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SYNTHESIS OF QUINAZOLINES

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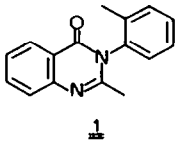
Abstract - Grignard reagents reacted with 2-aminobenzonitrile to give the intermediate (10), which readily could be cyclized to quinazolines by reaction with carbonyl compounds (e.g. acid chlorides, anhydrides, formates and oxalates). The intermediate (10) and aldehydes, e.g. benzaldehyde, gave 1,2-dihydroquinazolines, which readily underwent dehydrogenation.
The intermediate (10) reacted readily with chloroformate to give 4-phenyl-2-quinazolinone, which could be reduced to 3,4-dihydro-4-phenyl-2-quinazolinone by sodium borohydride in acetic acid.

In spite of the fact that a vast number of quinazolines has been synthesized in connection with the evaluation of drugs such as methaqualone (1), quinazodine (2) and proquazone (3) and studies of natural products such as febrifugin (4) and vasicinon (5), there is only a relatively limited number of nonfunctional quinazolines (e.g. 6) known.[1-6]



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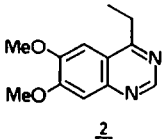

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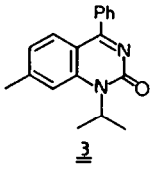

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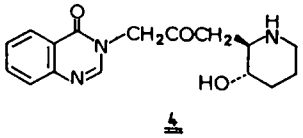

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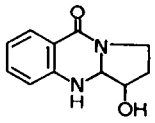

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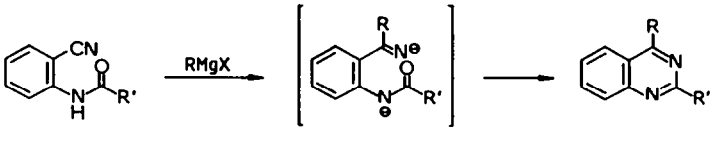
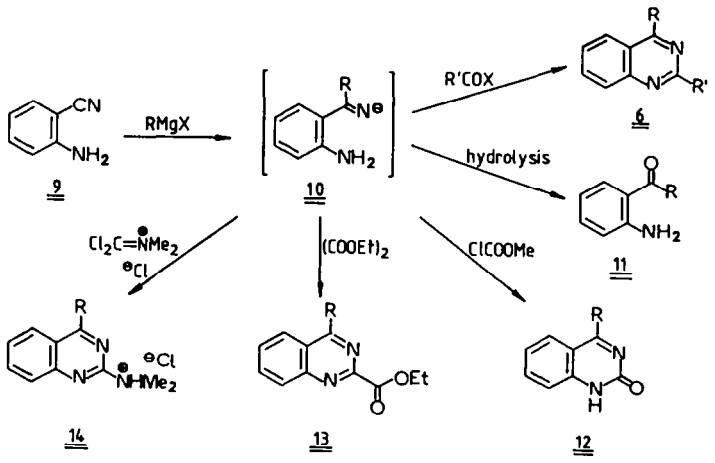
6

The available synthetic methods e.g. the Meerwein cyclization, have a limited scope or do require a relatively high input of experimental manipulations. The most general procedure, the Bischler cyclization, involves acylation of an 2-aminoacylbenzene followed by heating (200 °C) with ammonia in a sealed tube. In this paper[7] we report a complementary synthesis (in two variants, Scheme 1 and 2) using anthranilonitriles as starting material.



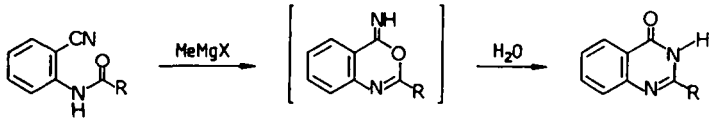
7 8 6

Scheme 1



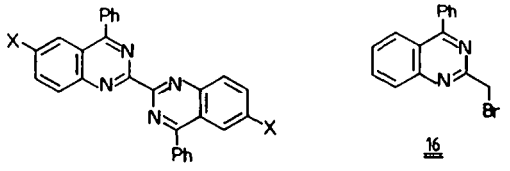
Scheme 2

Results and Discussion - 2-Aminobenzonitrile (anthranilonitrile) is nowadays readily available by reaction of 2-nitrotoluene with ammonia in vapour phase[8] and by ammoxidation[9] of o-toluidine and related processes.[10] Hence this interesting bifunctional compound has gained importance as a starting material in organic synthesis. Ketones of the type $RCOC_6H_4$-o-NH_2, can be prepared[11-15] in reasonable yields by addition of RMgX to anthranilonitrile followed by hydrolysis (Scheme 2). The intermediate (10) in this synthesis has now been found to be a suitable precursor for quinazolines (Table 1). The reaction time in the first step should be relatively short, 2.5 h (for C_6H_5MgBr) and 45 min (for C_2H_5MgBr), because the anthranilonitrile (as evidenced by GC) is relatively quickly consumed and prolonged reaction times will cause formation of byproducts. It thus seems likely that the yields of these industrially interesting ketones (11) can be improved by reducing the reaction times (in lit.[14] usually 15 h). For the preparation of quinazolines the method in Scheme 2 is superior to that in Scheme 1 because of higher flexibility and the generally better yields. Formation of 4(3H)-quinazolinones, as indicated in Scheme 3, was a disturbing side-reaction in this method, particularly when methylmagnesium bromide was utilized.



