

Studies with Reissert Compounds. Part 17. Mono-Reissert Compound Formation at the 1,2-Position of the Quinazoline System.^{1†}

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4-Substituted quinazolines have been selectively converted into mono-Reissert compounds at the 1,2-position by use of acid chlorides and trimethylsilyl cyanide. Various reactions of the quinazoline Reissert compounds are reported. For example, conjugate base generation at the 2-position leads to a 1,2-rearrangement, whereas substitution occurs in the presence of an alkyl halide, providing, after hydrolysis, 2-alkyl-4-phenylquinazolines in good yield. Ring annellation by intramolecular alkylation is also reported. The quinazoline Reissert compound conjugate base reacts with aldehydes to give alcohol esters which can further be converted, *via* the alcohol and use of phosgene, to novel oxazolo[4,3-*a*]quinazoline derivatives.

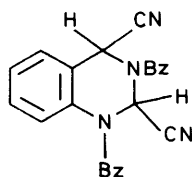
The formation of Reissert compounds of isoquinoline, quinoline and, more recently, phthalazine, has provided entry to a valuable methodology for the exploitation of the chemistry of these ring systems.² Quinazoline is of interest because it has two types of C=N bond for potential functionalisation by the Reissert approach. However, on attempted Reissert compound formation under the usual two-phase conditions with benzoyl chloride and potassium cyanide, ring opening is observed, giving 2'-formylbenzanilide and other products.^{3,4}

The demonstration that trimethylsilyl cyanide could be used as cyanide source in non-aqueous conditions for preparing Reissert compounds of isoquinoline and quinoline,⁵ led to examination of its use with quinazoline. It was shown that employment of benzoyl chloride, trimethylsilyl cyanide and quinazoline in a 2:2:1 molar ratio with aluminium chloride as catalyst gave the bis-Reissert compound (1), which could be

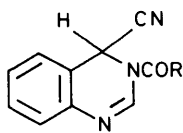
compound has also been prepared by Higashino *et al.*,⁸ by a two-step procedure employing hydrogen cyanide. The chemistry of Reissert compounds of type (2) has been reported by both the Japanese group^{8,9} and ourselves.^{7,10}

Blocking of the 4-position of quinazoline by use of 4-methylquinazoline in the Reissert reaction permits access to the alternative mono-Reissert compound, *e.g.* 1-benzoyl-1,2-dihydro-4-methylquinazoline-2-carbonitrile (3a) by selective addition across the 1,2-double bond.⁷ This paper reports the scope of this approach and the chemistry of this series of mono-Reissert compounds of quinazoline.

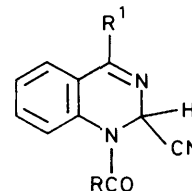
A number of 4-methylquinazoline-derived Reissert compounds of type (3; R¹ = Me) have been prepared though generally in moderate to poor yield [Table 1, [3a-e]. This appears to be due to partial decomposition of the product during purification. Oil formation tends to occur if the Reissert



(1)



(2)



(3)

a;	R ¹ = Me	R = Ph
b;	Me	PhO
c;	Me	4 - O ₂ NC ₆ H ₄
d;	Me	4 - ClC ₆ H ₄
e;	Me	4 - MeC ₆ H ₄
f;	Ph	Ph
g;	Ph	4 - O ₂ NC ₆ H ₄

h;	R ¹ = Ph	R = 4 - ClC ₆ H ₄
i;	Ph	4 - MeOC ₆ H ₄
j;	Ph	4 - MeC ₆ H ₄
k;	Ph	PhO
l;	Ph	Cl(CH ₂) ₃
m;	Ph	2 - ClCH ₂ C ₆ H ₄

alkylated at the 2-position with methyl iodide in the presence of sodium hydride.⁶ Use of equimolar amounts of acid chloride, trimethylsilyl cyanide and heterocycle gave selective mono-Reissert compound formation across the 3,4-double bond, *i.e.* 3-benzoyl-3,4-dihydroquinazoline-4-carbonitrile (2; R=Ph).⁷ This

compounds are exposed to moisture. In common with some other alkylquinazolines, 4-methylquinazoline is hygroscopic^{11,12} and requires drying *in vacuo* prior to use. Although covalent hydration of quinazolines occurs less readily in the neutral species than under acidic conditions, addition is normally at the 3,4-position but is decreased when a 4-substituent is present.¹¹ We have found that incorporation of a larger blocking group, Ph, at the 4-position leads to Reissert

† Also Part LV of the series 'Reissert Compound Studies' by F. D. Popp *et al.*

Table 1. Preparation of 4-methyl- and 4-phenyl-quinazoline Reissert compounds and analogues

Compd.	R ¹	R	Mol ratio Heterocycle: Me ₃ SiCN:ROCl	Yield (%)	M.p. (°C) ^a	ν _{max.} /cm ⁻¹ (C=O)	δ(2-H)	Formula	Found % (Required)		
									C	H	N
(3a)	Me	Ph	1:1.3:1.3	43 ^b	158—160	1 658	6.97	C ₁₇ H ₁₃ N ₃ O	74.3 (74.2)	4.8 (4.8)	15.6 (15.3)
(3b)	Me	PhO	1:1:1	17	129—131	1 745	<i>c</i>	C ₁₇ H ₁₃ H ₃ O ₂	70.1 (70.0)	4.5 (4.4)	14.3 (14.4)
(3c)	Me	4-NO ₂ C ₆ H ₄	1:1:1.07	15	168—169 ^d	1 669	7.03	C ₁₇ H ₁₂ N ₄ O ₃ ·0.5H ₂ O	62.4 (62.0)	3.7 (3.9)	17.1 (17.0)
(3d)	Me	4-ClC ₆ H ₄	1:1.07:1.2	10	149—150	1 667	6.99	C ₁₇ H ₁₂ ClN ₃ O	65.55 (65.9)	4.0 (3.9)	13.2 (13.6)
(3e)	Me	4-MeC ₆ H ₄	1:1.1:1.1	1	132—137 ^e	1 678	<i>c</i>	C ₁₈ H ₁₅ N ₃ O	<i>f</i>		
(3f)	Ph	Ph	1:1.3:1.3	85	159—160	1 667	7.24	C ₂₂ H ₁₅ N ₃ O	78.4 (78.3)	4.4 (4.4)	12.4 (12.4)
(3g)	Ph	4-NO ₂ C ₆ H ₄	1:1.2:1.2	62	205—206 ^g	1 680	7.29	C ₂₂ H ₁₄ N ₄ O ₃	68.7 (69.1)	3.5 (3.6)	14.5 (14.6)
(3h)	Ph	4-ClC ₆ H ₄	1:1.2:1.2	80	181—181.5	1 659	7.22	C ₂₂ H ₁₄ ClN ₃ O	71.1 (71.0)	3.5 (3.7)	11.1 (11.3)
(3i)	Ph	4-MeOC ₆ H ₄	1:1.4:1.4	65	164—166	1 655	7.23	C ₂₃ H ₁₇ N ₃ O ₂	75.1 (75.1)	4.6 (4.6)	11.3 (11.4)
(3j)	Ph	4-MeC ₆ H ₄	1:1.2:1.2	82	224—225 ^h	1 667	7.23	C ₂₃ H ₁₇ N ₃ O	78.7 (78.6)	4.7 (4.8)	11.9 (11.9)
(3k)	Ph	PhO	1:1.2:1.2	68	145—146	1 745	7.44	C ₂₂ H ₁₅ N ₃ O ₂	74.8 (74.7)	4.2 (4.2)	11.8 (11.8)
(3l)	Ph	Cl(CH ₂) ₃	1:1.3:1.3	66	92—93	1 675	7.50	C ₁₉ H ₁₆ ClN ₃ O	67.1 (67.5)	4.7 (4.7)	12.4 (12.4)
(3m)	Ph	2-ClCH ₂ C ₆ H ₄	1:1.2:1.2	70	Gum	1 668	<i>c</i>	C ₂₃ H ₁₆ ClN ₃ O	<i>i</i>		

