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The Synthesis of Some 3-Amino-2-halomethyl-, 2-Halomethyl-3-(subst.amino)- and 2-Halomethyl-3-hetarylquinazolin-4(3H)-ones as Potential Plant Protecting Agents

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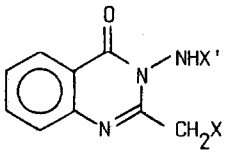
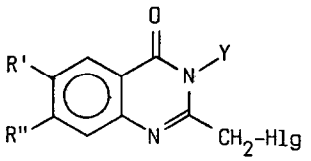
Abstract: A series of N(2)-(2-halomethyl-4-oxo-3,4-dihydroquinazolin-3-yl) carbazates **4** and **5** and 2-halomethyl-3-hetarylquinazolin-4-(3H)-ones **8** and **9** were obtained by reacting 2-halomethyl-4H-3,1-benzoaxin-4-ones (**12**) with alkyl carbazates and hetarylamines, respectively. Some of the carbazates **4** and **5** were obtained alternatively, by treatment of N-(2)-(2-aminobenzoyl)carbazate **15** with haloacetyl halides. The t-butyl carbazates **5** were converted into 3-amino-2-halomethylquinazolin-4(3H)-ones (**6**), some of which were further converted into 3-(2,5-dimethylpyrrol-1-yl)-2-halomethylquinazolin-4(3H)-ones (**7**). 3-Amino-2-bromomethylquinazolin-4(3H)-one (**6b**) was also obtained by brominating its 2-methyl analogue **1** with cyanogen bromide.

In at attempt to obtain the cyanoamino derivative (**2**) 3-amino-2-methylquinazolin-4(3H)-one (**1**)[1] was allowed to react with cyanogen bromide but, quite unexpectedly, the bromomethyl derivative **3** rather than the desired compound **2** was obtained. Since compound **3** was found to possess some pesticidal activity, a series of quinazolin-4(3H)-one derivatives of the general structures **4-9** was synthesised and subjected to biological screening.



1-3

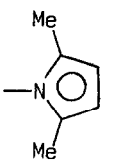
1 : X = X' = H
2 : X = H, X' = CN
3 : X = Br, X' = H

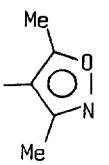


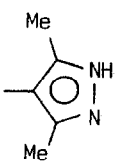
4-9

	R'	R''	Hlg
a	H	H	Cl
b	H	H	Br
c	H	H	F
d	O_2N	H	Cl
e	O_2N	H	Br
f	OCH_2O		Cl
g	OCH_2O		Br
h	OCH_2O		F

	Y	(Compounds prepared)
4 :	$NHCO_2Et$	(a, b, d, g)
5 :	$NHCO_2Bu^t$	(a, b, d-g)
6 :	NH_2	(a, b, d-g)

7 :  (a, c)

8 :  (a, d, f, h)

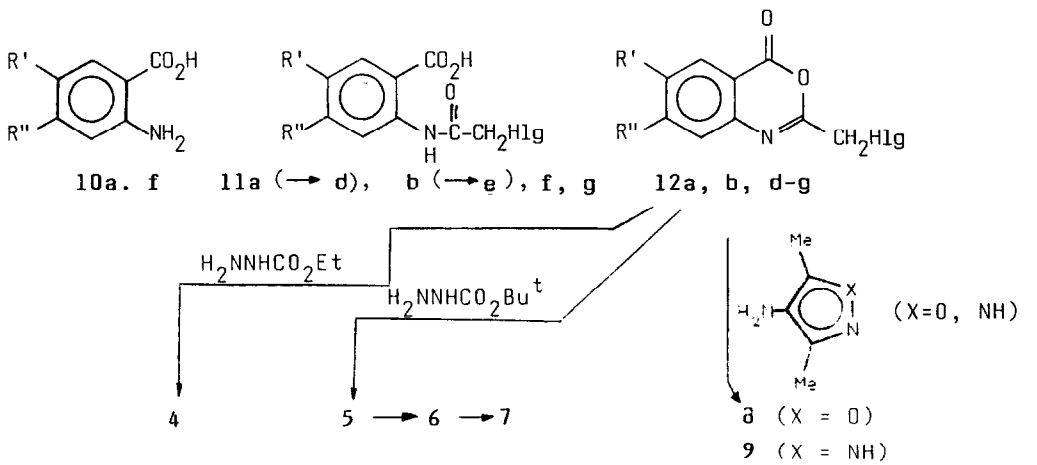
9 :  (a, c, d, f)