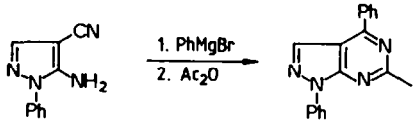
Scheme 3

The method according to Scheme 2 could also be used for the preparation of quinazolines with certain functional groups in 2-position. In particular the preparation of quinazolines with a CF_3-substituent in 2-position is of interest because this group should be susceptible to displacements with suitable nucleophilic reagents (c.f. refs. 16 and 17). As also indicated in Scheme 2 several different types of functionalized quinazolines such as 12 and 13 could also readily be prepared by this approach. In connection with the preparation of 13 it was found that this ester could react with a second molecule of 10 thus giving the known[18,19] 2,2'-coupled quinazoline 15a.



15 a X=H
b X=Cl

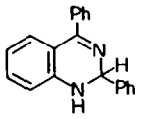
Carboxylic esters generally reacted with 10 and e.g. ethyl bromoacetate yielded 16. However the yield was modest (with α-halosubstituted esters) and several by-products were formed (including 2-bromomethyl-4(3H)-quinazolinone, cf. Scheme 3). The method could also be extended to the preparation of hetero-fused pyrimidines. Thus addition of phenylmagnesium bromide to the pyrazole 18 followed by addition of acetic anhydride yielded the pyrazolopyrimidine 19 (Scheme 4).



18 19

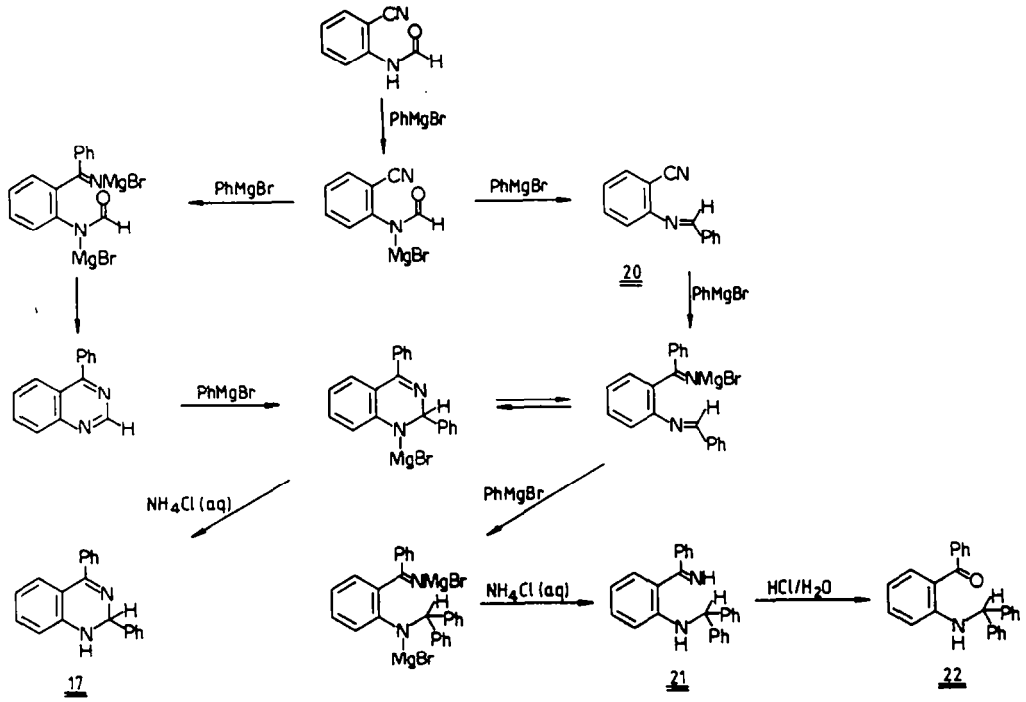
Scheme 4

The preparation of 2-unsubstituted quinazolines could readily be effected by reaction of the intermediate 10 with formic acetic anhydride (or alkyl formates). However attempted synthesis according to Scheme 1 (i.e. with 7, R'=H as reactant) resulted in the formation of the



17

air-sensitive compound 2,4-diphenyl-1,2-dihydroquinazoline (17). If this compound is recrystallized from ethanol without air-protection it undergoes dehydrogenation to 2,4-diphenylquinazoline. Compound 17 could also be prepared from 10 ($R=C_6H_5$) and benzaldehyde. Still another method is outlined in Scheme 5, namely reaction of C_6H_5MgBr with benzalanthranilonitrile (20), a compound that actually could be isolated in 20% yield from

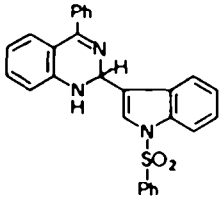


17 21 22

Scheme 5

reaction mixtures of 7 (R=H) and C_6H_5MgBr provided that not more than 2 equivalents of the Grignard reagent was used. In the transformation of 20 to 17 there is a competitive reaction leading to the non-cyclized compound 21 which could be hydrolyzed with aqueous HCl to 22 which also could be prepared by alkylation of 2-aminobenzophenone with diphenylmethyl chloride. Reaction between C_2H_5MgBr and 20 similarly gave compound 27.

