline (20) (0.07 g, 1.5%) while elution with toluene gave *N*-(α-oximinophenylacetyl)-*m*-toluidine (21) (0.64 g, 14%).

(c) *From* N-*propionyl*-3,5-*dimethoxyaniline*. Elution with toluene gave an unidentified gum followed by 2-*chloro*-5,7-*dimethoxy*-3-*methylquinoxaline* (22) (0.5 g, 11%), as pale yellow needles from n-butanol, m.p. 204—205 °C (Found: C, 55.4; H, 4.6; N, 11.9. $C_{11}H_{11}ClN_2O_2$ requires C, 55.4; H, 4.65; N, 11.7%); $\nu_{max.}$ (Nujol) 1 610, 1 580, 1 540, 1 310, 1 240, 1 210, and 1 150 cm^{-1}; δ ($CDCl_3$) 2.80 (s, Me), 3.90 (s, OMe), 4.03 (s, OMe), 6.68 (d, H-6), and 6.83 (d, H-8) ($J_{6,8}$ 3 Hz); *m/e* 240/238 (M^+, 22 and 67%), 239/237 (M^+—H, 18 and 54), 211/209 (M^+—CHO, 26 and 100), 210/208 (M^+ − CH_2O, 21 and 33), 209/207 (M − OMe, 100 and 38), and 173 (42). Further elution gave a mixture of the above compound and 2-*chloro*-3-*cyano*-5,7-*dimethoxyquinoxaline* (23) (0.22 g). Repeated recrystallisation from n-butanol gave almost pure cyanoquinoxaline (23), m.p. 240—242 °C. However, analytical data indicated some (22) still present {$\nu_{max.}$ (Nujol) 2 225 (CN), 1610, 1510d, 1 465, 1 400, 1 310, 1 210, 1 160, and 1 140 cm^{-1}; δ ($CDCl_3$) 4.00 (s, OMe), 4.09 (s, OMe), 6.80 (d, H-6), 6.95 (d, H-8) ($J_{6,8}$ 3 Hz) [n.m.r. spectra suggest *ca.* 15% of (22) present]; *m/e* 251/249 (M^+, 17 and 51%) and 222/220 (M − CHO, 22 and 100) (Found: M^+, 249.0304. $C_{11}H_8ClN_3O_2$ requires *M*, 249.0304}.

Reaction of 2-*Methylquinoxaline with* N-*Nitrosodimethylamine*.—A mixture of *N*-nitrosodimethylamine (1.54 g, 20.8 mmol) and phosphoryl chloride (7.46 g, 4.5 ml, 48.6 mmol) was prepared as above and to it was added 2-

methylquinoxaline (1.0 g, 69 mmol) and the mixture heated for 10 min at 75 °C. Work-up as above and elution with toluene–chloroform (9 : 1 v/v) gave a mixture of 2-methylquinoxaline and 2-cyanoquinoxaline (0.07 g), $\nu_{max.}$ (Nujol) 2 215 (CN), and 760 cm^{-1}; δ ($CDCl_3$) (s, Me), 7.5—8.5 (m, 8 H), 8.85 (s, H-3 of 2-methylquinoxaline), and 9.20 (s, H-3 of 2-cyanoquinoxaline) (n.m.r. spectrum indicated a 1 : 1 mixture); *m/e* 155 (M^+, cyanoquinoxaline, 100%), 144 (M^+, methylquinoxaline, 100), 117 (79%), 103 [M^+, (cyanoquinoxaline) — C_2N_2, 65], 76, and 50. Further elution gave tarry material.

Reaction of N-*Propionyl*-m-*toluidine with Phosphoryl Chloride in Dimethylformamide.*—Phosphoryl chloride (7.06 g, 4.25 ml, 46 mmol), *N*-propionyl-*m*-toluidine (3.0 g, 18.4 mmol), and dimethylformamide (2 drops) were stirred at ambient temperature for 30 min and cooled to 0 °C. Dimethylformamide (9.48 g, 10 ml, 0.13 mol) was added dropwise and the mixture was subsequently heated for 2 h at 75 °C, cooled, poured into ice–water (100 ml), and made alkaline with aqueous sodium hydroxide (40%). After stirring for 30 min it was extracted with chloroform and the organic layer was dried and evaporated, dimethylformamide being removed *in vacuo* at 100 °C. Chromatography of the residue on silica gel gave, by elution with toluene–chloroform (3 : 1 v/v) 2-chloro-3,7-dimethylquinoline (3; R = 7-Me) (0.23 g, 6.5%) followed by an oily solid (0.26 g) which was further purified by preparative t.l.c. on silica gel by elution first with toluene [giving further 2-chloro-3,7-dimethylquinoline (0.08 g, 2%), which was scraped off] then chloroform. The major band gave N-(1-*chloroprop*-1-*enyl*)-N-*formyl*-m-*toluidine* (0.07 g, 2%) which was distilled *in vacuo* in a Kugelrohr apparatus (b.p. 104 °C at 0.05 mmHg) as a pale yellow oil (Found: C, 63.4; H, 5.7; N, 6.8. $C_{11}H_{12}ClNO$ requires C, 63.0; H, 5.8; N, 6.7%); $\nu_{max.}$ (liquid film) 1 700 (CHO), 1 320—1 200br, and 770 cm^{-1}; δ ($CDCl_3$) 1.88 (d, *Me*CH), 2.35 (s, Me), 5.94 (q, *CH*Me), 7.0—7.4 (m, 4 H), and 8.46 (s, CHO), ($J_{Me\text{-}CH}$ 7 Hz).

