THE REACTION OF QUINAZOLIN-4-ONES WITH ORGANO-METALLIC AGENTS - A PERSISTENT PREFERENCE FOR RING RUPTURE OVER CYCLIZATION

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Abstract — A range of 3-substituted quinazolin-4-ones whose conjugate bases can undergo intramolecular cyclization to tricyclic systems, have been prepared (Scheme 2). The reaction of these with a variety of organolithium agents gave products arising from reagent addition to the quinazolin-4-one 1,2 bond, although experimental results tended to demonstrate that the desired conjugate bases existed in equilibrium with the tricyclic systems. The acetyl salt of 1a with NaH gave product 3c from ring fragmentation.

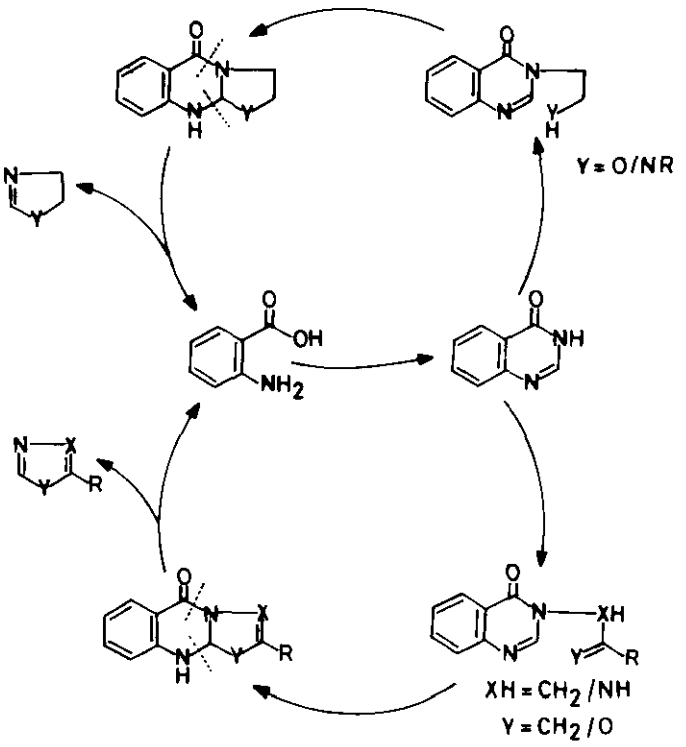
The imidazoquinazoline 8, the parent of which is markedly antihypotensive, resulted from endeavours to prepare a prototype of the desired tricyclic system by an alternate route.

Most compounds studied have more than one site for reactivity against the reagents used. The experimental results clearly highlight an overwhelming preference for addition to quinazolin-4-one 1,2 bond.

The successful chemical simulation of the salient features of the ATP-imidazole cycle involved, as the key step, the addition of a neutral, basic nitrogen function to a proximate electrophilic π system[1a,b]. Initially, this cyclization was studied, in a general manner, involving carbon, nitrogen and oxygen conjugate bases, generated in situ at the terminii of a number of specifically 3-substituted quinazolin-4-ones using organometallic reagents.

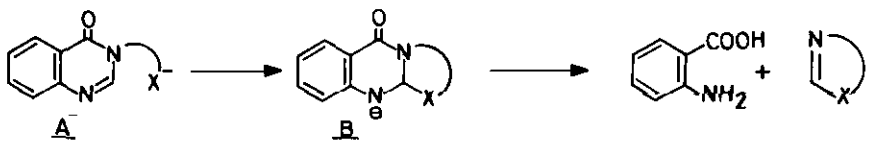
These endeavours were anticipated to delineate pathways for the template synthesis of a variety of heterocycles, as illustrated in Scheme 1.

Scheme 1



Scheme 2 summarizes the preparation of a range of specifically 3-alkylated quinazolin-4-ones from 1, which could be readily prepared from the template anthranilamide or anthranilic acid. Several of the important compounds of this series have been correlated to 3-allyl quinazolin-4-one 1a, whose site of alkylation has been independently confirmed[1a].

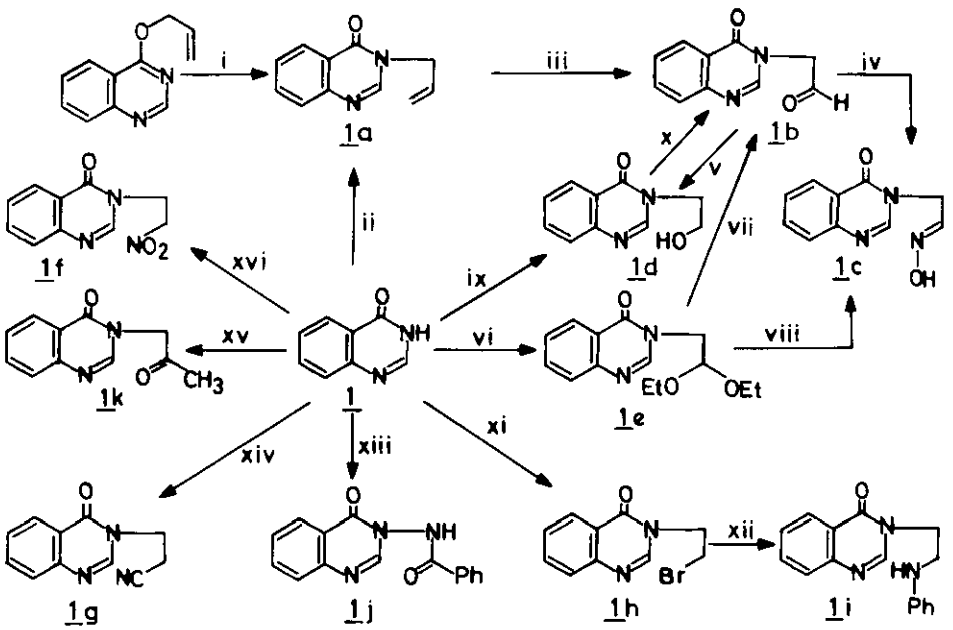
The objective for the preparation of such specifically 3-substituted quinazolin-4-ones was to take advantage of the properties of the side chain ligands -- wherever appropriate - to prepare, by intramolecular nucleophilic additions to the quinazolin-4-one 1,2-bond, tricyclic systems that could readily be transformed to template and derived products (Scheme 1).