The more sterically hindered 1,2-dihydroquinazoline (23), which could readily be prepared from 10 (R = C_6H_5) and N-sulphonylindole-3-carboxaldehyde, is much more stable than 17 and could be recrystallized from ethanol without air-protection. Reduction of 23 with sodium amalgam with concomitant cleavage of the benzenesulphonyl group yielded the known[20] compound 24.



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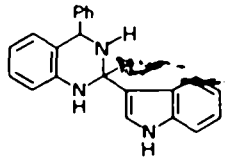
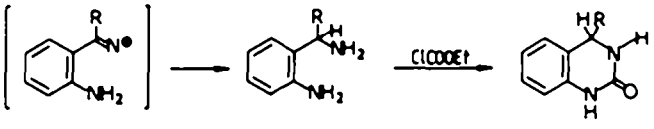


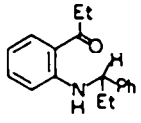
24

The intermediate 10 could be reduced *in situ* with lithium aluminium hydride and the new intermediate 25 could be trapped in much the same way as the intermediate 10 (Scheme 6). Several derivatives of 25 (e.g. R = C_6H_5) had previously[20] been prepared by other routes such as reduction of o-aminobenzophenone oxime.



10 25 26

Scheme 6



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In connection with these studies it was also found that reduction (cf. refs. 21-23) of 12 with sodium borohydride in acetic acid readily yielded 26 (see Table 2).

Experimental part - Elemental analyses were performed by Novo Microanalytical Laboratory, DK-2880 Bagsvaerd, Denmark. All melting points are uncorrected. IR spectra (KBr discs) were obtained by using a Perkin-Elmer 257 instrument. NMR spectra were recorded on a Bruker WP 200 or a Varian EM-360 instrument (DMSO-d_6 or $CDCl_3$ as solvents and TMS as internal standard). Mass spectra were obtained with a LKB 9000 (70 eV) mass spectrometer.

Anthranilonitrile (2-aminobenzonitrile) and 5-chloroanthranilonitrile of commercial quality (BASF) were generally used without further purification. All the yields refer to isolated, crystallized compounds.

Table 1

compound	m.p. [°C]	lit. m.p. [°C]	yield [%]	spectroscopic properties
2-Allyl-4-phenyl-quinazoline	79[a]		48(A)	MS: 247(9), 246(M^+,23), 245(24), 149(100), 135(36).
2-Benzyl-4-methyl-	80-1	76[26]	60(A)	
2-Benzyl-4-phenyl-	116-7		77(A)	
2-Benzyl-4-(*p*-tolyl)-	100.0-.5		75(B)	
2-(1-Bromo-1-ethylpropyl)-4-phenyl-	92		30(A)	IR: 2790, 1605, 1560, 1530, 1380, 1330, 780, 700 cm^{-1}.
2-(1-Bromo-1-methylethyl)-4-phenyl-	135[27]		33(A)	
2-Bromomethyl-4-phenyl-	156-7		16(A)	IR: 2970, 2920, 1615, 1565, 1540, 1490, 1450, 1390, 785, 770, 710 cm^{-1}.
2-(1-Bromopropyl)-4-phenyl-	110		52(A)	IR: 2790, 1625, 1565, 1540, 1490, 1390, 1350, 770, 710 cm^{-1}.
2-Butyl-4-phenyl-	75-7		76(A)	
2-(2-Chloro-1,1-dimethylethyl)-4-phenyl-	110		45(A)	IR: 2950, 1610, 1540, 1385, 780, 760, 700 cm^{-1}.
2-Chlorodifluoromethyl-4-phenyl-	101-2		90(A)	
6-Chloro-2,4-diphenyl-	194[d]		92(A)	MS: 319(39) 318(52) 317(M^+,97) 316(97) 282(23) 281(100) 149(71).
6-Chloro-2-ethyl-4-phenyl-	110	103-4[28]	25(A)	
6,8-Dibromo-2,4-diphenyl-	219[d]		85(A)	MS: 442(M^+,44) 441(49) 440(100) 399(67) 398(49) 397(27) 362(71) 360(67) 272(47) 271(82) 177(66).
6,8-Dibromo-2-(3-pyridyl)-4-phenyl-	230[d]		82(A)	MS: 443(M^+,51) 442(51) 441(100) 440(74) 439(54) 438(31) 364(20) 363(63) 362(23) 361(63).
1,2-Dihydro-2,4-diphenyl-	50-5		25(A),81(B)	see experimental section.
2,4-Dimethyl-	72	72($2H^2O$)[27]	60(A)	
2-Dimethylamino-4-phenyl-	127	122[21]	75(A)	see experimental section.
2,4-Diphenyl-	119-20	119-20[24]	80(A),50(B)	see experimental section.
4-Ethyl-	15-6	15-6[29]	57(A)	
2-Ethyl-4-phenyl-	55[a]	53[29]	41(B)	IR: 3050, 2960, 2920, 1615, 1600, 1560, 1545, 1485, 1465, 1450, 1430, 1380, 1350, 1280, 1210, 1135, 1115, 1060, 1070, 1025, 1000, 975, 935, 895, 845, 820, 780, 775, 710, 680 cm^{-1}.
4-Ethyl-2-trifluoromethyl-	66		42(A)	see experimental section.
2-Methoxymethyl-4-phenyl-	116-7[b]		54(A)	
2-Methyl-4-phenyl-	48-9	47-8[24]	80(A)	
2-Methyl-4-(*p*-tolyl)-	93.0-.5		92(A),53(B)	
2-Naphthyl-4-phenyl-	173-4[c]		96(A)	
4-Phenyl-	99-100	99-100[30]	66(A)	
2-(α-Phenoxy)propyl-4-phenyl-	101-2		85(A)	
4-Phenyl-2-propyl-	100[a]	99-100[28]	16(A)	IR:3060, 2960, 2930, 2900, 2870, 1610, 1575, 1565, 1545, 1485, 1465, 1420, 1385, 1355, 1330, 1315, 1260, 785, 770, 750, 705 cm^{-1}.
4-Phenyl-2-styryl-	154-6		63(A)	
4-Phenyl-2-thienyl-	145		80(A)	MS: 280(22) 288(M^+,30) 150(19) 149(100).
2-Phenyl-4-(*p*-tolyl)-	129.0-.5	128.5-130[30]	62(B)	
4-Phenyl-2-trichloromethyl-	109-10	109[24]	76(A)	
4-Phenyl-2-trifluoromethyl-	92		66(A)	see experimental section.
4-iso-Propyl-2-phenyl-	60		35(A)	MS: 248(M^+,65) 234(100) 220(77) 205(30).
Spiro[cyclohexane-1,2'(1'H)-4'-phenylquinazoline]	146[a]		7(A)	MS:276(M^+,28) 247(17) 234(28) 233(100) 220(40). ^{13}CNMR 22.05(t), 25.53(t), 37.07(t), 69.76(s), 114.43(d), 117.27(d), 117.53(s), 128.06(d), 128.60(d), 129.15(d), 132.37(d), 138.68(s), 145.35(s), 163.30(s) ppm.