^a Recrystallised from EtOH unless otherwise indicated. ^b 73% Prior to chromatography. ^c Signal obscured by aromatic multiplet. ^d From hexane-CH₂Cl₂(1:1). ^e Amorphous material, single spot by t.l.c. ^f Insufficient for microanalysis; *m/z* 289.1198 (*M*⁺, C₁₈H₁₅N₃O requires 289.1215). ^g From CH₂Cl₂-light petroleum (b.p. 40—60 °C). ^h From EtOAc. ⁱ Not analysed: compound used directly to prepare (15).

compounds of type (3; R¹ = Ph) in good yields (62—85%) [Table 1, (3f—m)], and which show little or no tendency to absorb moisture. In the ¹H n.m.r. spectrum of compound (3f) the 2-H signal appears as a singlet, at δ 7.24. In the i.r. spectrum of this compound the amide carbonyl absorbs at 1 667 cm⁻¹ and in the mass spectrum the base peak appears at *m/z* 105 (C₆H₅CO). As is also typical of Reissert compounds¹³ no significant nitrile absorption is seen in the i.r. spectrum. Use of benzenesulphonyl chloride as the acid chloride failed to give the corresponding Reissert analogue, returning only 4-phenyl-quinazoline. Quinazoline itself, in contrast, gives quinazoline-4-carbonitrile and 3,4-dihydroquinazoline-4-carbonitrile under the same conditions.¹⁰

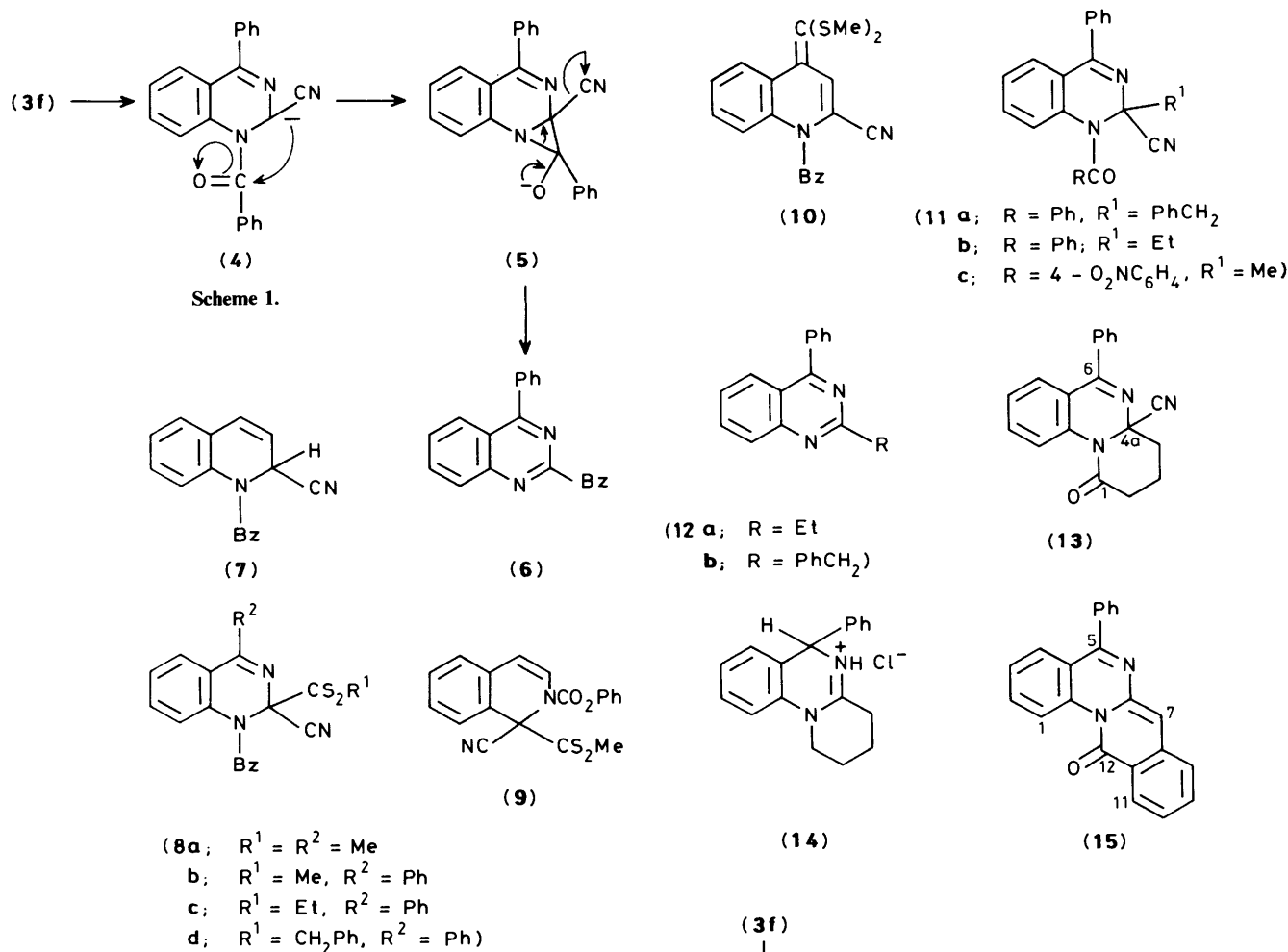
Base-catalysed hydrolysis of the Reissert compound (3f) with potassium hydroxide in aqueous ethanol regenerated 4-phenyl-quinazoline (61%), and treatment of (3i) with concentrated hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine gave the corresponding hydrazone of anisaldehyde in high yield. Both reactions are typical of Reissert compounds.¹³ 3-Benzoyl-3,4-dihydroquinazoline-4-carbonitrile (2; R = Ph) gives quinazoline on alkaline hydrolysis:⁸ the corresponding acid hydrolysis of (2; R = Ph), however, proceeds in low yield⁷ and if more dilute acid conditions are used a different pathway results.⁸

Conjugate base formation from Reissert compounds of type (3) occurs readily, addition of sodium hydride in dimethylformamide producing a red colouration at room temperature. In the absence of any added electrophile and under an atmosphere of nitrogen the conjugate base (4) of compound (3f) undergoes a 1,2-rearrangement producing 2-benzoyl-4-phenyl-quinazoline (6) (46%) hence providing simple access to derivatives of this type. The reaction presumably proceeds *via* the fused aziridine intermediate (5) (Scheme 1). Although an analogous rearrangement occurs with quinoline Reissert compound (7),^{14,15} the 3,4-quinazoline Reissert compound (2;

R = Ph) is reported by Higashino *et al.*⁸ to behave anomalously, giving quinazoline-4-carbonitrile, α -phenyl-4-quinazolinylmethyl benzoate and *O*-benzoylbenzoin: a curious mechanism is proposed involving generation of an acyl anion.^{8a} It is worth pointing out that the Japanese workers did not report conducting the reaction under nitrogen and so it is possible the quinazoline-4-carbonitrile may have resulted from the access of air. An analogous process occurs with the anion of (7) giving quinoline-2-carbonitrile and perbenzoic acid.¹⁶