A limited number of type (3) 2-(1-haloalkyl)-quinazolin-4(3H)-ones as well as some 3-aryl derivatives of these compounds are known from the literature[2-5]. In addition, some 2-(1-di- and -trihaloalkyl) analogues have been described,[4,6,7] but the only 3-amino-2-(1-haloalkyl)quinazolin-4(3H)-one hitherto know is the fluoro derivative **6c**.[8]

We have prepared compounds of types **4**, **5**, **8** and **9** starting with the appropriate anthranilic acids **10** *via* their haloacetyl derivatives **11** and the corresponding 2-halomethyl-4H-3,1-benzoxazin-4-ones **12** by hydrazinolysis of the latter with ethyl and t-butyl carbazate and by aminolysis with

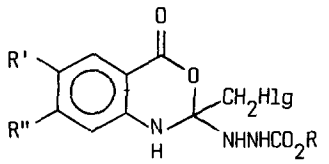
4-amino-3,5-dimethylisoxazole and -pyrazole, respectively, see Scheme 1. The 2-(haloacetylamino)benzoic acids **11a, b, f** and **g** were obtained by haloacetylation of the corresponding anthranilic acids either in the absence of base or in the presence of added triethylamine (Methods A and B, respectively, Table 1), while the nitro derivatives **11d** and **e** were prepared by nitration of compounds **11a** and **b**, respectively (Method C) in 64-98% yields. The ring closures of the compounds **11** to the corresponding 2-(halomethyl)-4H-3,1-benzoxazin-4-ones (**12**) were effected in 63-95% yields by refluxing with acetic anhydride (Methods D and E, Table 2).

The key steps of our synthesis sequence are the hydrazinolyses and the aminolyses, respectively, of the halomethylbenzoxazinones **12**. These reactions are established methods for the conversion of 2-alkyl- and 2-aryl-4H-3,1-benzoxazin-4-ones into the corresponding 3-(subst.)aminoquinazolin-4(3H)-ones[9, 10b, 11c] as well as their analogues not bearing amino groups attached to position 3.[11b] They have, however never been used for the conversion of 2-(1-halomethyl)-4H-3,1-benzoxazin-4-ones into the corresponding 2-(1-haloalkyl)-3-(subst.)aminoquinazolin-4(3H)-ones where the reactive (1-haloalkyl) substituent might have caused complications; and only two 2-(dichloromethyl) derivatives have been obtained, by allowing the appropriate benzoxazinone to react with ammonia and o-toluidine, respectively.[4,6]

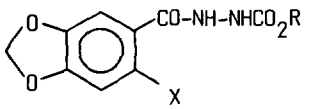


Scheme 1 (**a, b, d-g**: as for **4-9**)

We have used alkyl carbazates rather than hydrazine in the hydrazinolyses of the benzoxazinones **12** to obtain the 3-(alkoxycarbonylamino) derivatives **4** and **5** (Methods F and G, Table 3) and converted the latter into the 3-(unsubstituted amino) derivatives **6** in a subsequent step. In the course of the preparation of the bromomethyl derivative **5e** the starting (bromoacetylamino)benzoic acid **11e** was converted into the product without purification of the benzoxazinone **12e** (Method K, Table 3). The conversions of the benzoxazinones **12** into the (oxodihydroquinazolin-3-yl)-carbamates **4** and **5** are two-step processes and probably involve the adducts **13** as the intermediates which were not isolated but were immediately converted into compounds **4** and **5** in one-pot processes simply by refluxing the suspensions of the benzoxazinones in benzene. The halomethyl groups of the starting benzoxazinones **12** remained



13
(R=Et, Bu^t; R', R'' and Hlg as in **4** and **5**)



14: X = NO_2
15: X = NH_2 **a**: R = Bu^t
16: X = $NHCOCH_2Br$ **b**: R = Et
17: X = $NHCOCH_2Cl$

intact in all cases and the same was found to be true for the aminolyses leading to compounds of type **8** and **9** (Method R, Table 5).

The reaction of the bromomethylbenzoxazinone **12g** with t-butylcarbazate furnished the (oxodihydroquinazolin-3-yl)carbamate **5g** in low yield (17%). An alternative method was therefore devised for the preparation of this product. 4,5-Methylenedioxy-2-nitrobenzoic acid[12] was converted into the carbazate **14a** and the latter reduced to the amino analogue **15a**. Reaction of **15a** with bromoacetyl chloride afforded compound **5g** in 73% yield without isolation of the intermediate **16a** (Method J, Table 3). Treatment of compound **15a** with chloroacetyl chloride similarly led to compound **5f** without isolation of the intermediate **17a**. By ring closure of ethyl N(2)-(2-amino-4,5-methylenedioxybenzoyl)carbazate **15b** (Method H, Table 3) compound **4g** was similarly obtained via the non-isolated intermediate **16b**.