Notes: see table 2.

Table 3

compound	m.p. [°C]	lit. m.p. [°C]	yield [%]	spectroscopic properties
1-Benzyl-4-phenyl-2-quinazolinone	181[a]		58(A)	see experimental section.
6-Bromo-4-phenyl-	306-6	321-2[35]	76(A)	IR: 3600-200, 1650, 1590, 1540, 1460, 1340, 825, 780, 700 cm^{-1}.
4-Butyl-	133[a]		18(A)	MS: 202(M^+,25) 174(17) 173(100) 160(58).
6-Chloro-3,4-dihydro-4-phenyl-	182		87	see experimental section.
6-Chloro-4-phenyl-	318	310-2[36]	96(A)	
3,4-Dihydro-4-phenyl-	194	193[41]	83	see experimental section.
3,4-Dihydro-4-iso-propyl-	214-5		100	see experimental section.
4-Naphthyl-	306-7[a]		27(A)	MS: 272(M^+,58) 271(100) 127(20).
4-Phenyl-	260-2	255-6[22]	82(A)	see experimental section.
4-iso-Propyl-	188-92[a]	231-2[34]	73(A)	IR: 3030, 2850, 1700-1660, 1620, 1600, 1440, 1300, 1150, 760, 690 cm^{-1} ^1H NMR 1.3(d,6H,J=3.5Hz) 3.7(m,1H) 7.1-8.0(m,4H) ppm MS: 188(M^+,100) 187(68) 173(67).
4-Phenyl-2-quinazolinethione	235[c]	230-2[38]	16[f]	MS: 240(15) 239(85) 238(M^+,100) IR: 3040, 2880, 1640, 1610, 1540, 1485, 1420, 1370, 1280, 1240, 1160, 1115, 1030, 1000, 980, 925, 840, 765, 735, 700, 690 cm^{-1}.

a) Recrystallized from di-iso-propylether.
b) Recrystallized from iso-propanol.
c) Recrystallized from acetonitrile.
d) Sublimed.
e) Recrystallized from ethanol.
f) The method from ref. 32 was used.
g) Hayashi *et al.*[34] have reported only melting point and elemental analysis, i.e. no spectral data. Structural evidence was based on further reactions of the product. Thus, "4-isopropylquinazolinone" treated with phosphoryl chloride gave 2-chloro-4-isopropylquinazoline but even for this compound there is a lack of spectral data. As Hayashi's "4-isopropylquinazolinone" is an oxidation product in the reaction between 4-isopropylquinazoline and monoperphtalic acid we believe that a possible explanation for the disagreement (of the melting points) is that Hayashi's reaction involves in fact an oxidation of the isopropyl group. This type of oxidation has been reported for 2-isopropylquinazolinones with hydrogen peroxide in acetic acid[42] as well as with chromic acid[43].