It was anticipated that the envisaged $\underline{A}^- \rightarrow \underline{B}^-$ change would be favoured, in a number of the 3-substituted quinazolin-4-ones prepared, on account of the higher basicity of systems represented by $\underline{A}^-$ on one hand and the well known propensity exhibited by quinazolin-4-ones to 1,2 addition on the other.

3-Allyl quinazolin-4-one (1a) was chosen for extensive cyclization studies using organometallic agents, as strong bases, to generate $\underline{A}^-$. Such cyclizations, if successful, would result in a template synthesis of pyrroles (Scheme 1).

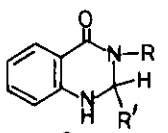
Scheme 2



i : Δ, 200°C, 1d; 75%[1a]. ii : MeOH-KOH, allylbromide, reflux 2h; 85%. iii : OsO_4 - IO_4^-, dioxan, rt, O.N; 40%. iv : $HONH_3Cl$-NaOAc, EtOH, 0.5 h reflux ; 44%. v : $NaBH_4$, MeOH, rt; 86%. vi : NaOMe-HMPT, $BrCH_2CH(OEt)_2$, 100°C, 1d; 63%. vii : conc. H_2SO_4, 90°C, 0.1 h; 74%. viii : $HONH_3Cl$-EtOH, reflux 5h; 71%. ix : NaOMe-MeOH, $BrCH_2CH_2OH$, reflux 1d; 62%. x : PCC-CH_2Cl_2, 3h, 0°C; 90%. xi : NaOMe-HMPT, $BrCH_2CH_2Br$, 60°C, 12h; 54%. xii. $PhNH_2$-EtOH, reflux 8h; 94%. xiii : H_2NNH_2, reflux, 0.25 h; PhCOCl, rt, 16h; 89%[5] xiv : $H_2C{=}CHCN$, Et_3N, MeOH, rt, 12h; 92%. xv : KOH-MeOH, $BrCH_2Ac$, rt, O.N; 50%[1a]. xvi : $H_2C{=}CHNO_2$, PhH-EtOAc, rt, 36h; 88%.

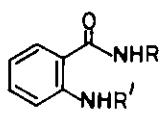
The reaction of 1a with phenyl lithium yielded none of the products arising from the conjugate base of 1a but gave compound 2a arising from 1,2 addition and the resulting hydrolysis product 3a. In order to promote the conjugate base formation and consequent cyclization, over the addition to 1,2 bond, the enhanced electrophilic system, namely, 3-allyl-4-trimethylsilyloxyquinazoline chloride (4a) and 3-allyl-4-acetoxyquinazoline chloride (4b) were prepared. The reaction of 4a with n-BuLi gave products 2b and 5a, the pattern of reaction being similar to that of 1a. It is possible that this may be due to prior de-silylation of 4a → 1a. The reaction of the acetyl salt with MeLi followed a similar pattern leading to the formation of 3b.

The cyclization attempts described above, were not successful because of the preference exhibited by the organometallic reagent for 1,2 addition over proton abstraction. Therefore, the reaction of 4b with sodium hydride - a strong base and ineffective nucleophile -- was examined. In the event, surprisingly, this reaction gave 3c in good yields[2]. The observed isomerization of the terminal π bond to an internal one present in the product 3c not only is an indication that the desired conjugate base was formed but also enables the rationalization of the 4b → 3c change as illustrated in Scheme 3.



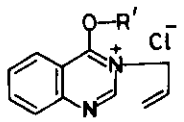
2

	R	R′
a:	$CH_2-CH=CH_2$	Ph
b:	$CH_2-CH=CH_2$	Bu^n
c:	CH_2-CH_2-OH	Ph
d:	CH_2-CH_2-OH	Bu^n
e:	H	Ph



3

	R	R′
a:	$CH_2-CH=CH_2$	H
b:	$CH_2-CH=CH_2$	$CHMe_2$
c:	$CH=CH-CH_3$	CHO



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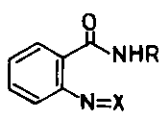
	R′
a:	$SiMe_3$
b:	$-COCH_3$



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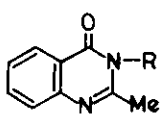
	R	X
a:	$-CH_2-CH=CH_2$	$CHBu^n$
b:	CH_2CH_2NHPh	$CHNBu^n_2$