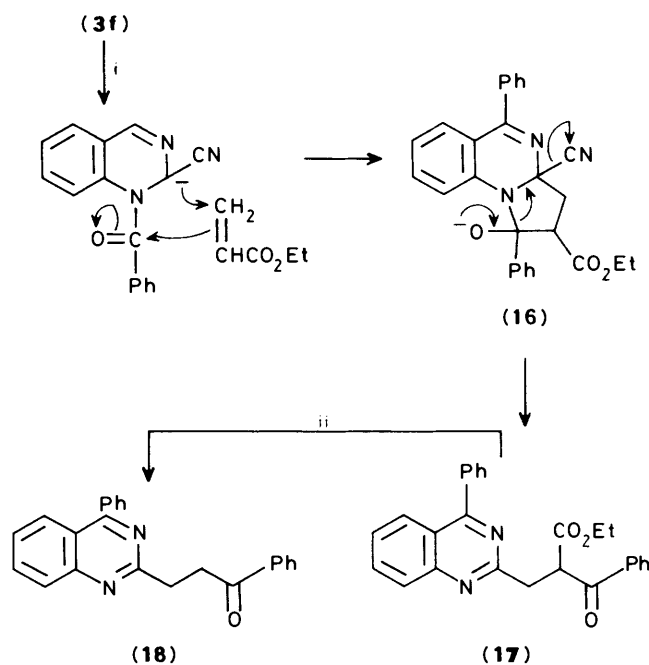
On generation of the conjugate bases of (3; R = Ph, R¹ = Me, Ph) and addition of carbon disulphide followed by alkyl halides, the corresponding dithio ester derivatives (8) of the Reissert compounds are readily produced. 1,2-Dihydro-2-phenoxycarbonylisoquinoline-1-carbonitrile¹⁷ reacts in a similar manner giving (9). This is in contrast to the conjugate base of quinoline Reissert compound (7) which undergoes allylic addition of carbon disulphide and two moles of methyl iodide, to yield structure (10).¹⁸ Direct alkylation, in the absence of carbon disulphide, also occurs allylically, giving, after alkaline hydrolysis, 4-substituted quinolines.^{2c} In the quinazoline case, however, direct alkylation of the conjugate base of (3; R = Ph, R¹ = Ph, 4-O₂NC₆H₄) provides derivatives (11) in good yield which can be hydrolysed to the corresponding 2-substituted 4-phenylquinazolines (12). This procedure complements that for the analogous preparation of 4-substituted quinazolines *via* the alkylation of Reissert compounds of type (2).^{9,10}

Intramolecular alkylation can also be achieved, using appropriately substituted quinazoline Reissert compounds. Thus, 1-(4-chlorobutanoyl)-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (3l) on treatment with sodium hydride in dimethylformamide gives the pyrido[1,2-*a*]quinazoline derivative (13), though in low yield (13%). The ring system is of interest pharmacologically, 2,3,4,6-tetrahydro-6-phenyl-1-*H*-pyrido[1,2-*a*]quinazoline hydrochloride (14), for example,



showing hypotensive properties and blood platelet aggregation inhibitory activity.¹⁹ Generation of the conjugate base of 1-(2-chloromethylbenzoyl)-1,2-dihydro-4-phenylquinazolin-2-carbonitrile (3m) leads to cyclisation and concomitant loss of HCN to give 5-phenyl-12*H*-isoquino[2,3-*a*]quinazolin-12-one (15). In the i.r. spectrum the lactam carbonyl appears at 1660 cm⁻¹ and the n.m.r. spectrum includes two broadened doublets at δ 9.82 and 8.8, and a singlet at 7.12, probably due to the 1-H, 11-H, and 7-H respectively. The structure of (15) appears to be the first proven example of the ring system: Schefczik obtained a product of unknown structure from the condensation of *o*-cyanomethylbenzoic acid and *o*-aminobenzylamine, which was considered to be either an isoquino[2,3-*a*]quinazoline derivative or a linear-fused isomer.²⁰ The conjugate base of (2; R = *o*-ClCH₂C₆H₄) cyclises in an analogous manner to (3m), giving a 5-azaberberine derivative,¹⁰ but the chlorobutanoyl Reissert compound [2; R = Cl(CH₂)₃] behaves anomalously.¹⁰

Michael addition of the conjugate base of (3f) to acrylonitrile did not yield a tractable product, but with ethyl acrylate an oil thought to be (17) was obtained: on hydrolysis under acidic or basic conditions decarboxylation followed to give phenyl 2-(4-phenylquinazolin-2-yl)ethyl ketone (18). It seems likely that the pathway proceeds *via* the tetrahydropyrrolo[1,2-*a*]quinazoline intermediate (16) (Scheme 2). The 4-substituted quinoline Reissert compounds give the corresponding cyano analogues of (17) with acrylonitrile under similar conditions,²¹ and compound (2; R = Ph) gives 2-benzoyl-3-(quinazolin-4-yl)propionitrile,⁹ but the conjugate base of (7) undergoes simple



Scheme 2. Reagents: i, NaH, DMF; ii, H₃O⁺ or HO⁻-H₂O

Michael addition,²² probably at the 4-position,²¹ with no intramolecular involvement. An attempted cyclodehydration of ketone (18) to the corresponding diphenylpyrrolo[1,2-*a*]quinazoline, with orthophosphoric acid, failed.

Table 2. α -(4-Phenylquinazolin-2-yl)benzyl benzoates (21) and corresponding alcohols (22)

R in (21), (22)	(21) M.p. (°C)	(21) Yield (%)	(21) ν_{\max} (KBr)/ cm^{-1} (C=O)	(21) Formula	(21) Found % (Required)		
					C	H	N
(a) H	Gum	78	1 718	$\text{C}_{28}\text{H}_{20}\text{N}_2\text{O}_2$	<i>a</i>		
(b) Me	184–185 ^c	71	1 713	$\text{C}_{29}\text{H}_{22}\text{N}_2\text{O}_2$	81.1 (80.9)	5.2 (5.1)	6.4 (6.5)
(c) Cl	179–180 ^c	77	1 713	$\text{C}_{28}\text{H}_{19}\text{ClN}_2\text{O}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$	72.8 (73.1)	4.3 (4.3)	5.9 (6.0)
(d) OMe	154–155 ^c	70	1 721	$\text{C}_{29}\text{H}_{22}\text{N}_2\text{O}_3$	78.1 (78.0)	4.9 (4.9)	6.3 (6.2)

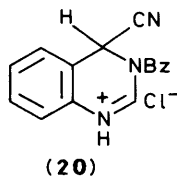
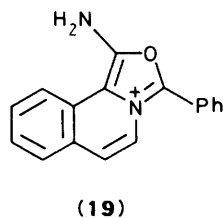
R in (21), (22)	(22) M.p. (°C)	(22) Yield (%)	(22) ν_{\max} (KBr)/ cm^{-1} (C=O)	(22) δ (CDCl_3) (CHOH)	(22) Formula	(22) Found % (Required)		
						C	H	N
(a) H	154–155 ^b	65	3 428	6.15	$\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$	80.9 (80.7)	5.1 (5.1)	9.0 (8.9)
(b) Me	175–176 ^d	76	3 440	6.14	$\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$	80.6 (80.9)	5.5 (5.5)	8.5 (8.5)
(c) Cl	156–156.5 ^d	77	3 430	6.11	$\text{C}_{21}\text{H}_{15}\text{ClN}_2\text{O}$	72.6 (72.7)	4.3 (4.3)	8.1 (8.0)
(d) OMe	142–144 ^d	70	3 400	6.12	$\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$	80.6 (80.9)	5.5 (5.5)	8.5 (8.5)

^a Gum not analysed: converted directly into (22a). ^b Colourless needles from EtOH. ^c Colourless rhombs from CH_2Cl_2 -EtOH. ^d Colourless needles from CH_2Cl_2 -EtOH.