2,4-Diphenylquinazoline

Method A

2-Aminobenzonitrile (11.8 g, 0.1 mol) dissolved in dry ether (100 ml) was added dropwise to a well-stirred solution of phenylmagnesium bromide (from bromobenzene, 27.4 ml, 0.26 mol and magnesium 5.4 g, 0.2 mol) in ether (600 ml) at reflux. After completed addition the mixture was refluxed for 2 h, whereupon benzoyl chloride (17.4 ml, 0.15 mol) was added dropwise to the cooled (ice-bath) reaction mixture. The reaction was completed by a reflux period (2h). After cooling ammonium chloride (aq, 20%, 300 ml) was added and the ether phase was separated, washed with water, dried and evaporated. The residue, crystallized from ethanol gave 2,4-diphenylquinazoline, yield 23 g (80%) m.p. 119-120 °C (lit.[24] m.p. 119-120 °C).
IR: 3060, 1615, 1590, 1570, 1540, 1500, 1490, 1460, 1445, 1395, 1370, 1345, 1315, 1260, 1230, 1190, 1150, 1080, 1030, 1000, 980, 960, 925, 875, 850, 820, 790, 770, 765, 740, 705, 690, 670 cm^{-1}.

Method B

Phenylmagnesium bromide (70 ml, 1M) as a solution in THF was added dropwise during 5 minutes to a well-stirred solution of o-benzamidobenzonitrile (4.44 g, 20 mmol) in THF (150 ml). After completed addition the reaction mixture was refluxed for 4 h, cooled and treated with NH_4Cl (aq, 10%, 500 ml) and ether (300 ml). The ether phase was washed with water, dried (Na_2SO_4) and evaporated. Crystallization from ethanol gave 2,4-diphenylquinazoline, yield 2.80 g (50%) m.p. 119-120 °C (lit.[24] 119-120 °C).

4-Phenyl-2-quinazolinone (general procedure).

Magnesium (2.4 g, 0.1 mol) was reacted with bromobenzene (13.7 ml, 0.13 mol) in dry ether (50 ml) under reflux. After completed reaction 2-aminobenzonitrile (5.9 g, 0.05 mol) dissolved in dry ether (40 ml) was added dropwise. After a reflux period (2 h) methyl chloroformate (5.8 ml, 0.075 mol) was added dropwise at 0-5 °C and the solution refluxed (14 h) and then poured into 2M HCl-solution. The mixture was neutralized with $NaHCO_3$ (aq, 10%) and the product was collected and washed with hot ether. Yield: 9.1 g (82%); m.p. 260-2 °C (lit.[22] 255-6 °C)
IR: 3120 (br.), 2960 (br.), 2840 (br.), 1650 (br.), 1600 (br.), 1550, 1495, 1460, 1440, 1370, 1355, 1310, 1290, 1270, 1150, 1135, 1080, 1040, 990, 955, 900, 850, 810, 795, 760, 750, 710, 705, 685 cm^{-1}.
This product was also synthesized by Yamada's[32] method. Yield: 2.05 g (18%), m.p. 260-2 °C.