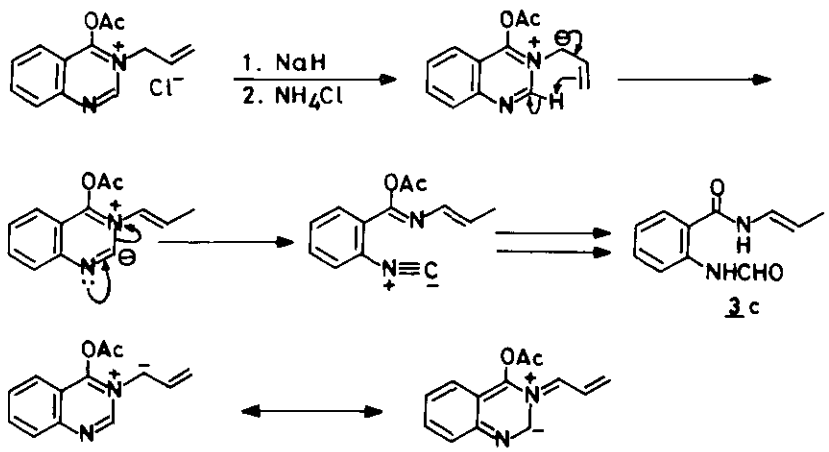
6

	R
a:	$-CH_2-CH=CH_2$

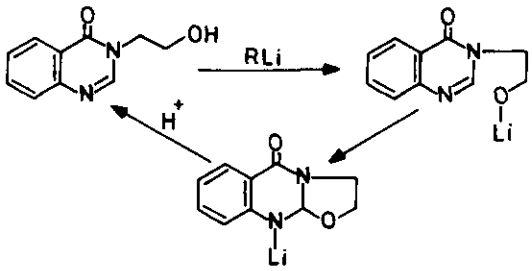
Thus, the 4b → 3c change can be understood on the basis of the preference of the conjugate base to abstract the quinazoline 2-proton rather than undergo addition to the 1-2 bond. A reason for this might be that the contributing structures would make the system less susceptible to cyclization (Scheme 3).

The reaction of phenyl lithium with the acrylonitrile adduct 1g was quite revealing. This compound offers an exceptionally large number of pathways for interaction with phenyl lithium. The important information sought in this experiment was however, the comparative ease with which phenyl lithium could add either to the quinazolin-4-one 1,2 bond - as was uniformly observed in the earlier cases -- or to the nitrile function that would lead to a template synthesis of pyrimidines. In the event however, the reaction gave a 20% yield of the quinazolin-4-one 1,2 adduct 2e and 70% of quinazolin-4-one (1). The high yield of 1, arising from a retro-Michael reaction clearly shows that the reagent functions effectively as a base, which supports the view that similar conjugate bases were generated in the reactions with 1a. Therefore, it should be possible, in principle, to discourage intermolecular addition of the organometallic reagent by blocking the 2-position and thus favour the intramolecular conjugate base cyclization. With this objective, 2-methyl-3-allylquinazolin-4-one (6a) was prepared and reacted with phenyl lithium. Surprisingly, the only product that could be obtained in the pure form from the complex mixture, was 3a, whose formation is rationalized on the basis of 1,2 addition of the reagent, ring rupture and hydrolysis during chromatography.

Scheme 3

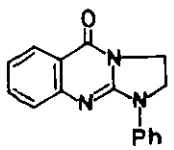


The p-TsOH mediated cyclization of 3-enamino quinazolin-4-ones provided the solution to template synthesis of imidazoles[1a,b]. During early investigations, similar cyclizations involving nitrogen conjugate bases at the terminus of 3-ligand of quinazolin-4-ones was examined. 3-(2'-Anilinoethyl)-quinazolin-4-one (1i) was considered as a proper substrate for such studies since the conjugate base generation would be easy and the anticipated cyclization can be expected to be thermodynamically quite favourable on pKa considerations (vide supra). The reaction of 1i with lithium di-n-butylamide gave none of the products arising from cyclization and related to template synthesis of imidazolines, but instead, product 5b arising from 1,2 addition of the reagent. The formation of 5b is particularly noteworthy in the sense that it represents an overwhelming preference for 1,2 addition of the lithium reagent over proton abstraction from the 3-ligand. It is possible that this might be a result of highly favourable interactions involving lithium and the 1-N of quinazolin-4-ones. To assess the significance of this, the reaction of 3-(2'-hydroxyethyl)-quinazolin-4-one (1d) with organo-lithium reagents was studied. It was anticipated, that the reagent would exhibit a preference for proton abstraction over 1,2 addition. The -OLi compound thus generated could then undergo intramolecular 1,2 addition resulting in the formation of the lithium salt of the desired tricyclic system. In the event, the reaction of 1d with either phenyl lithium or n-BuLi gave the 1,2 adducts 2c and 2d in 34% and 43% yield respectively. Of significance however, was the finding that nearly half of the starting material was recovered in each case although adequate amount of the reagent was used. This result would imply that the organo-lithium reagents here function both as nucleophiles and bases. It would also imply that the formation of the -OLi compound is able to prevent addition to the 1,2 bond. These conclusions could be understood on the basis of the formation of the desired tricyclic systems which revert to the starting material 1d on acidification.



Parenthetically, whilst most of the endeavours outlined above highlighted the persistent preference for addition to the 1,2 bond of quinazolin-4-one, exactly opposite behaviour was exhibited by the interesting tricyclic quinazolin-4-one 7. It was anticipated that compound 7 -- prepared by the known procedure[3] from 2,4-dichloro quinazoline -- could undergo reduction of the C=N bond. The resulting tricyclic compound would be the same as sought earlier via cyclization of 1i and which could be processed to the parent and derived imidazoline.