Table 3. Oxazolo[3,4-*a*]quinazolinones (23)

R in (23)	M.p. (°C) ^a	Yield (%)	ν_{\max} (KBr)/ cm^{-1} (C=O)	λ_{\max} (CH_2Cl_2)/nm (log ϵ)	Formula	Found % (Required)		
						C	H	N
(a) H	293–294 ^b	70	1 758	268 (4.24), 297 (4.29), 453 (3.85)	$\text{C}_{22}\text{H}_{14}\text{N}_2\text{O}_2$	77.9 (78.0)	4.0 (4.1)	8.3 (8.3)
(b) Me	278–279 ^c	56	1 754	271 (3.96), 301 (4.35), 458 (3.83)	$\text{C}_{23}\text{H}_{16}\text{N}_2\text{O}_2$	78.3 (78.3)	4.5 (4.5)	7.7 (7.9)
(c) Cl	245–247 ^d	81	1 778	269 (4.42), 299 (4.42), 505 (3.96)	$\text{C}_{22}\text{H}_{13}\text{ClN}_2\text{O}_2$	70.7 (70.8)	3.5 (3.5)	7.3 (7.5)
(d) OMe	264–266 ^c	83	1 755	269 (4.47), 297 (4.54), 449 (4.04)	$\text{C}_{23}\text{H}_{16}\text{N}_2\text{O}_3$	75.3 (75.0)	4.4 (4.3)	7.5 (7.6)

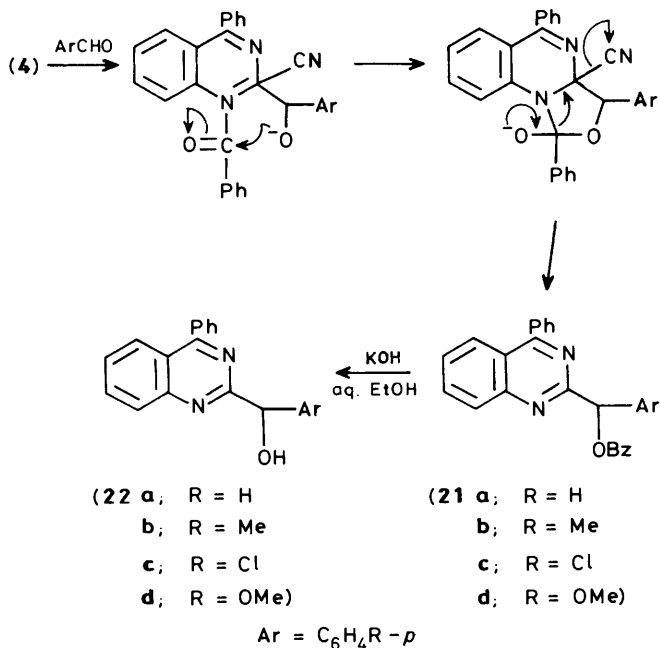
^a From CH_2Cl_2 - CH_3OH . ^b Red needles. ^c Crimson needles. ^d Orange needles.



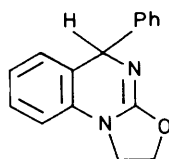
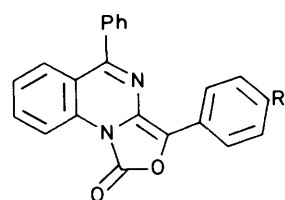
Fluoroborate and other salts of isoquinoline Reissert compounds can be isolated and have been shown to contain the oxazolo[4,3-*a*]isoquinolinium cation, e.g. compound (19);²³ they undergo cycloaddition reactions with alkenes and alkynes in high yields.^{2,24} Reissert compound salts of the diazaheterocycles phthalazine and pyridazine will undergo similar cycloaddition processes.^{24,25} Analogous procedures in the quinoline series are much less satisfactory, the hydrochloride of 1-benzoyl-1,2-dihydroquinoline-2-carbonitrile (7) in dimethylformamide undergoing cycloaddition with dimethyl acetylenedicarboxylate in only 10% yield.²⁶ With the quinazoline

system, the Reissert compound (2) gives only the salt (20).^{8a} The 1,2-dihydro-4-phenyl-1-(4-toluoyl)quinazoline-2-carbonitrile (3j) forms a yellow precipitate when stirred with fluoroboric acid in acetic acid. However, the salt could not be satisfactorily isolated and its colour was lost on contact with most solvents. Solutions in dimethoxymethane remained yellow in the cold but heating under reflux in the presence of dimethyl acetylenedicarboxylate returned only the starting Reissert compound (3j). The fluoroborate salt of 2-acetyl-1,2-dihydro-5,7-dimethoxyisoquinoline-1-carbonitrile is also reported to decompose slowly in the solid at 0 °C and rapidly in solution.²³

The condensation of the Reissert anion (4) with aromatic aldehydes proceeds smoothly, giving the esters (21) (ν_{\max} , ca. 1 718 cm^{-1}) which can be hydrolysed to the secondary alcohols (22) (ν_{\max} , ca. 3 430 cm^{-1} ; Table 2). In the n.m.r. spectrum the methine proton, obscured in (21), appears at ca. δ 6.1 in (22). Ester formation probably involves the intramolecular process shown in Scheme 3: similar behaviour occurs with quinoline²⁷ and 3,4-quinazoline Reissert compounds.^{9,10} We examined conversion of the 2-quinazolyl(aryl)methanols (22) to the little known²⁸ oxazolo[3,4-*a*]quinazoline ring system by use of

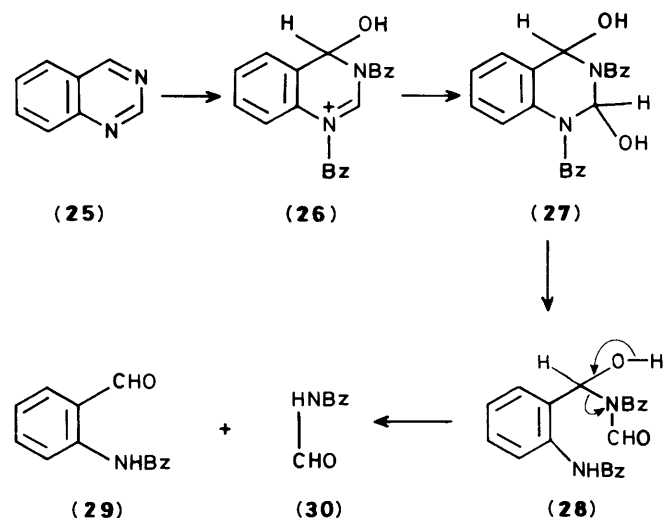


Scheme 3.