The reaction of 2-aminobenzamides and 2-aminobenzohydrazides with derivatives of carboxylic acids (including esters, ortho esters and anhydrides) to afford quinazolinones[10a, 11a] and their 3-(subst.)amino derivatives,[13-16] respectively, is an established method of synthesis of these compounds, it has, however, not yet been used for the synthesis of 2-(1-haloalkyl)-3-(unsubst. or subst. amino)quinazolin-4(3H)-ones and we are aware of but one 2-(1-haloalkyl)quinazolin-4(3H)-one which has been synthesised by this method.[5]

Most 3-aminoquinazolin-4(3H)-ones **6** were obtained by ester cleavage of the t-butyl carbazates **5** and decarboxylation of the resulting carbamic acids which was brought about either by refluxing the carbazates **5** with acetic acid in a one-pot process (Method L, Table 4) or by fusion of the same starting compounds **5** (Method M). Compound **6b** (≡3) was also obtained by bromination of methylquinazolin-4(3H)-one **1** (Method N) as mentioned above. Reaction of compound **6a** with hexane-2,5-dione furnished the pyrrolylquinazolinone **7a** (Method P, Table 5) from which the fluoro analogue **7c** was obtained by halogen exchange (Method S). The 2-fluoromethyl-3-isoxazolyl- (**8h**) and the 2-fluoromethyl-3-pyrazolylquinazolinone (**9c**) were similarly obtained.

Among the quinazolinone derivatives tested for plant protecting activities compound **6a**, which significantly inhibits the growth of various phytopathogenic fungi, was found to be the most promising. On the other hand, compound **9c** was found to have an effect on various functions of the CNS.

EXPERIMENTAL

M.p.s were taken in glass capillaries and are not corrected. KBr i.r. and 60 MHz ^{1}H n.m.r. spectra were recorded on Specord 75 (Carl Zeiss Jena) and Perkin-Elmer R 12 spectrometers with tetramethylsilane as internal reference, respectively.

2-(Haloacetylamino)benzoic acids (11) (Table 1)

Method A: By haloacetylation of 2-aminobenzoic acids in the absence of added base.

A mixture of anthranilic acid (13.7 g, 0.1 mol), dry benzene (250 ml) and chloroacetyl chloride (7.95 ml, 0.1 mol) was refluxed with continuous stirring until the evolution of HCl ceased (ca. 2 h), and allowed to cool to yield the colourless crystals of the chloroacetyl derivative **11a** (20.7 g, 97%).

Method B: By haloacetylation of 2-aminobenzoic acids in the presence of added triethylamine.

Chloroacetyl chloride (0.88 ml, 11 mmol) was added by drops to a mixture of 2-amino-4,5-methylenedioxybenzoic acid[12] (1.87 g, 10 mmol), dry dioxan (20 ml) and triethylamine (1.54 ml, 11 mmol) with continuous stirring and water cooling. The mixture was stirred for another 1/2 h and the product **11f** (1.65 g, 64%) filtered off and washed with water.

Method C: By nitration.

Compound **11a** (22.7 g, 97 mmol) was added to conc. nitric acid (ϱ 1,5; 100 ml) with continuous stirring within ca. 1/2 h below 5°C. Stirring was continued for another 1/2 h with ice-water cooling. The mixture was poured onto ice (200 g) and the product **11d** (23 g, 92%) filtered off and washed with water (3x50 ml).

2-Halomethyl-4H-3,1-benzoxazin-4-ones (**12**) (Table 2)

(a) Chloromethyl derivatives (**12a**, **d** and **f**) (Method D)

The 2-(chloroacetylamino)benzoic acids **11a**, **d** and **f** were refluxed with acetic anhydride (10-15 parts) for 30-40 min. The resulting solutions were evaporated to dryness at reduced pressure to yield crystalline or gradually crystallizing oily residues which were purified by trituration with ether. Compound **12f** obtained by this method was chemically pure, compound **12a** had to be recrystallized for microanalytical purposes and compound **12d** was used without further purification in the following step.