In the event, conditions that are normally employed for the reduction of the 1,2 bond of quinazolin-4-ones failed. Thus, attempted reduction of 7 with B_2H_6 -THF, B_2H_6 -BF_3THF, $NaBH_4$, catalytic hydrogenation, reduction of either the trimethylsilyl or acetyl salt of 7 failed. Under forcing conditions involving treatment of $AlCl_3$ complex of 7 with $NaBH_4$ in diglyme at 85°C, the 1,2 bond survived but the 4-oxo grouping was completely reduced to yield the interesting tricyclic system 8[4] in 83% yield. Finally, the reaction of 7 with phenyl lithium -- a reagent that was quite effective in addition to quinazolin-4-one. 1,2 bond -- gave product 9, again resulting from addition to the 4-oxo grouping.



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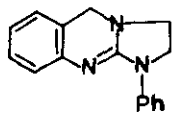

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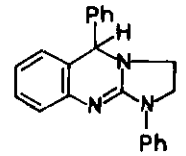

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Apart from the synthesis and characterization of a number of 3-substituted quinazolin-4-ones (Scheme 2), the work reported in this paper is of value for several reasons. Most of the compounds encountered here have more than one site for reactivity against a particular reagent. The experimental results clearly highlight an overwhelming preference for addition to the 1,2 bond. Conjugate base formation involving the 3-ligand has been established although the demonstration of its addition to the 1,2 bond in an intramolecular manner could not be accomplished. Convincing evidence for the involvement of such intermediates have however been obtained.

EXPERIMENTAL[6]

The Reaction of Quinazolin-4-one(1) with Allyl Bromide : Preparation of 3-Allylquinazolin-4-one (1a) :

Allyl bromide (1.3g, 11 mmol) was added to a solution of the potassium salt of 1[8] in MeOH-prepared from 0.45 M KOH (20 ml) and 1 (1.2g, 8.2 mmol) - the resulting solution refluxed for 2 h, evaporated, triturated with dry benzene, the organic extract passed through a column of basic alumina evaporated and crystallized from hot hexane to give 1.3g (85%) of 1a, mp 65°C (lit.[7] mp 65°C) ; IR ν_{max} (KBr) cm^{-1} 1675, 1615, 1570; NMR δ ($CDCl_3$) 4.55 (m, 2H), 5.18 (m, 2H), 5.88 (m, 1H), 7.2-7.7 (m, 3H), 7.9 (s, 1H), 8.1 (m, 1H).

The Reaction of 3-Allylquinazolin-4-one (1a) with OsO_4- IO_4^- : Isolation of 3-(2'-Oxoethyl)-quinazolin-4-one (1b) :

Under stirring and protection from light, OsO_4 (0.065g, 0.25 mmol) was added to a solution of 1a (1.0g, 5.4 mmol) in dry dioxan (20 ml). The reaction mixture was left stirred for 0.75 h,

the resulting brown solution admixed with, in drops, over 2.5 h, a solution of $NaIO_4$ (2.25 g, 10 mmol) in distilled water (20 ml), left stirred over night, filtered, the filtrate extracted with ethyl acetate (3 x 50 ml), dried, evaporated and the residue on crystallization from hexane-EtOAc gave 0.4g (40%) of 1b, mp 152°C; (Found : C, 63.88; H, 4.65; N, 14.70. Anal. Calc. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.25; N, 14.89%) ; IR ν_{max} (KBr) cm^{-1} 1720, 1675.

The Reaction of 3-(2'-Oxoethyl)-quinazolin-4-one (1b) with Hydroxylamine : Isolation of Oxime 1c

A solution of the aldehyde 1b (0.05g, 0.27 mmol) in 95% ethanol (5 ml) was admixed with hydroxylamine reagent solution - prepared from saturated aqueous solutions of hydroxylamine hydrochloride (0.027g, 0.4 mmol) and NaOAc (0.048g, 0.54 mmol) - the reaction mixture refluxed for 0.5 h, solvents evaporated, the residue triturated with water, filtered, washed with cold water and dried to give, 0.024g, (45%) of oxime 1c, mp 163-164°C; (Found : C, 59.13; H, 4.05. Anal. Calc. for $C_{10}H_9N_3O_2$: C, 59.11 ; H, 4.43%); IR ν_{max} (KBr) cm^{-1} 1680, 1615, 1515; NMR δ (DMSO-d_6) 200 MHz : 4.75 (d, d, 2H), 6.88, 7.5 (t,t, 1H), 7.5 (m, 1H), 7.65 (d, 1H), 7.8 (t, 1H), 8.15 (d, 1H), 8.35 (d, 1H), 11.0, 11.35 (s,s, 1H); m/z 203 (M^+).

The Reaction of 3-(2'-Oxoethyl)-quinazolin-4-one(1b) with $NaBH_4$: Isolation of 3-(2'-Hydroxyethyl)-Quinazolin-4-one (1d) :

Under ice-cooling and stirring, $NaBH_4$ (0.315g, 8.5 mmol) was added to the aldehyde 1b (0.780g, 4 mmol) in dry methanol (20 ml), then admixed with AcOH (0.25 ml), evaporated and chromatographed on silica gel. Elution with EtOAc gave 0.675g (86%) of 1d, mp 157°C (lit.[9] mp 155°C); IR ν_{max} (KBr) cm^{-1} 3250, 1670, 1610, 1560 : NMR δ (DMSO-d_6) 500 MHz : 3.7 (2H), 4.05 (2H), 4.9 (1H); 7.5-8.3 (5H).