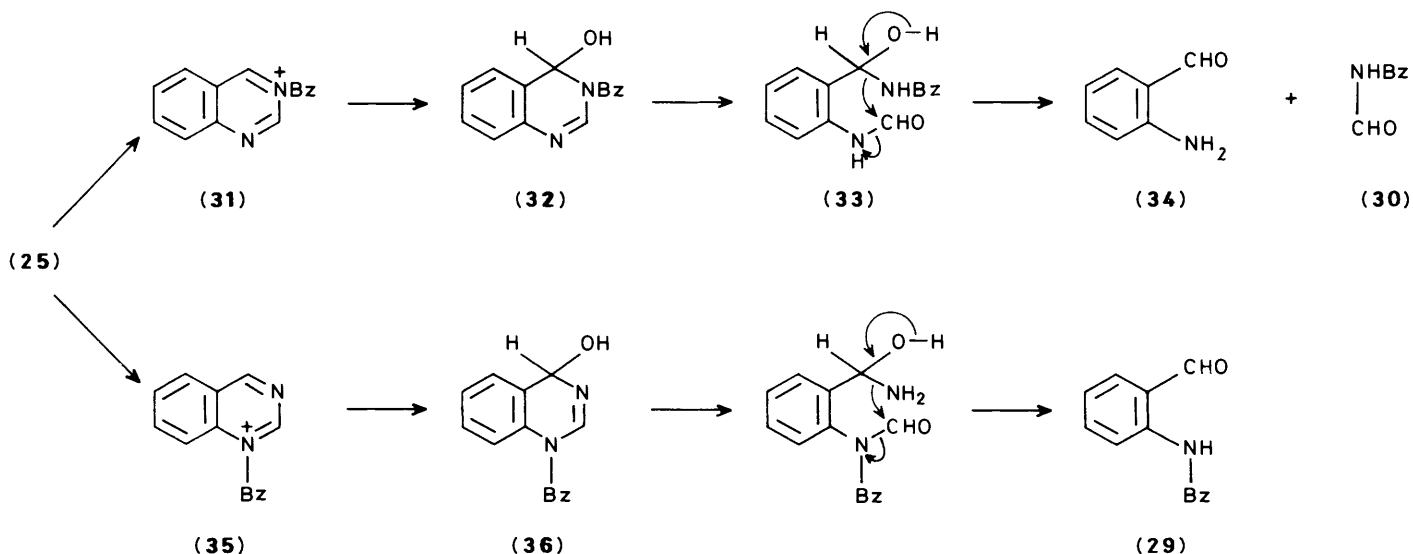
phosgene, related procedures having been observed with isoquinolylmethanols²⁹ and phthalaziny analogues.³⁰ We found that the best procedure involved addition of a solution of phosgene in ether to a mixture of the alcohol (22) in ether-dichloromethane and triethylamine at room temperature. A vigorous reaction ensues and the orange-red product (23) is

precipitated in good yield (Table 3). The product ring system is of potential interest since derivatives of the isomeric oxazolo-[3,2-*a*]quinazoline system, e.g. structure (24), show hypotensive and blood platelet aggregation inhibitory activity.¹⁹



Scheme 4.

Mention was made earlier of the failure of the Reissert reaction with quinazoline under two-phase conditions: ring opening is observed,^{3,4} with the isolation, in low yield, of 2-formylbenzanilide (29) and *N*-formylbenzamide (30) in approximately equal amounts together with a trace of *o*-aminobenzaldehyde (34).⁴ There has been some discussion⁴ of the mechanism suggested³ for this process. We proposed³ that, using a 2:1 molar ratio of benzoyl chloride to heterocycle, intermediacy of the bis-*N*-acyl pseudo base (27) may be involved, followed by cleavage of the 1,2- and 3,4-bonds (Scheme 4). Although the bonds may not necessarily cleave in this order the opening of the 1,2-bond of (27) would be somewhat analogous to that observed with quinoline on treatment with benzoyl chloride and aqueous alkali,^{3,31-34} and the breakdown of (28) would be assisted by the electron withdrawal at N-3. Higashino *et al.*,⁴ however, who used equimolar amounts of acid chloride and quinazoline, proposed cleavage of the 2,3-bond to be involved, suggesting (29) and (30) to result from two



Scheme 5.

separate pathways, (30) via the mono-*N*-benzoyl pseudo base (32), and (29) from the isomer (36) (Scheme 5). If the mechanism does proceed from (32) to (33) it is not clear what the subsequent driving force then is to convert (33) into (30). Also, 2'-formylformanilide is not isolated. Furthermore, since mono-Reissert compound formation from quinazoline results from selective addition across the 3,4-position in good yield,^{7,10} it seems unlikely that (35) would be significantly involved in ring-opening pathways. Certainly under conditions of an excess of acid chloride a second acylation of (32), at N-1 to give (26) and hence (27), would not seem unreasonable. Indeed a process analogous to this must presumably be invoked to explain the observed formation of the bis-Reissert compound (1)⁶ from quinazoline under non-aqueous conditions.

Experimental

¹H N.m.r. spectra were recorded on a Perkin-Elmer R32 instrument (90 MHz) or a Varian EM360A spectrometer (60 MHz). I.r. spectra were recorded on a Perkin-Elmer 177 grating spectrometer and u.v. spectra with a Unicam SP800 machine. Mass spectra were obtained on a Kratos MS80 spectrometer with DS-55 data system. M.p.s were taken on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was normally carried out by the flash chromatography technique³⁵ with Merck silica gel 60 for column chromatography (0.040–0.063 mm mesh). T.l.c. used plates coated with silica gel G254 (0.5 mm layers). Sodium hydride, usually a 50% dispersion in oil, was washed with dry light petroleum (b.p. 40–60 °C) before use.

4-Methylquinazoline.—A suspension of *o*-formamidoacetophenone³⁶ (8.9 g, 54 mmol) in molten ammonium acetate (90 g, 1.17 mol) was maintained at an internal temperature of 137 °C for 3 h, during the passage of ammonia gas. The resulting yellow solution was cooled, diluted with water (20 ml), and extracted with ether (3 × 100 ml). The organic extract was washed with 2M sodium hydroxide (100 ml) and dried (MgSO₄). Removal of ether and distillation of the residue gave a clear pale yellow oil (6.9 g), b.p. 98–100 °C/5 mmHg which showed two components, *R_f* 0.11 (*o*-aminoacetophenone) and 0.46 (product) when examined by t.l.c. with ethyl acetate–light petroleum (b.p. 40–60 °C) (2:3). Flash chromatography with this solvent mixture provided 4-methylquinazoline (4.7 g, 60%), m.p. 34–35 °C (lit.,³⁷ 36–37 °C); δ_H(CDCl₃) 9.20 (1 H, s, 2-H), 8.2–7.5 (4 H, m, ArH), and 2.95 (3 H, s, Me). On first isolation the product showed an OH peak at 3 400 cm⁻¹ in the i.r. spectrum which disappeared when the product was dried *in vacuo* for several days.

4-Phenylquinazoline.—*o*-Aminobenzophenone (8 g, 40 mmol), formamide (90.7 g, 80 ml, 2.01 mol), and formic acid (24.4 g, 20 ml, 0.54 mol) were heated at 150 °C for 20 min. The mixture was cooled, poured into water, and the solid filtered off, washed with water, dried, and crystallised from ethanol as shining pale yellow pearls of 4-phenylquinazoline (6.12 g, 73%), m.p. 100–101 °C (lit.,³⁸ 97 °C); δ_H(CDCl₃) 9.42 (1 H, s, 2-H), and 8.28–7.15 (9 H, m, ArH).

Trimethylsilyl Cyanide.—The method of Reetz and Chatziiosifidis³⁹ was used in which potassium cyanide, trimethylsilyl chloride, and *N*-methylpyrrolidone (mol ratio 5:5:1), were stirred with potassium iodide (0.5 mol) at room temperature for 12 h. Distillation of the mixture through a Vigreux column gave the nitrile (38%; 85% based on recovered trimethylsilyl chloride), b.p. 112–118 °C (lit.,³⁹ 112–117 °C); ν_{max}(liquid film) 2 200 (C≡N), 2 098 (N≡C), 1 265, and 850 cm⁻¹.