Reaction of N-*Propionyl*-m-*toluidine with Dimethylformamide and Phosphoryl Bromide.*—Phosphoryl bromide (12.3 g, 42.7 mmol) and dimethylformamide (1.14 g, 1.2 ml, 15.6 mmol) were mixed with cooling and *N*-propionyl-*m*-toluidine (2.0 g, 12.3 mmol) was added. After heating for 15 min at 75 °C, 15 min at 100 °C, 15 min at 117 °C, and finally 1 h at 155 °C, the mixture was cooled and ice added. After 30 min the mixture was extracted with chloroform. The organic layer was dried and evaporated and the residue (2.23 g) chromatographed on silica gel. Elution with toluene gave a mixture of three components which was further purified by preparative t.l.c. on silica gel, eluting twice with toluene. The three bands gave (in order of decreasing R_F) 2,5-*dibromo*-3,7-*dimethylquinoline* (25) (0.52 g, 13%) as white needles from toluene–petroleum, m.p. 158—161 °C (Found: C, 42.1; H, 2.9; N, 4.5. $C_{11}H_9Br_2N$ requires C, 41.9; H, 2.9; N, 4.45%); $\nu_{max.}$ (Nujol) 1 590 cm^{-1}; δ ($CDCl_3$) 2.50 (s, Me), 2.55 (s, Me), 7.72 (s, H-6), 7.81 (s, H-8), and 7.89 (s, H-4); *m/e* 317/315/313 (M^+, 50, 100, and 50%), 236/234 (M^+ — Br, 50), 155 (M^+ — Br_2, 100), and 140 (29); 2-*bromo*-3,7-*dimethylquinoline* (24) (0.07 g, 2%) as white needles from toluene–petroleum, m.p. 86—88 °C; $\nu_{max.}$ (Nujol) 1 590 and 1 010 cm^{-1}; δ ($CDCl_3$) 2.51 (s, 2 Me), 7.35 (dd, H-6), 7.62 (d, H-5), 7.79br (s, H-8), and 7.88 (s, H-4), $J_{5,6}$ 9, $J_{6,8}$ 1.5 Hz); *m/e* 237/235 (M^+, 59%), 156 (M^+ — Br, 100), 129 (18), and 127 (13) (Found: M^+, 234.9997. $C_{11}H_{10}BrN$ requires *M*, 234.9997); and N-(α-*bromopropionyl*)-4-*bromo*-3-*methylaniline* (26) (0.11 g, 3%) as fawn needles from toluene–petroleum, m.p. 166—167 °C; $\nu_{max.}$ (Nujol) 3 250 (NH), 1 660 (amide CO), 1 600, and 1 530 cm^{-1} (amide II); δ ($CDCl_3$) 1.95 (d, *Me*CH), 2.39 (s, Me), 4.54 (q, *CH*Me), 7.24 (dd, H-6), 7.48 (s, H-2), 7.50 (d, H-5), and 8.00 br (NH) ($J_{5,6}$ 8, $J_{2,6}$ 2, $J_{Me\text{-}CH}$ 7 Hz); *m/e* 323/321/319 (M^+, 30, 60, and 30%), 214/212 (M^+ — C_2H_4Br, 16 and), 187/185 (M^+ — C_3H_3BrO, 100) (Found: M^+, 318.9213. $C_{10}H_{11}Br_2NO$ requires *M*, 318.9308). From the aqueous phase after making alkaline with aqueous sodium hydroxide (40%), extraction with chloroform gave N-(*m*-tolyl)-*NN'*-dimethylformamidine as an oil (0.9 g), b.p. 224—228 °C at 0.02 mmHg, identical with that reported earlier.[3]

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