(b) Bromomethyl derivatives (**12b** and **g**) (Method E)

The 2-(bromoacetyl)benzoic acids **11b** and **g** (5 g) were refluxed for 3/4 - 1 h with acetic anhydride (50 ml). The resulting red solutions were evaporated to dryness at reduced pressure, the residues were dissolved in dichloromethane and the solutions poured through Kieselgel G columns (adsorbent 10 g, column height 3 cm). The columns were then washed with dichloromethane (50 ml). The resulting faint yellow solutions were evaporated to dryness at reduced pressure to afford the crystalline products **12b** and **g** which were purified by trituration with hexane or pentane

The 6-nitro analogue **12e** was similarly prepared. The yellow amorphous material, obtained by evaporation of the reaction mixture was, however, not purified but instead directly subjected to reaction with t-butyl carbazate (see below).

t-Butyl N(2)-(4,5-methylenedioxy-2-nitrobenzoil)carbazate (**14a**)

A mixture of 4,5-methylenedioxy-2-nitrobenzoic acid[12] (4.2 g, 20 mmol), thionyl chloride (5 ml) and dry dioxan (15 ml) was refluxed for 1 h and evaporated to dryness at reduced pressure. The residue was taken up in CH_2Cl_2 (10 ml) and the solution added within ca. 1.5 h to

Table 1: 2-(Haloacetylamino)benzoic acids (**11**)

Compound	Method[a]	Yield %	M.p., °C (recryst. from)	Formula (Mol. wt.)	C	H	Hlg[b]	N	ν_{max}(KBr) cm^{-1}
11a[c]	A	97	185[c]						
11b[d]	A	98	173-4	$C_9H_8BrNO_3$	41.65	3.4	31.15	5.55	3330-2300,[e] 1700, 1645
			(EtOH)	(258.1)	41.9	3.1	31.10	5.45	
11d	C	92	226-7	$C_9H_7ClN_2O_5$			13.9	5.25	3350-2500, 1700, 1660, 1540,
			(EtOH)	(258.6)			13.7	5.4	1345
11e	C	98	206-7	$C_9H_7BrN_2O_5$	35.9	2.6	26.65	8.95	3300-2300,[e] 1730, 1695,
			(dioxan)	(303.1)	35.65	2.35	26.35	9.23	1540, 1350
11f	B	64	223	$C_{10}H_8ClNO_5$			13.55	5.65	3300-2300,[e] 1690sh, 1670,
			(EtOH)	(257.7)			13.75	5.45	1620, 1270, 1240, 1040
11g	B	96	220-1	$C_{10}H_8BrNO_5$	40.05		25.95		3300-2300,[e] 1690, 1630,
			(BuOH)	(302.1)	39.75		26.45		1280, 1045

[a] For Methods A-C, see text

[b] Cl or Br, respectively

[c] Known compound, m.p.[19] 186-8°C

[d] Faint yellow crystals

[e] With several local maxima

Table 2: 2-Halomethyl-4H-3,1-benzoxazin-4-ones (**12**)

Compound	Method[a]	Yield %	M.p., °C (recryst. from)	Formula (Mol. wt.)	Found/calc., % C	H	Hlg[b]	N	$\tilde{\nu}_{max}$(KBr) cm^{-1}
12a	D	88	95 (benzene-acetone)	$C_9H_6ClNO_2$ (195.6)			17.95 18.15	7.35 7.15	1745, 1640, 1605, 1270, 1025
12b	E	75	106-7	$C_9H_6BrNO_2$ (240.1)	45.45 45.05	2.75 2.50	32.8 33.3	6.05 5.85	1760, 1650, 1620, 1260, 1025
12d	D	88[c]							
12f	D	63	148	$C_{10}H_6ClNO_4$ (239.6)			14.55 14.8	5.65 5.85	1735, 1600, 1280, 1240, 1070, 1010
12g	E	95	140-1	$C_{10}H_6BrNO_4$ (284.1)	42.45 42.30		27.85 28.15		1760, 1610, 1290, 1210, 1070, 1015

[a] For Methods D and E, see text

[b] Cl or Br, respectively

[c] Crude amorphous product which was used without purification in the subsequent step

a mixture of t-butyl carbazate (2.65 g, 20 mmol), triethylamine (3.1 ml, 22 mmol) and CH_2Cl_2 with continuous stirring at -5°C. The mixture was stirred for 1/2 h at room temperature, washed with water (3x10 ml), dried ($MgSO_4$) and evaporated to dryness. The residue was triturated with benzene (20 ml) to give the crystalline title compound (5.6 g, 82%), m.p. 143°C, Found C, 48.25; H, 4.9; N, 13.05. $C_{13}H_{15}N_3O_7$ (325.4) requires C, 48.0; H, 4.65; N, 12.9%. ν_{max}(KBr) 3400-3250, 1750, 1690, 1540, 1360, 1260, 1045 cm^{-1}.