The Reaction of Quinazolin-4-one (1) with Bromoethanol : Preparation of 3-(2'-Hydroxyethyl)-quinazolin-4-one (1d) :

Bromoethanol (2.75g, 21 mmol) was added to a solution of sodium salt of 1 in MeOH - prepared from 0.4 M NaOMe (50 ml) and 1 (2.92g, 20 mmol) - the reaction mixture refluxed for 24 h, evaporated, the residue admixed with water (150 ml), saturated with NaCl, extracted with ethyl acetate (3 x 100 ml), washed with NaOH solution (5%, 100 ml), dried and evaporated to give 2.35 g (62%) of 1d, mp 157°C (lit.[9] mp 155°C). This compound was identical to sample obtained from experiment described above.

The Reaction of Quinazolin-4-one (1) with 2-Bromo-1, 1-diethoxyethane : Preparation of 3-(2'-Diethoxyethyl)- quinazolin-4-one (1e) :

2-Bromo-1,1-diethoxyethane (1.52g, 7.7 mmol) was added to a solution of the sodium salt of 1 in HMPT - prepared from 1.4 M NaOMe (10 ml) and 1 (2.0g, 13.7 mmol) - the mixture left stirred at 100-120°C for 24 h, cooled, poured onto water (300 ml), extracted with hexane

(3 x 150 ml), washed with water, dried and evaporated to give 2.25g (63%) of 1e, mp 79°C (Found : C, 64.02; H, 6.45. Anal. Calc. for $C_{14}H_{18}N_2O_3$: C, 64.18; H, 6.87%) ; IR ν_{max} (KBr) cm^{-1} 1680, 1615, 1565; NMR δ ($CDCl_3$) 1.15 (t, 6H), 3.58 (m, 4H), 4.0 (d, 2H), 4.65 (t, 1H), 7.1-7.7 (m, 3H), 7.95 (s, 1H), 8.15 (d, 1H).

Hydrolysis of 3-(2'-Diethoxyethyl)-quinazolin-4-one (1e) : Isolation of 3-(2'-Oxoethyl)-quinazolin-4-one (1b) :

Compound 1e (3g, 11.4 mmol) was gradually added to cold conc. H_2SO_4 (5 ml), warmed to 80-90°C for 0.1 h, cooled, poured onto crushed ice ($\sim$ 100g), adjusted to pH $\sim$ 7.5 with aqueous NH_3, saturated with NaCl, extracted with EtOAc (3 x 150 ml), the organic extract passed through a short column of silica gel and evaporated to give 1.6g (71%) of 1b mp 152°C, whose properties were identical to sample obtained from reaction of 1a with OsO_4 - IO_4^-.

The Reaction of the Acetal 1e with $NH_2OH.HCl$: Direct Preparation of Oxime 1c :

A stirred solution of the acetal 1e (1.0g, 3.8 mmol) in ethanol (10 ml) was admixed with aqueous $NH_2OH.HCl$ (0.53g, 7.6 mmol, 10 ml), refluxed for 5 h -during which 1e was consumed (tlc) -- concentrated, cooled, filtered, washed with ice-cold water (3 x 10 ml), dried and crystallized from hot EtOAc to give 0.55g (71%) of oxime 1c, mp 163-164°C whose properties were identical to the sample obtained by reaction of 1b with hydroxylamine.

The Reaction of Quinazolin-4-one (1) with 1,2-Dibromoethane : Preparation of 3-(2'-Bromoethyl)-quinazolin-4-one (1h) :

1,2-Dibromoethane (7.63g, 40.6 mmol) was added to a solution of the sodium salt of 1 in HMPT-prepared from 0.7 M NaOMe (25 ml) and 1 (5.84g, 40 mmol), the reaction mixture stirred at room temperature for 12 h, then at 60°C for 12 h, cooled, poured onto ice-water (11), filtered, the residue washed with cold water, dried and crystallized from benzene-hexane to give 4.66g (46%) of 1h, mp 116°C (lit.[10] mp 114°C); IR ν_{max} (KBr) cm^{-1} 1670, 1620, 1610, 1560; NMR δ ($CDCl_3$) 3.7 (t, 2H), 4.35 (t, 2H), 7.2-7.8 (m, 3H), 8.05 (s, 1H), 8.2 (m, 1H).

The Reaction of 3-(2'Bromoethyl)-quinazolin-4-one (1h) with Aniline : Preparation of 3-(2'-Anilinoethyl)-quinazolin-4-one (1i) :

A mixture of 1h (0.253g, 1 mmol) and aniline (0.186g, 2 mmol) in abs. ethanol (25 ml) was refluxed for 8 h, evaporated, residue admixed with water (15 ml), extracted with benzene (3 x 25 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (7 : 3) gave 0.25g (94%) of 1i, mp 143-145°C (Found : C, 72.85; H, 5.61. Anal. Calc. for $C_{16}H_{15}N_3O$: C, 72.45; H, 5.66%); IR ν_{max} (KBr) cm^{-1} 3260, 1675, 1600, 1560; NMR δ ($CDCl_3$) 3.5 (m, 2H), 4.2 (m, 3H), 6.4-6.78 (m, 8H), 7.85 (s, 1H), 8.25 (m, 1H).

The Reaction of Quinazolin-4-one (1) with Acrylonitrile : Preparation of 3-(2'-Cyanoethyl)-quinazolin-4-one (1g) :

Under stirring and protection from moisture, a solution of 1 (5.0g, 34.2 mmol) in dry methanol (100 ml) was admixed with triethylamine (5 ml, 36 mmol) followed by acrylonitrile (5 ml, 76 mmol), left stirred at room temperature for 12 h, filtered, washed with chilled dry methanol (3 x 25 ml), dried and crystallized from benzene-hexane to give 6.264g (92%) of 1g, mp 144-145°C (lit.[11] mp 136-138°C); IR ν_{max} (KBr) cm^{-1} 2250, 1670, 1610; NMR δ ($CDCl_3$) 2.85 (t, 2H), 4.2 (t, 2H), 7.5 (m, 3H), 8.1 (s, 1H), 8.25 (m, 1H).