N-Benzyl-4-phenyl-2-quinazolinone.
N-Benzyl-2-aminobenzonitrile[39] (4.16 g, 0.02 mole) was dissolved in dry ether (40 ml) and added dropwise to phenylmagnesium bromide (0.04 mol) at 5 °C. After completed addition the mixture was refluxed (4 h) whereupon methyl chloroformate (3.1 ml, 0.04 mol) was added dropwise under cooling (0-5 °C). The work-up followed the general procedure. Yield: 3.6 g (58%), m.p. 181 °C.
IR: 3400 (br.), 3020 (br.), 1650, 1600, 1535, 1485, 1445, 1365, 1325, 1305, 950, 935, 845, 805, 770, 760, 740, 730, 700, 675 cm^{-1}.
MS: 313 (24), 312 (M^+, 100), 311 (49), 221 (21), 207 (31).
2-Dimethylamino-4-phenylquinazoline hydrochloride (14).
Magnesium (1.08 g, 0.045 mol) was reacted with bromobenzene (5.1 ml, 0.05 mol) in dry ether (40 ml). 2-Aminobenzonitrile (1.77 g, 0.015 mol) was added and the solution was refluxed for 3 h. Dichloromethylenedimethylimmonium chloride (3.66 g, 0.023 mole) was added and the solution was refluxed (15 h). The reaction was quenched with saturated NH_4Cl-solution, the product collected and washed with hot light petroleum. Yield: 3.2 g (75%), m.p. >260 °C.
The free quinazoline was liberated by treatment (reflux) with a mixture of ethanol and $NaHCO_3$ (aq., 10%). M.p. 127 °C (lit.[31] 122 °C).
IR: 3050, 2900 (br.), 2975, 1615, 1550 (br.), 1480, 1450, 1400, 1380, 1345, 1255, 1130, 1025, 1000, 970, 870, 805, 785, 765, 740, 730, 710, 675, 655 cm^{-1}.
2-Dimethylamino-4-phenylquinazoline was also synthesized by refluxing 4-phenyl-2-quinazolinone in HMPA (4 h).[25] Yield: 32%, m.p. 124 °C.
1,2-Dihydro-2,4-diphenylquinazoline (17).
Method A.
Benzaldehyde (7.65 ml, 0.075 mole) was added dropwise, under nitrogen to the complex 10 (0.05 mol) (generated from phenylmagnesium bromide and 2-aminobenzonitrile). The solution was refluxed (21 h) and quenched with 2 M HCl. The crystals formed were collected and washed with hot light petroleum and recrystallized from ethanol. Yield 7 g (44%), m.p.. 255 °C of the hydrochloride of 17.
IR: 3400 (br.), 3140, 3100, 3020, 2960, 2890, 1615, 1560, 1475, 1440, 1405, 1340, 1295, 1265, 1245, 1175, 1150, 1135, 1085, 1070, 1025, 1000, 985, 925, 865, 850, 820, 790, 760, 755, 735, 710, 700 cm^{-1}.
The free base 17 was liberated when the hydrochloride was treated with hot NaOH (aq, 50%) under nitrogen. Yield: 3.5 g (25%). M.p. 50-5 °C.
IR: 3370, 3230, 3060, 3040, 1610, 1560, 1540, 1470, 1455, 1445, 1420, 1390, 1335, 1245, 1175, 1155, 1120, 1065, 1030, 1000, 965, 915, 850, 785, 755, 700, 670 cm^{-1}.
MS: 284 (M^+, 24), 283 (21), 282 (24), 281 (35), 208 (18), 207 (100), 180 (15), 129 (15).
Method B
To a freshly prepared THF solution of phenylmagnesium bromide (30 ml, 0.91 M) 2-formamidobenzonitrile (1.0 g, 6.8 mmol), dissolved in 20 ml of THF was added dropwise at room temperature. After 14 h reflux, under a dry nitrogen atmosphere, the reaction was terminated by the addition of 10 ml of saturated aqueous NH_4Cl. The crude material (obtained after phase separation, drying and evaporation of solvent) was chromatographed on a column, packed with silica (flash) gel (Merck 0.04-0.063 mm), with a diameter of 3 cm and with EtOH/CH_2Cl_2 (1:99) as eluent. Compound 17 was obtained 1,58 g(81%) as a yellow oil that crystallized on standing.
^1H NMR: 4.29 (s, 1H, NH), 5.89 (2, 1H, 2-quinazolinyl), 6.60 (d, J=8 Hz, 1H, 8-quinazolinyl), 6.69 (t, J=8 Hz, 1H, 6-quinazolinyl), 7.15 (d, J=8 Hz, 1H, 5-quinazolinyl), 7.22 (t, J=8 Hz, 1H, 7-quinazolinyl), 7.33-7.40 (m, 5H, phenyl) and 7.51-7.59 (m, 5H, phenyl) ppm.
Method C
Magnesium (1.92 g, 0.08 mol) was reacted with bromobenzene (9.5 ml, 0.09 mol) in dry ether (40 ml). N-Benzal-2-aminobenzonitrile[39] (4.9 g, 0.024 mol) dissolved in dry toluene (20 ml) was added dropwise at 0-5 °C. The solution was refluxed (5 h) and quenched with 2 M HCl. The product was collected and washed with hot light petroleum. Yield: 8.8 g of the hydrochloride of 17, m.p. 255 °C.
Together with the dihydroquinazoline (17) another yellow compound could be isolated in the chromatographic procedure (0.40 g). As this material was contaminated with small amounts of 6 (R=R'=phenyl), it was rechromatographed on silica gel and eluated with petroleum ether/CH_2Cl_2 (25:75), which yielded pure material 0.073 g with the following ^1H NMR-data; δ 5.72 (d, J=5.4 Hz, 1H), 6.47 (t, J ≈ 7.5 Hz, 1H), 6.61 (d, J=8.3 Hz, 1H) and 7.09-7.44 (m, 29 H). Treating this compound with aqueous HCl transformed it to compound 22 whose structure was confirmed by the comparison with an authentic sample of 22.
o-Propionyl-N-(1-phenylpropyl)aniline (27)
The procedure given above for C_6H_5MgBr and benzalanthranilonitrile was used with C_2H_5MgBr as reactant, yield 65%, m.p. 78-9 °C[5] (after recrystallization from 2-propanol).
^{13}C NMR: 203.3 (s), 149.7 (s), 143.3 (s), 134.4 (d), 131.8 (d), 128.4 (d), 126.7 (d), 126.2 (d), 116.7 (s), 114.1 (d), 112.7 (d), 57.3 (d), 31.6 (t), 36.9 (t), 10.4 (q), 8.7 (q) ppm.
2-(N-Benzenesulphonyl-3-indolyl)-4-phenyl-1,2-dihydroquinazoline (23).
N-Benzenesulphonylindole-3-carboxaldehyde[40] (5.70 g, 20 mmol) in ether (100 ml) was added dropwise to phenylmagnesium bromide (50 mmol) in ether (120 ml) at reflux. After completed addition the reaction mixture was refluxed for 6 h and then quenched by addition of ammonium chloride (aq, 20%, 80 ml). The ether phase was separated, washed with water, dried, evaporated and the residue recrystallized from acetonitrile, yield 7.80 g (84%), m.p. 208-210 °C (with slow decomposition).
IR: 3390, 1615, 1450, 1370, 1185, 1130, 790, 760, 740, 715, 690 cm^{-1}.
MS: 463 (M^+), 322 (75), 321 (base peak).
^1H NMR: 4.4 (br. s, 1 H, NH), 6.2 (s, 1 H, CH), 6.7-8.2 (m, 19 H, ar) ppm.
^{13}C NMR: 164.6 (s), 147.4 (s), 137.7 (s), 136.9 (s), 134.8 (d), 134.3 (d), 132.5 (d), 129.6 (d), 129.1 (d), 128.8 (s), 128.5 (d), 127.9 (s), 127.7 (d), 126.3 (d), 124.7 (d), 124.1 (d), 123.9 (s), 123.1 (d), 121.6 (d), 116.8 (d), 116.3 (s), 114.4 (d), 113.0 (d), 65.1 (d) ppm.