The ethyl carbazate **14b** (m.p. 183°C; ν_{max} 3390, 3270, 1770, 1700, 1540, 1360, 1260, 1050 cm^{-1}) was similarly obtained in 93% yield.

t-Butyl N(2)-(2-amino-4,5-methylenedioxybenzoyl)carbazate (**15a**)

An ethanolic solution (1000 ml) of compound (**14a**) (69 g, 0.21 mol) was reduced in the presence of a 10% Pd-C catalyst (5 g) at room temperature. The catalyst was filtered off, the filtrate evaporated to dryness at reduced pressure and the residue purified by trituration with ether to give the crystalline title compound (50 g, 80%), m.p. 182°C. Found N, 14.35. $C_{13}H_{17}N_3O_5$ (295.3) requires N, 14.35%. ν_{max} 3430, 3330, 3200 b, 1740, 1680, 1250, 1055 cm^{-1}.

The ethyl carbazate **15b** (m.p. 175°C; ν_{max} 3460 w, 3370, 3310, 3180, 1750 sh, 1730, 1250, 1030 cm^{11}) was similarly obtained in 98% yield.

Ethyl N-(2-halomethyl-4-oxo-3,4-dihydroquinazolin-3-yl)carbamates (**4a**, **b**, **d** and **g**) (Table 3)

Method F: By the reaction of 2-halomethyl-4H-3,1-benzoxazin-4-ones (**12**) with ethyl carbazate

(a) A mixture of compound **12a** (9.7 g, 50 mmol), ethyl carbazate (5.7 g, 55 mmol) and benzene (80 ml) was stirred for 10 min. at room temperature and subsequently refluxed in an apparatus equipped with a water separator until the reaction was complete. The mixture was evaporated to dryness at a reduced pressure and the product **4a** purified by trituration with ether.

(b) A mixture of compound **12b** (13.0 g, 54 mmol), ethyl carbazate (6.2 g, 59.5 mmol) and benzene (50 ml) was refluxed for 1 h as above, evaporated to dryness and the product (**4b**) purified by column chromatography (Kieselgel G; CH_2Cl_2 - acetone, 10:1).

(c) A mixture of compound **12d** (2.4 g, 10 mmol), ethyl carbazate (1.15 g, 11 mmol) and benzene (25 ml) was stirred at room temperature whereby the initially homogeneous mixture turned into a thick paste (ca. 10 min). The mixture was then refluxed as above, evaporated to dryness at reduced pressure and the residue (**4d**) purified by chromatography (Kieselgel G; CH_2Cl_2 - acetone, 10:0.5).

Method H: By ring closure of ethyl N(2)-(2-amino-4,5-methylenedioxybenzoyl) carbazate (**15b**) with bromoacetyl bromide

Bromoacetyl bromide (13.8 ml, 158 mmol) was added dropwise to a mixture of ethyl N(2)-(2-amino-4,5-methylenedioxybenzoyl)carbazate (**15b**) (20 g, 74,8 mmol), Na_2CO_3 (8.25 g, 78 mmol) and dry dioxan (350 ml) with continuous stirring and ice-water cooling. The cooling bath was removed and the mixture stirred for another 6 h and evaporated to dryness at reduced pressure. The residue was taken up in water and CH_2Cl_2 (100 ml, each) and the aqueous phase extracted with CH_2Cl_2 (50 ml) The combined CH_2Cl_2 solutions were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (Kieselgel G; CH_2Cl_2 - acetone, 10:1) to furnish compound **4g**.

t-Butyl N-(2-halomethyl-4-oxo-3,4-dihydroquinazolin-3-yl)carbamates (**5a, b, d-g**) (Table 3)

Method G: By the reaction of 2-halomethyl-4H-3,1-benzoxazin-4-ones (**12**) with t-butyl carbazate

(a) Mixtures of the benzoxazinones **12a**, crude **12d** and **12f**, respectively, t-butyl carbazate (1.2 mol-equivalents) and dry benzene (10 parts) were refluxed for 1 h in an apparatus equipped with a water separator and allowed to cool to give the crystalline products **5a**, **5d** and **5f**, respectively, which were washed with ether.