General Procedure for the Preparation of Quinazoline Reissert Compounds (3).—To a well stirred solution of 4-methyl or 4-phenylquinazoline (7 mmol) in dry dichloromethane (25 ml) and trimethylsilyl cyanide was added anhydrous aluminium chloride (0.05 g), followed by dropwise addition of the acid chloride in dry dichloromethane over 30 min. (Mol ratio of reagents are given in Table 1.) The pale yellow reaction mixture was stirred at room temperature for 48 h, and then washed with water, 5% hydrochloric acid, water, 5% aqueous sodium hydroxide, and water. The organic layer was dried, evaporated under reduced pressure, and the residue crystallised from the appropriate solvent (Table 1). Compounds (3a), (3c), and (3l) required further purification prior to recrystallisation, by chromatography on silica gel, eluting with light petroleum (b.p. 40–60 °C)–ethyl acetate (60:40).

Hydrolysis of Quinazoline Reissert Compounds (3).—(a) *Under basic conditions: general procedure.* The Reissert compound (0.9 mmol) in ethanol (8 ml) and aqueous potassium hydroxide (8 ml, 33%) was heated under reflux for 2 h. After cooling and dilution with water (10 ml), most of the ethanol was removed under reduced pressure and the mixture brought to pH 7 with dilute hydrochloric acid and extracted with dichloromethane (3 × 15 ml). The combined extracts were washed with water, dried (MgSO₄), and evaporated to give the product which was recrystallised. Use of 1-benzoyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (3f) in this procedure gave 4-phenylquinazoline (61%), m.p. 98–100 °C, identical with a sample prepared previously.

(b) *Under acidic conditions.* Concentrated hydrochloric acid (11 ml) was added to 1,2-dihydro-1-(4-methoxybenzoyl)-4-phenylquinazoline-2-carbonitrile (3i) (0.5 g) and 2,4-dinitrophenylhydrazine (0.5 g). The mixture was heated under reflux for 30 min and stirred at room temperature for 2 d. The orange-red precipitate was filtered off and recrystallised from dichloromethane-*t*-butyl alcohol to give 4-methoxybenzaldehyde 2,4-dinitrophenylhydrazone (0.36 g, 83%), m.p. 255–256 °C (lit.,⁴⁰ 249 °C).

2-Benzoyl-4-phenylquinazoline (6).—A 50% oil dispersion of sodium hydride (0.48 g, providing 10 mmol) was washed free of oil with dry light petroleum (b.p. 40–60 °C) and suspended in dry dimethylformamide (2 ml) in a 3-necked flask fitted with a nitrogen inlet and pressure equalising dropping funnel. The remaining exit was closed by a bubbler containing paraffin oil. 1-Benzoyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (3f) (1.7 g, 5 mmol) in dimethylformamide (10 ml) was added dropwise to the stirred suspension at room temperature. A deep red colour was generated and hydrogen gas evolved. The mixture was stirred for 6 h, poured into water, and the precipitated solid filtered off, washed with water, and dried. Column chromatography on silica gel with ethyl acetate–light petroleum (b.p. 40–60 °C) (1:4) as eluant, gave a cream solid after evaporation of solvent, which crystallised from ethyl acetate–hexane as colourless needles of 2-benzoyl-4-phenylquinazoline (6) (0.71 g, 46%), m.p. 121–122 °C (Found: C, 81.2; H, 4.5; N, 8.9. C₂₁H₁₄N₂O requires C, 81.2; H, 4.5; N, 9.0%); ν_{max}(KBr) 1 673 (C=O), 1 614, and 1 596 cm⁻¹; δ_H(CDCl₃) 8.36–7.36; *m/z* 310.1096 (*M*⁺, 68%, C₂₁H₁₄N₂O requires 310.1106), 282 (16), 105 (64, C₆H₅CO), and 77 (100, C₆H₅).

1-Benzoyl-1,2-dihydro-4-methyl-2-[(methylthio)thio-carbonyl]quinazoline-2-carbonitrile (8a).—1-Benzoyl-1,2-dihydro-4-methylquinazoline-2-carbonitrile (3a) (0.3 g, 1.1 mmol) in dimethylformamide (3 ml), was added dropwise to a well stirred suspension of potassium hydride (35% oil dispersion; 0.12 g, 1.1 mmol) in dimethylformamide (5 ml) under a nitrogen atmosphere, maintained at or below room tempera-

ture by ice cooling. Carbon disulphide (0.33 g, 4.4 mmol) was added immediately, causing the red colouration to be discharged and to leave a yellow solution. The mixture was stirred for 5 min after which methyl iodide (0.31 g, 2.2 mmol) was added, and the stirring continued for 4 h; the mixture was then poured into water. The yellow precipitate was filtered off, washed with cold water, and dried. The aqueous solution was extracted with dichloromethane (3 × 10 ml), and the combined extracts washed with water, dried (MgSO₄), and evaporated. The solid residues were combined and recrystallised from ethanol to give the title compound (**8a**) as yellow rhombs. (0.2 g, 50%), m.p. 169–170 °C (Found: C, 62.5; H, 3.8; N, 11.2. C₁₉H₁₅N₃OS₂ requires C, 62.4; H, 4.1; N, 11.4%); ν_{\max} (KBr) 1 670 (C=O) and 1 620 cm⁻¹; δ_{H} (CDCl₃) 7.9–6.4 (9 H, m), 2.73 (3 H, s, S-Me), and 2.56 (3 H, s, Me); m/z 365.0631 (M^+ , 0.29%, C₁₉H₁₅N₃OS₂ requires 365.0656) 316 (4), 234 (3, M - CN, C₆H₅CO), 188 (9), 143 (8), 105 (100, C₆H₅CO), and 77 (41, C₆H₅).

By a similar procedure the following analogues were prepared. 1-Benzoyl-1,2-dihydro-2-[(methylthio)thiocarbonyl]-4-phenylquinazoline-2-carbonitrile (**8b**) (75%), m.p. 181–183 °C (Found: C, 66.1; H, 3.9; N, 9.5. C₂₄H₁₇N₃OS₂·0.5 H₂O requires C, 66.0; H, 4.1; N, 9.6%); ν_{\max} (Nujol) 1 660 cm⁻¹ (C=O); δ_{H} (CDCl₃) 7.9–7.0 (13 H, m), 6.61 (1 H, d), and 2.64 (3 H, s, SMe); m/z 427.0803 (M^+ , 2%, C₂₄H₁₇N₃OS₂ requires 427.0812), 380 (18, M - SMe), 296 (6), 250 (6), 245 (9), 105 (100, C₆H₅CO), 91 (10, CS₂Me), and 77 (44, C₆H₅).

1-Benzoyl-2-[(ethylthio)thiocarbonyl]-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**8c**) (60%), m.p. 145–146 °C (Found: 67.8; H, 4.2; N, 9.4. C₂₅H₁₉N₂OS₂ requires C, 68.0; H, 4.3; N, 9.5%); ν_{\max} (KBr) 1 674 (C=O) and 1 604 cm⁻¹; δ_{H} (CDCl₃) 7.96–6.95 (13 H, m), 6.6 (1 H, d), 3.28 (2 H, q, CH₂), and 1.32 (3 H, t, CH₃); m/z 441.0966 (M^+ , 0.06%, C₂₅H₁₉N₂OS₂ requires 441.0969), 390 (33, M - SC₂H₅), 311 (10), 105 (100, C₆H₅CO), and 77 (61, C₆H₅).