2-(3-Indolyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline (24).
Compound (23), (4.63 g, 0.01 mol) was dissolved in DMF (50 ml) containing water (5 ml). Sodium amalgam (25 g) was added in portions to the stirred mixture during 1 h, whereupon the mixture was stirred at 40 °C for 4 h. The reaction mixture was filtered, evaporated and the residue recrystallized from CH_3CN, yield 2.95 g (90%), m.p. 128-130 °C (lit.[20] 128-130 °C).
1,4-Diphenyl-6-methylpyrazolo[3,4-d]-pyrimidine (19). 5-Amino-4-cyano-1-phenylpyrazole (18) (1.84 g, 10 mmol) dissolved in dry THF (15 ml) was added dropwise to a well-stirred solution of phenylmagnesium bromide (26 mmol) in THF (25 ml) at reflux. After completed addition the mixture was refluxed for 4 h, whereupon acetyl chloride (20 mmol) was added dropwise to the cooled (ice-bath) reaction mixture. The cyclization was completed by a reflux-period (3 h). After cooling ammonium chloride (aq, 20%, 200 ml) and ether (250 ml) was added. When the complexes had decomposed the ether phase was separated, washed with water, dried (Na_2SO_4) and evaporated. The residue crystallized from ethanol, yield 1.95 g (68%) m.p. 159-160 °C.
IR: 3060, 2970, 1590, 1560, 1500, 1460, 1435, 1410, 1385, 1355, 1295, 1275, 1250, 1180, 1150, 1030, 955, 930, 885, 855, 830, 805, 760, 710, 700, 695 cm^{-1}.
MS: 287 (M + 1, 30), 286 (M^+, 100), 285 (30), 149 (83), 142 (30), 135 (30).
4-Ethyl-2-trifluoromethylquinazoline.
2-Aminobenzonitrile (4 g, 0.03 mol) in ether (50 ml) was added to a solution of ethylmagnesium bromide (0.1 mol) in ether (50 ml). After a short reflux period (0.5 h) the reaction mixture was cooled to 0 °C and trifluoroacetic anhydride (3 ml) was added dropwise. The mixture was stirred overnight at ambient temperature and then refluxed for 0.5 h. The reaction was quenched with NH_4Cl (aq., ≈40 %, 50 ml). The phases were separated and the water phase extracted with ether. The combined organic phases were dried ($MgSO_4$) and evaporated. Crystallization from ether-light petroleum gave 2.8 g (42%) m.p. 62 °C.
IR: 3040 (w), 2990 (w), 2940 (w), 2900 (w), 1615, 1570, 1500, 1400, 1380, 1150, 905, 765, 740 cm^{-1}.
MS: 226 (M^+), 225 (base peak), 149 (84%), 91 (79%).
^{13}C NMR: 174.6 (s), 149.3 (s), 134.3 (d), 129.7 (d), 129.3 (d), 124.5 (d), 117.3 (s), 99.7 (s), 27.6 (t), 12.3 (q) ppm.
4-Phenyl-2-trifluoromethylquinazoline.
This compound was prepared in the same manner as 4-ethyl-2-trifluoromethylquinazoline. Yield: 66% m.p. 92 °C.
IR: 3060, 1615, 1570, 1550, 1490, 1400, 1240, 1100, 770, 705 cm^{-1}.
MS: 274 (M^+), 214 (69), 145 (100).
N-(Diphenylmethyl)-o-aminobenzophenone (22).
o-Aminobenzophenone (0.49 g, 2.5 mmol) and diphenylmethylchloride (0.5 ml, 2.5 mmol) were dissolved in DMF (5 ml) and the solution was refluxed. When the reaction mixture was poured into water an oil separated. The solvent was decanted and the oily residue treated with ethanol gave crystals, yield 0.5 g (55%) m.p. 190 °C.
IR: 3300, 3050, 3010, 1630, 1565, 1510, 1230, 750, 740, 700 cm^{-1}.
2-Carboethoxy-4-phenylquinazoline (11, R=C_6H_5).
2-Aminobenzonitrile (4 g, 0.03 mol) in ether (50 ml) was added to a stirred solution of phenylmagnesium bromide (0.1 mol) in ether (50 ml). After a reflux period (4 h) the mixture was cooled to 0 °C and diethyl oxalate (5 ml) was added dropwise. The reaction mixture was stirred at ambient temperature for 20 h and then poured into NH_4Cl (aq, ≈40%, 100 ml). After 0.5 h the phases were separated, the water phase was extracted with ether and the combined organic phases were dried ($MgSO_4$). The solvent was evaporated in vacuum and the residue gave crystals on treatment with ethanol. Yield 3.4 g (41%), m.p. 131-135 °C.
IR: 2970, 1730, 1615, 1560, 1530, 1485, 1390, 1380, 1240, 780, 705 cm^{-1}.
MS: 278 (M^+, 4), 206 (100).
2-Carbomethoxy-4-phenylquinazoline. This compound was prepared in the same manner as 2-carboethoxy-4-phenylquinazoline described above. Yield: 46%, m.p. 154-157 °C.
IR: 3060, 2950, 1730, 1610, 1560, 1490, 1390, 1240, 780, 705 cm^{-1}.
MS: 264 (M^+, 31), 206 (100).
2,2'-Bis-4-phenylquinazoline.
Method A.
2-Aminobenzonitrile (4 g, 0.03 mol) in ether (50 ml) was added dropwise to a stirred solution of phenylmagnesium bromide (0.1 mol) in ether (50 ml). The reaction mixture was refluxed for 2 h and then cooled to 0 °C. Diethyl oxalate (5 ml) was added dropwise. After a period of reflux (5 h) the reaction was quenched with NH_4Cl (aq, ≈40%, 100 ml) and then stirred for 1 h. The solid formed was collected, yield 1.2 g (20%) of 2,2'-bis-4-phenylquinazoline. M.p. 300-304 °C (lit.[19] 295-296 °C).
IR: 3050, 1615, 1565, 1530, 1480, 1390, 1085, 850, 775, 760, 700 cm^{-1}.
MS: 410 (M^+, 77), 409 (100), 205 (38).
Method B (from 2-carbomethoxy-4-phenylquinazoline).
2-Aminobenzonitrile (0.4 g, 3.4 mmol) in ether (10 ml) was added dropwise to a stirred solution of phenylmagnesium bromide (10 mmol) in ether (20 ml). After completed addition the reaction mixture was refluxed (0.5 h) and then 2-carbomethoxy-4-quinazoline (0.4 g, 1.7 mmol) dissolved in THF (20 ml) was added dropwise. The reaction mixture was stirred at ambient temperature for 54 h and then poured into NH_4Cl (aq, ≈40%, 50 ml). The mixture was stirred for 1 h and the solid formed was collected to give 68 mg (10%) of 2,2'-bis-4-phenylquinazoline.
3,4-Dihydro-4-phenyl-2-quinazolinone.
4-Phenyl-2-quinazolinone (1.11 g, 0.005 mol) was suspended (under N_2) and stirred (1 h) in acetic acid (20 ml). $NaBH_4$ (0.38 g, 0.01 mol) was added in small portions during 1 h. After 20 h the suspension was cooled and NaOH (aq, 50%, 15 ml) was added (pH >10).The crystals formed were collected, yield 1.1 g (83%), m.p. 194 °C (lit.[41] 193 °C, 197 °C). IR: 3230, 3070, 2910, 1680, 1605, 1455, 1345, 1300, 1270, 1180, 1115, 1080, 1035, 1005, 970, 940, 930, 865, 750, 700, 625 cm^{-1}. MS: 225 (M+1, 0.3), 224 (M^+, 2.4), 223 (1.4), 180 (1.4), 149 (2.8), 148 (1.0), 147 (100). 3,4-Dihydro-4-phenyl-2-quinazolinone was also synthesized by Gabriel's and Stelzner's[41] method (heating of 2-aminobenzhydrol with urea).