(b) A mixture of the benzoxazinone **12b** (3.4 g, 14 mmol), t-butyl carbazate (2.1 g, 16 mmol) and dry benzene (30 ml) was stirred for ca. 1 h at room temperature (whereby a thick paste formed) and then refluxed as above to give a clear solution. The white solid (0.4 g) which separated from the solution on cooling was filtered off and the filtrate worked up by column chromatography (Kieselgel G 60, 150 g; CH_2Cl_2 - acetone, 10:1) to afford, in addition to two non-identified by-products (0.15 and 0.33 g, respectively), the desired product **5b** (2.56 g, 51%).

(c) A mixture of the benzoxazinone **12g** (4.3 g, 15 mmol), t-butyl cabazate (2.2 g 17 mmol) and dry benzene (25 ml) was stirred at room temperature (to afford a thick paste) and then refluxed as above whereby a clear solution resulted from which a white solid (0.4 g) separated. This was filtered off and the filtrate evaporated to dryness. The residue was dissolved in CH_2Cl_2 and worked up by chromatography (Kieselgel G 60, 250 g; CH_2Cl_2 - acetone, 10:1, 2 L) to afford the desired product **5g** (1.0 g, 16.7%) along with three unidentified co-products (1.1, 0.6 and 0.1 g, respectively).

Method J: By ring closure of t-butyl N(2)-(2-amino-4,5-methylenedioxybenzoyl)carbazate **15a** with haloacetyl chlorides

(a) Chloroacetyl chloride (24.2 ml, 300 mmol) was added dropwise

Table 3: Ethyl and t-butyl-N-(2-halomethyl-4-oxo-3,4-dihydroquinazolin-3-yl)carbamates 4 and 5

Compound	Method[a]	Yield %	M.p., °C (recryst. from)	Formula (Mol. wt.)	Found/calc., % C	H	Hlg[b]	N	$\nu_{max}^{(KBr)}$ cm^{-1}
4a[c]	F	54	148	$C_{12}H_{12}ClN_3O_3$			12.35	14.7	3180, 1760, 1700, 1240,
				(281.7)			12.6	14.9	1030
4b[d]	F	51	143	$C_{12}H_{12}BrN_3O_3$				13.0	3220, 1770, 1690, 1240
			(EtOH	(326.2)				12.9	1040
4d	F	66	146-7	$C_{12}H_{11}ClN_4O_5$			10.6	16.95	3200, 1720sh, 1700, 1560,
				(326.7)			10.85	17.15	1340, 1260, 1240, 1060, 1020
4g	H	65	194	$C_{13}H_{12}BrN_3O_5$				11.15	3220, 1760, 1670, 1260,
			(EtOH)	(370.2)				11.35	1240, 1050sh, 1020
5a	G	80	180 (dec)	$C_{14}H_{16}ClN_3O_3$			11.7	13.3	3270, 1760, 1680, 1240
			(benzene)	(309.8)			11.45	13.55	
5b	G	51	180-1	$C_{14}H_{16}BrN_3O_3$			22.25	12.05	3250, 1770, 1680, 1240
			(benzene)	(354.2)			22.55	11.85	
5d	G	88	178 (dec)	$C_{14}H_{15}ClN_4O_5$			9.7	15.7	3200, 1760, 1700, 1520,
				(354.8)			10.0	15.8	1345, 1240
5e	K	55	170-1	$C_{14}H_{15}BrN_4O_5$	42.4	3.8	20.0	14.05	3180, 1760, 1705, 1520,
			(i-PrOH)	(399.2)	42.1	4.0	20.05	13.85	1350, 1250
5f	G	90	187 (dec)	$C_{15}H_{16}ClN_3O_5$			9.35	11.1	3190, 1755, 1695, 1270
	J	59	187 (dec)	(353.8)			10.05	11.9	1230w, 1030
5g	G	17	181-2[e]	$C_{15}H_{16}BrN_3O_5$			19.65	11.05	3150, 1745, 1585, 1270,
			(benzene)	(398.2)			20.05	10.55	1250, 1030
	J	73	190[e]	$C_{15}H_{16}BrN_3O_5$	45.4	4.15	20.03	10.8	
				(398.2)	45.25	4.05	20.05	10.55	

Footnotes to Table 3

[a] For Methods F-K, see text

[b] Cl or Br, respectively

[c] $_{H}$ ($CDCl_3$) 1.27t + 4.23q, J 7 Hz, CO_2Et; 4.58s + 4.60s, CH_2; 7.4-8.25m, 4xArH + NH

[d] $_{H}$ ($CDCl_3$) 1.22t + 4.19q, J 7 Hz, CO_2Et; 4.38s, CH_2; 7.3-8.2m 4xArH + NH

[e] In spite of their different m.p.s the two samples of compound 5g were identical (i.r., t.l.c.)