The Reaction of Quinazolin-4-one (1) with Nitroethylene : Preparation of 3-(2'-Nitroethyl)-quinazolin-4-one (1f) :

A 10% solution of nitroethylene in benzene (10 ml, 13.6 mmol) was added over 0.75 h to a stirred and ice-cooled solution of 1 (1.0g, 6.8 mmol) in dry EtOAc (150 ml), left stirred at room temperature for 36 h, solvents evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (9 : 1) gave 1.32g (88%) of 1f, mp 118-119°C (Found : C, 54.8; H, 4.32; N, 19.42. Anal. Calc. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.11; N, 19.16%); IR ν_{max} (KBr) cm^{-1} 1660, 1615, 1550, 1355; NMR δ ($CDCl_3$) 500 MHz : 4.54 (t, 2H), 4.88 (t, 2H), 7.53, 7.78 (t,t,1H,1H), 7.72 (d, 1H), 8.1 (s, 1H), 8.28 (d, 1H); m/z 219 (M^+).

The Reaction of 3-Allylquinazolin-4-one (1a) with PhLi : Isolation of Anthranilallylamide (3a) and 2-Phenyl-3-allyl-1,2,3,4-tetrahydroquinazolin-4-one (2a) :

Under nitrogen, ethereal PhLi (0.6 M, 20 ml) was added in drops to an ice-cooled and stirred solution of 1a (1.86g, 10 mmol) in dry ether (50 ml), the reaction mixture left stirred overnight, poured onto cold saturated NH_4Cl, extracted with ether (3 x 50 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (9 : 1) gave 1.0g (35%) of 2a, mp 129-130°C; IR ν_{max} (KBr) cm^{-1} 3300, 1630; NMR δ ($CDCl_3$) 4.5-5.2 (m, 4H), 5.65 (d, 1H), 6.4 (m, 1H), 6.75 (m, 1H), 7.0 (d, 1H), 7.2 (s, 5H), 7.8 (d, 1H); m/z 264 (M^+), 223 ($M^+ - CH_2-CH=CH_2$).

Further elution with benzene : EtOAc (4 : 1) gave 0.2g (8%) of 3a, mp 95-97°C (lit.[12] mp 92-93°C); IR ν_{max} (KBr) cm^{-1} 3440, 3320, 1620, 1590; NMR δ ($CDCl_3$) 4.0 (m, 2H), 5.2 (m, 2H), 6.0 (m, 1H), 6.3-7.3 (m, 4H); m/z 176 (M^+).

The Reaction of 3-Allyl-4-trimethylsilyloxyquinazoline Chloride (4a) with n-BuLi : Isolation of 2-n-Butyl-3-allyl-1,2,3,4-tetrahydroquinazolin-4-one (2b) and n-Pentylideneaminoanthranilallylamide (5a) :

Trimethylsilyl chloride (8.64g, 80 mmol) was added in drops to a stirred and ice-cooled solution of 1a (3.0g, 21 mmol) in dry ether (200 ml), the reaction mixture left stirred for 2h, filtered, residue washed with dry ether (3 x 25 ml) and dried to give 3-allyl-4-trimethylsilyloxy quinazoline chloride (4a), 4.7g (99%) mp 160°C; IR ν_{max} (KBr) cm^{-1} 2600 (br), 1610, 1580, 1550, 960, 900; m/z 186 ($M^+ - Me_3SiCl$).

Under nitrogen, ethereal n-BuLi (0.9 M, 18 ml) was added in drops to an ice-cooled and stirred

suspension of 4a (4.5g, 15 mmol) in dry ether (100 ml), the reaction mixture left stirred for 1 h, poured onto saturated NH_4Cl solution, extracted with EtOAc (3 x 50 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (9 : 1) gave 0.615g (17%) of 2b as a thick viscous liquid, bp 160°C /0.2 torr; IR ν_{max}(neat) cm^{-1} 3340, 2960, 2920, 2860, 1690, 1650, 1580; NMR $\delta(CDCl_3)$ 0.8-1.9 (m, 9H), 4.0 (m, 2H), 5.2 (m, 2H), 5.6-6.2 (m, 2H), 7-7.6 (m, 4H).

Further elution with benzene : EtOAc (9 : 1) gave 0.650g (18%) of 5a as a viscous liquid, bp 190°C/0.2 torr, IR ν_{max} (neat) cm^{-1} 3320, 2960, 2930, 2860, 1640 (br); NMR δ $(CDCl_3)$ 0.8-1.9 (m, 9H), 4.5 (m, 2H), 5.2 (m, 2H), 5.9 (m, 1H), 6.4-8.0 (m, 6H).

The Reaction of 3-Allyl-4-acetoxyquinazoline Chloride (4b) with MeLi : Isolation of N, N-Dimethylaminoanthranilallylamide (3b) :

Acetyl chloride (15 ml) was added in drops to a stirred and ice-cooled solution of 1a (1.0g, 6.85 mmol) in dry ether (30 ml), the reaction mixture left stirred for 2 h, evaporated, the residue washed with dry ether and dried to give 3-allyl-4-acetoxyquinazoline chloride (4b) 1.4g (98%) as a white powdery solid, mp 145-150°C (Found : C, 58.91; H, 4.88; N, 10.70. Anal. Calc. for $C_{13}H_{13}N_2O_2Cl$: C, 58.97; H, 4.91; N, 10.58%); IR ν_{max} (KBr) cm^{-1} 2640 (br), 1715.