1-Benzoyl-2-[(benzylthio)thiocarbonyl]-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**8d**) (59%), m.p. 183.5–184.5 °C (Found: C, 71.2; H, 4.3; N, 8.0. C₃₀H₂₁N₃OS₂ requires C, 71.5; H, 4.2; N, 8.3%); ν_{\max} (KBr) 1 683 (C=O) and 1 602 cm⁻¹; m/z 503.1125 (M^+ , 1%, C₃₀H₂₁N₃OS₂ requires 503.1125), 398 (12, M - C₆H₅CO), 372 (6, M - CN, C₆H₅CO), 353 (8), 250 (8), 205 (7, M - CN, CS₂CH₂C₆H₅, COC₆H₅), 105 (100, C₆H₅CO), 91 (31, C₆H₅CH₂), and 77 (48, C₆H₅).

1,2-Dihydro-1-[(methylthio)thiocarbonyl]-2-phenoxycarbonylisoquinoline-1-carbonitrile (**9**) (51%), m.p. 177–179 °C (Found: C, 62.1; H, 3.8; N, 7.4. C₁₉H₁₄N₂O₂S₂ requires C, 62.2; H, 3.8; N, 7.6%); ν_{\max} (KBr) 1 760 (C=O) and 1 660 cm⁻¹; δ_{H} (CDCl₃) 7.92 (d, 1 H), 7.55–7.15 (9 H, m), 5.93 (d, 1 H), and 2.63 (3 H, s, SCH₃).

1-Benzoyl-2-ethyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**11a**).—A mixture of 1-benzoyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**3f**) (1.01 g, 3 mmol) and benzyl bromide (0.68 g, 4 mmol) in dimethylformamide (15 ml) was added to sodium hydride (50% oil dispersion; 0.144 g, 3 mmol) in dimethylformamide (5 ml) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 1 h and then overnight at room temperature. The initial dark red colour of the anion faded to an orange-yellow. The mixture was poured into ice-cold water and the white solid which formed, during filtration, became a gum. A stable white powder was obtained by trituration of the latter with ethanol at room temperature and crystallisation of this from ethanol gave (**11a**) as colourless rhombs (0.93 g, 73%), m.p. 148.5–150 °C (Found: C, 81.5; H, 4.9; N, 9.7. C₂₅H₂₁N₃O requires C, 81.4; H, 4.9; N, 9.8%); ν_{\max} (KBr), 1 670 cm⁻¹; δ_{H} (CDCl₃) 7.9–6.8 (18 H), 6.5 (1 H, d), and 3.81 (2 H, s, CH₂); m/z 427.1667 (M^+ , 4%, C₂₅H₂₁N₃O requires 427.1684), 401 (3,

M - CN), 311 (6), 296 (5, M - COC₆H₅, CN), 295 (7), 105 (100, C₆H₅CO), and 91 (7).

By a similar procedure the following analogues were prepared. 1-Benzoyl-2-ethyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**11b**, 60%), as colourless plates from ethanol-dichloromethane, m.p. 157–159 °C (Found: C, 78.7; H, 5.1; N, 11.3. C₂₄H₁₉N₃O requires C, 78.8; H, 5.2; N, 11.5%); ν_{\max} (KBr) 1 669 cm⁻¹ (C=O); δ_{H} (CDCl₃) 7.9–7.0 (13 H), 6.6 (1 H, d), 2.5 (2 H, q, CH₂), and 1.23 (3 H, t, CH₃); m/z 365.1527 (M^+ , 3%, C₂₄H₁₉N₃O requires 365.1528), 310 (5, M - C₂H₅, CN), 234 (63, M - CN, C₆H₅CO), 233 (59), 232 (10), 205 (6, M - CN, C₂H₅, C₆H₅CO), 105 (100, C₆H₅CO), and 77 (39, C₆H₅).

1,2-Dihydro-2-methyl-1-(4-nitrobenzoyl)-4-phenylquinazoline-2-carbonitrile (**11c**) (57%), as pale yellow needles from ethanol-dichloromethane, m.p. 171–172 °C (Found: C, 69.3; H, 4.0; N, 13.8. C₂₃H₁₂N₄O₃ requires C, 69.6; H, 4.0; N, 14.1%); ν_{\max} (KBr) 1 668 (C=O) and 1 604 cm⁻¹; δ_{H} (CDCl₃) 8.28 (2 H, d), 8.0–7.1 (10 H), 6.55 (1 H), and 2.21 (3 H, s, CH₃); m/z 396.1237 (M^+ , 11%, C₂₃H₁₆N₄O₃ requires 396.1223), 319 (9, M - C₆H₅), 246 (36, M - COC₆H₄NO₂), 219 (100), 155 (33), 104 (76, COC₆H₄), and 77 (25, C₆H₅).

2-Ethyl-4-phenylquinazoline (**12a**).—Hydrolysis of 1-benzoyl-2-ethyl-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**11b**) (0.81 g, 2.4 mmol) with potassium hydroxide (7.92 g) in water (24 ml) and ethanol (24 ml) for 2 h under reflux gave (**12a**) (0.32 g, 60%) as colourless needles from ethanol, m.p. 86–87 °C (lit.,⁴¹ 83 °C); ν_{\max} (KBr) 1 616 and 1 552 cm⁻¹; δ_{H} (CDCl₃) 8.2–7.5 (9 H), 3.25 (2 H, q, CH₂), and 1.52 (3 H, t, CH₃).

2-Benzyl-4-phenylquinazoline (**12b**).—Hydrolysis of (**11a**) with potassium hydroxide in aqueous ethanol, as for (**11b**) gave (**12b**) (49%), as colourless needles from ethanol-hexane, m.p. 120–120.5 °C (Found: C, 84.8; H, 5.5; N, 9.2. C₂₁H₁₆N₂ requires C, 85.1; H, 5.4; N, 9.4%); ν_{\max} (KBr) 1 603 and 1 600 cm⁻¹; δ_{H} (CDCl₃) 8.2–7.2 (14 H) and 4.52 (2 H, s, CH₂); m/z 296.1316 (M^+ , 86%, C₂₁H₁₆N₂ requires 296.1313), 295 (100), 219 (6, M - C₆H₅), 218 (8), 91 (40, C₆H₅CH₂), and 77 (26, C₆H₅).

4a-Cyano-2,3,4,4a-tetrahydro-6-phenyl-1H-pyrido[1,2-a]-quinazolin-1-one (**13**).—1-(4-Chlorobutanoyl)-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**3l**) (0.5 g, 1.5 mmol) in dimethylformamide (10 ml) was added to a stirred suspension of sodium hydride (80% oil dispersion, 0.09 g, 3 mmol) in dimethylformamide (5 ml) at room temperature under nitrogen, and the mixture stirred overnight. The mixture was poured into water and the cream solid so formed was filtered off and passed down a column of silica gel using ethyl acetate-light petroleum (b.p. 40–60 °C) (40:60) as eluant. Removal of solvent gave an oil which, after several days, formed a solid which crystallised from ethanol as yellow rhombs of (**13**) (0.06 g, 13%), m.p. 131–133 °C (Found: C, 76.0; H, 5.2; N, 13.7. C₁₉H₁₅N₃O requires C, 75.7; H, 5.0; N, 13.9%); ν_{\max} (KBr) 2 246 (CN), 1 690 (C=O), 1 602, and 1 565 cm⁻¹; δ_{H} (CDCl₃) 8.17–7.12 (9 H) and 3.04–1.96 (6 H); m/z 301.1216 (M^+ , 16%, C₁₉H₁₅N₃O requires 301.1215), 274 (4), 273 (7), 232 (100), 205 (9), and 77 (14, C₆H₅).