Table 4: 3-Amino-2-halomethylquinazolin-4(3H)-ones (6)

Compound	Method[a]	Yield %	M.p., °C (recryst. from)	Formula (Mol. wt.)	Found/calc., % C	H	Hlg[b]	N	$\nu_{max}^{(KBr)}$ cm^{-1}
6a	L	70	158 (EtOH)	$C_9H_8ClN_3O$ (209.6)			16.7 16.9	20.20 20.05	3300, 3200, 1675, 1640w
6b	L	56	176-7 (crude						3310, 3205, 1675
6b[c]	N	54	185-6 (Et_2O)	$C_9H_8BrN_3O$ (254.1)	42.7 42.55	3.35 3.15	31.8 31.45	16.35 16.55	
6d	L	78	151.2	$C_9H_7ClN_4O_3$			13.65	21.95	3350, 3280, 3230w, 1685,
	M	57	(BuOH)	(254.6)			13.9	22.0	1620, 1550, 1330
6e	L	76	151-2	$C_9H_7BrN_4O_3$	36.3			19.1	3320, 3280sh, 3220,
			(BuOH)	(299.1)	36.15			16.75	1695, 1520, 1350
6f	L	80	208	$C_{10}H_8ClN_3O_3$			13.85	16.45	3330, 3280, 3220, 1680,
	M	88	(BuOH)	(253.9)			13.95	16.55	1640w, 1260, 1045
6g	L	67	181-2	$C_{10}H_8BrN_3O_3$ (298.1)	40.55 40.3		36.65 26.8		3320, 3270, 3200sh, 1660, 1275, 1030

[a] For Methods L-N, see text [b] Cl or Br, respectively

[b] Identical (i.r., t.l.c.) with an authentic sample obtained according to method L

to a suspension of compound **15a** (75 g, 254 mmol) and Na_2CO_3 (29.6 g, 280 mmol) in dry dioxan (1200 ml) with continuous stirring and ice-water cooling at such a rate (ca. 3/4 h) that the mixture did not congeal. Stirring was continued for 1 h at room temperature and the mixture was kept overnight at this temperature. The resulting crystalline product was washed with dioxan and then with water (1 L) to give compound **5f**. The filtrate and the dioxan washings were combined and evaporated to dryness at reduced pressure. The residue was dissolved in ether, the solution washed (5% aq. $NaHCO_3$, then water), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by trituration with benzene (100 ml) and washed with light petroleum to afford a second crop of compound **5f** (m.p. identical with that of the first crop; total yield 56 g, 59%).

(b) Bromoacetyl chloride (3.3 g, 21 mmol) was added dropwise to a suspension of compound **15a** (5.9 g, 20 mmol) and Na_2CO_3 (2.2 g, 21 mmol) in dry dioxan (120 ml) with continuous stirring and ice-water cooling at such a rate that the mixture did not congeal. The ice-water bath was removed and the mixture stirred for another 3 h and then replaced into the icewater bath. A further amount of bromoacetyl chloride (3.3 g, 21 mmol) was added as above. The bath was removed and stirring continued for 3 h. The resulting suspension was evaporated to dryness at reduced pressure. The residue was taken up in CH_2Cl_2 (60 ml), the solution washed with water (3x20 ml), dried ($MgSO_4$) and evaporated to dryness. The resulting crystals of compound **5g** (5.8 g, 73%) were purified by trituration with ether.

Method K: From 2-bromoacetylamino-5-nitrobenzoic acid (11e) without isolation of the intermediate benzoxazinone **12e** in pure form

Compound **11e** (5.0 g, 16.5 mmol) was refluxed with acetic anhydride (60 ml) for 1 h and the resulting clear solution evaporated to dryness at reduced pressure. The residue was triturated with pentane to give the crude benzoxazinone **12e** as a yellow amorphous material. A mixture of this product, t-butyl carbazate (2.4 g, 18 mmol) and dry benzene (20 ml) was stirred for 1 h at room temperature to give a thick paste which was refluxed for 1 h in an apparatus equipped with a water separator. A clear solution first formed and then the yellow crystals of the desiered compound **5e** gradually started to separate. The mixture was allowed to cool and the product (3.6 g, 55%) filtered and washed with ether.