Under nitrogen, 4b (1.28g, 4.85 mmol) was added to stirred and ice-cooled ethereal MeLi (0.5 M, 20 ml), the reaction mixture left stirred for 8 h, poured onto saturated NH_4Cl solution extracted with EtOAc (3 x 50 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (9 : 1) gave 0.23g (42%) of 3b, bp 110°C/0.3 torr (Found : C, 71.30; H, 8.20. Anal. Calc. for $C_{13}H_{18}N_2O$: C, 71.56; H, 8.26%); IR ν_{max} (neat) cm^{-1} 3340, 3090, 1630, 1580, 1520; NMR δ $(CDCl_3)$ 200 MHz : 1.1 (d, 6H), 3.5 (m, 1H), 3.86 (m, 2H), 5.1 (m, 2H), 5.8 (m, 1H), 6.22 (br, 1H), 6.42 (t, 1H), 6.62 (t, 1H), 7.15 (m, 1H), 7.25 (d, 1H); m/z 218 (M^+).

The Reaction of 3-Allyl-4-acetoxyquinazoline Chloride (4b) with NaH : Isolation of N-Formylanthranilpropenylamide (3c) :

Under nitrogen, NaH (1.04g, 50% suspension in mineral oil, 22 mmol) was added to a suspension of acetyl salt 4b (1.4g, 5.3 mmol) in dry DME (100 ml) at room temperature, the reaction mixture refluxed for 12 h, cooled, poured onto saturated NH_4Cl solution, extracted with EtOAc (3 x 50 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (9 : 1) gave 0.404g (69%) of 3c, mp 109-111°C. IR ν_{max} (KBr) cm^{-1} 3300, 1670, 1640, 1600, 1580, 1525; NMR $\delta(CDCl_3)$ 200 MHz : 1.63 (dd, 3H), 4.9 (q, 1H), 6.7 (m, 1H), 6.98 (t, 1H), 7.35 (m, 2H), 7.95 (d, 1H), 8.25 (d, 1H), 8.38 (d, 1H); m/z 204 (M^+).

The Reaction of 3-(2'-Cyanoethyl)-quinazolin-4-one (1g) with PhLi : Isolation of 2-Phenyl-1, 2,3,4-tetrahydroquinazolin-4-one (2e) and Quinazolin-4-one (1) :

Under nitrogen, ethereal PhLi (0.6 M, 50 ml) was added, in drops, to a stirred and ice-cooled solution of 1g (3.0g, 15 mmol) in dry THF (50 ml), the reaction mixture left stirred for 12 h, poured onto saturated NH_4Cl solution, extracted with EtOAc (3 x 75 ml), dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (3 : 2) gave 0.625g (19%) of 2e, mp 228°C (lit.[13] mp 228°C); IR ν_{max} (KBr) cm^{-1} 3300, 3200, 1670, 1620, 1510; NMR δ (DMSO-d_6) 500 MHz: 5.72 (m, 1H), 6.7-7.65 (m, 10H), 8.22 (d, 1H); m/z 224 (M^+). Further elution with benzene : EtOAc (1 : 4) gave 1.28g (66%) of 1, mp 214°C (lit.[8] mp 216°C).

The Reaction of 2-Methyl-3-allylquinazolin-4-one (6a) with PhLi : Isolation of Anthranilallylamide (3a) :

Allyl bromide (13.98g, 114 mmol) was added to a stirred solution of the potassium salt of 2-methyl-quinazolin-4-one[14] in MeOH - prepared from 1.6 M KOH (50 ml) and 2-methyl quinazolin-4-one (10.8 g, 67.5 mmol) - the resulting solution refluxed for 2 h, evaporated, triturated with dry benzene, the organic extract passed through a short column of basic alumina, evaporated and crystallized from hot hexane to give 2-methyl-3-allyl quinazolin-4-one (6a), 6g (45%), mp 79-80°C (lit.[15] mp 80-81°C); IR ν_{max} (KBr) cm^{-1} 1660, 1585, 1560; NMR δ ($CDCl_3$) 2.5 (s, 3H), 4.67 (m, 2H), 5.2 (m, 2H), 5.7 (m, 1H), 7.1-8.3 (m, 4H).

Under nitrogen, ethereal PhLi (0.1 M, 10 ml) was added in drops to a stirred, ice-cooled solution of 6a (1.0g, 5 mmol) in dry THF (50 ml), the reaction mixture left stirred for 8 h, neutralized with 2N H_2SO_4, extracted with EtOAc (3 x 50 ml), dried, evaporated and chromatographed on silica gel. Elution with benzene : EtOAc (9 :1) gave 0.073g (8%) of 3a mp 95°C. This compound was found to be identical in all respects to the sample obtained from reaction of 1a with PhLi.

The Reaction of 3-(2'-Anilinoethyl)-quinazolin-4-one (1i) with Lithium di-n-Butylamide : Isolation of di-n-Butylaminomethenylanthranil (2'-Anilinoethyl) amide (5b) :

Under nitrogen, a solution of 1i (0.9g, 3.4 mmol) in dry ether (25 ml) was added in drops to a stirred and ice-cooled, ethereal 0.35M Lithium di-n-butylamide (20 ml), the reaction mixture left stirred overnight, poured onto saturated NH_4Cl solution, extracted with ether, dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (4 : 1) gave 0.325g (26%) of 5b as a syrup. IR ν_{max} (neat) cm^{-1} 3350, 2960, 2920, 2860, 1670; NMR δ (DMSO-d_6) 0.6-1.7 (m, 14H), 3.2 (m, 6H), 3.55 (t, 2H), 6.2-8.2 (m, 5H).