5-Phenyl-12H-isoquino[2,3-a]quinazolin-12-one (**15**).—1-(2-Chloromethylbenzoyl)-1,2-dihydro-4-phenylquinazoline-2-carbonitrile (**3m**) (2.33 g, 6 mmol) in dimethylformamide (15 ml) was added to a stirred suspension of sodium hydride (80% oil dispersion; 0.21 g, 7 mmol) in dimethylformamide (5 ml) at 0 °C under nitrogen. The orange-red solution gradually became dark red and then dark yellow. The mixture was stirred at 0 °C for 2 h and then at room temperature overnight when a yellow precipitate was formed. The solid and reaction mixture were poured into cold water, the precipitate filtered off, and the filtrate extracted with dichloromethane, washed (water), and

dried (MgSO_4). Removal of solvent left a yellow oil which was combined with the solid residue and crystallised from methylene chloride-ethanol to give orange flakes of (**15**) (1.4 g, 72%), m.p. 229–230 °C (Found: C, 81.8; H, 4.3; N, 8.6. $\text{C}_{22}\text{H}_{14}\text{N}_2\text{O}_3$ requires C, 81.9; H, 4.3; N, 8.6%); λ_{max} (EtOH) 236 (log ϵ 4.69), 246sh (4.68), 270sh (4.43), 303 (4.41) and 400 nm (4.42); ν_{max} (KBr) 1 660 (C=O), 1 598, and 1 539 cm^{-1} ; δ_{H} (CDCl_3) 9.82 (1 H, d, 1-H), 8.8 (1 H, d, 11-H), 7.9–7.3 (11 H), and 7.12 (1 H, s, 7-H); m/z 322.1116 (M^+ , 100%, $\text{C}_{22}\text{H}_{14}\text{N}_2\text{O}_3$ requires 322.1106), 294 (7), 293 (16), 190 (4), 161 (7), 146 (5) and 77 (4, C_6H_5).

Phenyl 2-(4-Phenylquinazolin-2-yl)ethyl Ketone (18).—A mixture of ethyl acrylate (3 g, 30 mmol) and 1-benzoyl-1,2-dihydro-4-phenylquinazolin-2-carbonitrile (**3f**) (3.37 g, 10 mmol) in dry dimethylformamide (20 ml) was added dropwise to sodium hydride (80% dispersion in oil; 0.45 g, 15 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 1 h and overnight at room temperature, and then poured into water and neutralised. The mixture was extracted with dichloromethane (5 × 20 ml), and the extract washed with water (4 × 30 ml), dried (MgSO_4), and evaporated to give a dark brown oil. Column chromatography of this on silica gel, with ethyl acetate-light petroleum (b.p. 40–60 °C) (2:3) as eluant, gave 1-ethoxycarbonyl-2-(4-phenylquinazolin-2-yl)-propiophenone (**17**) as an oil (3.5 g, 85%) which could not be induced to crystallise; ν_{max} (film) 1 728 (C=O, ester), 1 688 (C=O, aryl ketone), 1 618, and 1 550 cm^{-1} . The oil (**17**) (0.5 g) was heated under reflux with concentrated hydrochloric acid (20 ml) for 2 h and then neutralised to give a precipitate which crystallised from ethanol to afford the title ketone (**18**) (0.3 g, 60%) as colourless needles, m.p. 154–155 °C (Found: C, 81.4; H, 5.1; N, 8.4. $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$ requires C, 81.6; H, 5.3; N, 8.2%); ν_{max} (KBr) 1 683 (C=O), 1 615, and 1 600 cm^{-1} ; δ_{H} 8.1 (2 H, d), 8.0–7.2 (12 H), and 3.72 [4 H, s, CH_2CH_2 ; signal separates into 2 × t on addition of $\text{Eu}(\text{fod})_3$]; m/z 338.1417 (M^+ , 3% $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}$ requires 338.1419), 233 (100, $M - \text{C}_6\text{H}_5\text{CO}$), 105 (15, $\text{C}_6\text{H}_5\text{CO}$), and 77 (22). Hydrolysis of (**17**) with 16% aqueous potassium hydroxide in ethanol also yielded the ketone (**18**) (30%), m.p. 154–155 °C.

α -(4-Phenylquinazolin-2-yl)benzyl Benzoate Esters (21).—*General procedure.* Sodium hydride (80% oil dispersion; 0.12 g, 4 mmol) was washed free of oil with dry light petroleum (b.p. 40–60 °C) and then under an atmosphere of nitrogen, dimethylformamide (5 ml) was added to it and the slurry cooled to 0 °C. 1-Benzoyl-1,2-dihydro-4-phenylquinazolin-2-carbonitrile (**3f**) (3 mmol) in dimethylformamide (12 ml) and the freshly distilled aromatic aldehyde (4 mmol) were added dropwise with stirring over 30 min. During addition the reaction mixture became dark red and changed gradually to a reddish brown. When the addition was complete the mixture was stirred for a further 30 min at 0 °C and then at room temperature overnight. It was then poured into ice-cold water and the solid formed was filtered off, washed water, and dried. The filtrate was neutralised with dilute hydrochloric acid, extracted with dichloromethane (4 × 10 ml), and the extract washed with water and dried (MgSO_4). The product obtained on evaporation was combined with that initially precipitated and recrystallised to give the appropriate benzoate ester (**21**) (Table 2).

Aryl(4-phenylquinazolin-2-yl)methanols (22).—*General procedure.* A mixture of α -(4-phenylquinazolin-2-yl)benzyl benzoate ester (**21**), ethanol, and aqueous potassium hydroxide (16%) was heated under reflux, in an atmosphere of nitrogen, for 3 h. Work-up in the usual manner and recrystallisation gave the appropriate methanol (**22**) (Table 2).

3-Aryl-5-phenyl-1H-oxazolo[3,4-a]quinazolin-1-ones (23).—*General procedure.* Dry ether (35 ml) was placed in a 2-necked flask fitted with an inlet tube which extended beneath the surface of the ether, and a solid CO_2 condenser (containing solid carbon dioxide in acetone) connected to an exit bubbler. With the flask cooled in ice, phosgene gas was bubbled in at a rate of three bubbles per s over 30 min. During this time ca. 4 g of phosgene was dissolved. In a separate flask the aryl(4-phenylquinazolin-2-yl)methanol (**22**) (0.2 g) was dissolved in dichloromethane (5 ml) and ether (10 ml), and triethylamine (5 ml) added. The ethereal phosgene solution was added dropwise from a pressure equalising dropping funnel to the ice-cooled methanol solution over 15 min. A vigorous reaction occurred with the evolution of white fumes and formation of a heavy orange or crimson precipitate. After being stirred overnight, the mixture was poured into ice-cold water and the precipitate filtered off. The ether layer of the filtrate was washed with water, hydrochloric acid (5%), and sodium hydrogen carbonate (8%) and then dried (MgSO_4). Evaporation gave a solid which was combined with the precipitate previously collected and recrystallised from dichloromethane-methanol to give the appropriate 3-aryl-5-phenyl-1H-oxazolo[3,4-a]quinazolin-1-one (**23**) (Table 3).

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