3,4-Dihydro-4-isopropyl-2-quinazolinone
Yield: 0.95 g (100%), mp 214-5 °C.
MS: 190 (M^+, 0.3), 173 (0.5), 149 (2.6), 148 (1.3), 147 (100).
^{1}H NMR: 0.87 (d, J=6.8 Hz), 0.99 (d, J=6.9 Hz), 1.96 (m), 4.35 (m), 5.3 (br. s), 6.6-7.2 (ar), 7.36 (br. s) ppm.
6-Chloro-3,4-dihydro-4-phenyl-2-quinazolinone
Yield: 0.9 g (87%), mp 182 °C.
IR: 3240, 3100, 2920, 1690, 1605, 1496, 1450, 1400, 1290, 1265, 1180, 1135, 1095, 1080, 1035, 1005, 975, 935, 885, 825, 765, 720, 700, 675 cm^{-1}.
2-Aminobenzhydrol.
2-Aminobenzophenone (5 g, 0.025 mole) was dissolved in warm ethanol (100 ml) and $NaBH_4$ (1.15 g, 0.03 mole) was added in small portions. The solution was kept at 60 °C for 1 h and after 22 h at 25 °C water (200 ml) was added. The crystals formed were collected, yield 4.78 g (95%), m.p. 117 °C (in microscope 105 °C) (lit.[41] 120 °C, 107 °C).
IR: 3450, 3370, 3220 (br.), 3030, 2880, 1635, 1605, 1590, 1495, 1465, 1455, 1320, 1290, 1245, 1185, 1160, 1080, 1035, 1010, 940, 925, 880, 830, 765, 755, 735, 705 cm^{-1}.

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