The Reaction of 3-(2'-Hydroxyethyl)-quinazolin-4-one (1d) with PhLi : Isolation of 2-Phenyl 3-(2'-Hydroxyethyl)-1 ,2,3,4-tetrahydroquinazolin-4-one (2c) :

Under nitrogen, ethereal PhLi (0.6 M, 35 ml) was added in drops to a solution of 1d (3.0g, 16 mmol) in dry THF (100 ml), the reaction mixture left stirred for 5 h, poured onto saturated NaCl solution, extracted with ether (2 x 100 ml), dried, evaporated and the residue chromato-

graphed on silica gel. Elution with benzene : EtOAc (2 : 3) gave 0.73g (34%) of 2c, mp 115-116°C (Found : C, 71.8; H, 6.22; N; 10.81. Anal. Calc. for $C_{16}H_{16}N_2O_2$: C, 71.64; H, 5.97; N, 10.44%); IR ν_{max} (KBr) cm^{-1} 3400, 3320, 1620, 1620, 1610, 1580; NMR δ ($CDCl_3$) 3.1 (m, 2H), 3.6 (m, 3H), 4.8 (br, 1H), 5.8 (d, 1H), 6.4 (m, 1H), 6.8 (m, 1H), 7.1 (m, 1H), 7.3 (s, 5H), 7.85 (dd, 1H); m/z 268 (M^+). Further elution with benzene : EtOAc (3 : 7) gave 1.48g (48%) of unreacted 1d.

The Reaction of 3-(2'-Hydroxyethyl)-quinazolin-4-one (1d) with n-BuLi : Isolation of 2-n-Butyl-3-(2'-hydroxyethyl)-1,2,3,4-tetrahydroquinazolin-4-one (2d) :

Under nitrogen, ethereal n-BuLi (0.55 M, 60 ml) was added in drops, to a solution of 1d (3.0g, 16.0 mmol) in dry THF (50 ml), the reaction mixture left stirred overnight, poured onto saturated NH_4Cl, extracted with EtOAc, dried, evaporated and the residue chromatographed on silica gel. Elution with benzene : EtOAc (2 : 3) gave 0.79g (43%) of 2d, as a white crystalline solid, mp 94-95°C (Found : C, 68.03; H, 7.76; N, 11.32. Anal. Calc. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.06; N, 11.29%); IR ν_{max} (KBr) cm^{-1} 3300, 2950, 2800, 1630, 1570; NMR δ ($CDCl_3$) 500 MHz :0.86 (t, 3H), 1.25 (m, 4H), 1.65, 1.85 (m,m,2H), 3.18 (br, 1H), 3.63 (br, 1H), 4.65 (m, 2H), 6.65 (d, 1H), 6.84 (t, 1H), 7.25 (m, 1H), 7.85 (d, 1H), 3.8 (m, 2H), 4.0 (m, 1H). Further elution with benzene : EtOAc (3 : 7) gave 1.56g (53%) of unreacted 1d.

The Reaction of 1-Phenyl-1,2,3,5-tetrahydro-5-oxoimidazo [2,1-b] quinazoline (7) with $NaBH_4$-$AlCl_3$: Isolation of 1-Phenyl-1,2,3,5-tetrahydroimidazo [2,1-b] quinazoline (8) :

A solution of the $AlCl_3$ complex of 7[16] - prepared by addition of $AlCl_3$ (0.66g, 5 mmol) over 0.5 h to a stirred and cooled (0°C) solution of 7 (1.31g, 5 mmol) in dry diglyme (125 ml) - was added in drops to a solution of $NaBH_4$ (0.95g, 25 mmol) in dry diglyme. The reaction mixture was left stirred at 85°C for 1.5 h, cooled, admixed with water (30 ml) then with conc. HCl (0.5 ml), evaporated, triturated with EtOAc, adjusted to pH ~ 9 with aqueous NH_4OH, the white solid separated, filtered, washed with distilled water, dried and crystallized from benzene to give 1.1g (83%) of 8 as colourless prisms mp 188-189°C; IR ν_{max} (KBr) cm^{-1} 1620, 1580, 1560; NMR δ ($CDCl_3$) 3.2 (m, 2H), 3.7 (m, 2H), 4.2 (s, 2H), 6.7-7.4 (m, 8H), 7.75 (dd, 1H); m/z 249 (M^+).

The Reaction of 7 with PhLi : Isolation of 1,5-Diphenyl-1,2,3,5-tetrahydroimidazo[2,1-b]-quinazoline (9) :

Under nitrogen, ethereal PhLi (1.3 M, 0.8 ml) was added to a solution of 7 (0.131g, 0.5 mmol) in dry THF (15 ml), the reaction mixture left stirred for 2 h, poured onto saturated NH_4Cl solution, extracted with CH_2Cl_2, dried, evaporated, the residue triturated with dry ether, hot dry benzene and crystallized from MeOH to give 0.14g (88%) of 9, mp 193-195°C; IR ν_{max} (KBr) cm^{-1} 3030, 1630, 1570; NMR δ ($CDCl_3$+ DMSO-d_6)3.3 (m, 2H), 3.75 (m, 2H), 6.5-8.0 (m, 15H); m/z 325 (M^+).

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