3-Amino-2-(halomethyl)quinazolin-4(3H)-ones **6** (Table 4)

Method L: Mixtures of the carbamates **5** and dry (99%) acetic acid (5-10 parts) were refluxed until the evolution of CO_2 ceased, and evaporated to dryness at reduced pressure. The residues were triturated with

methanol, the products filtered and washed with methanol. Alternatively, the reaction mixtures were concentrated by evaporation of part of the solvent at reduced pressure until the product started to crystallize. The crystals were filtered and washed with ether.

Method M: The carbamates **5** were fused and heated at ca. 185°C until the evolution of CO_2 ceased (ca. 10 min). The products which solidified when allowed to cool were pulverised and triturated with butanol or ethanol and, if not sufficiently pure, recrystallized.

Method N

A mixture of 3-amino-2-methylquinazolin-4(3H)-one[1] (**1**) (30 g, 0.17 mol), ethanol (350 ml) and cyanogen bromide (21.2 g, 0.2 mol) was refluxed under a well-ventilated hood for 5 h in a flask eqipped with an efficient condenser and an absorber containing aqueous alkali. A homogeneous solution formed with vigorous gas evolution. After ca. 1 h a colourless crystalline powder started to separate. The product, **6b**, was isolated by filtration of the hot reaction mixture and proved identical (i.r., t.l.c.) with an authentic product obtained according to Method L.

Attempts to prepare the methylenedioxy derivative **6g** by the same method failed.

2-(Halomethyl)-3-hetarylquinazolin-4(3H)-ones **7-9** (Table 5)

Method P

A mixture of compound **6a** (10.4 g, 50 mmol) and hexane-2,5-dione (20 ml) was stirred for ca. 1 h at 150°C under argon and evaporated to dryness at reduced pressure. The oily residue crystallized when triturated with ether. The crude blue product was purified by medium-pressure chromatography (Kieselgel G, 100 g; CH_2Cl_2; 200 kPa) to afford 2-(chloromethyl)-3-(2,5-dimethylpyrrol-1-yl)quinazolin-4(3H)-one **7a**. The product turns coloured when exposed to light or air.

Method R: By the reaction of 4H-3,1-benzoxazin-4-ones (**12**) with 4-amino-3,5-dimethylisoxazole and 4-amino-3,5-dimethylpyrazole.

(a) Mixtures of the benzoxazinones **12a**, **d** and **f**, respectively, (50-55 mmol), 4-amino-3,5-dimethylisoxazole[17] (1.05-1.1 mol-equivalent) and dry benzene (100 ml) were stirred for 1/2 - 4 h at room temperature whereby a clear solution (**a**), a crystalline product with a clear supernatant (**b**) and a suspension (**f**), respectively, resulted. The mixtures were the refluxed for 1/2 (**a**, **d**) - 4 h (**f**) in an apparatus equipped with a water separator. The clear solution obtained in the **a** series was treated with Norite and evaporated to dryness at reduced pressure. The residue was crystallized from ethanol. In the **d** series the wine-red solid which separated when the mixture was allowed to cool was recrystallized from benzene (in the presence of Norite or Kieselgel G).

Table 5: 2-Halomethyl-3-hetarylquinazolin-4(3H)-ones **7-9**

Compound	Method[a]	Yield %	M.p., °C (recryst. from)	Formula (Mol. wt.)	Found/Calc., % C	H	Cl	N	ν_{max}(KBr) cm^{-1}
7a	P	67	132-3	$C_{15}H_{14}ClN_3O$			12.55	14.35	1700, 1600
				(287.7)			12.3	14.6	
7c	S	31	88-9	$C_{15}H_{14}FN_3O$				15.7	1690, 1605
			(benzene-pentane)	(271.3)				15.5	
8a	R	67	172-3	$C_{14}H_{12}ClN_3O_2$			11.85	14.0	1700, 1650, 1600
			(EtOH)	(289.7)			12.25	14.5	
8d	R	72	207-8	$C_{14}H_{11}ClN_4O_4$	50.1	3.2	10.55		1705, 1650, 1620, 1600,
			(benzene)	(334.7)	50.25	3.3	10.6		1525, 1350
8f	R	65	225-7	$C_{15}H_{12}ClN_3O_4$	53.7	3.85	10.7		1680, 1640, 1620, 1250,
			(BuOH)	(333.7)	54.0	3.65	10.6		1030
8h	S	64	192-4	$C_{15}H_{12}FN_3O_4$				13.3	1660, 1630sh, 1610, 1245,
			(EtOH)	(317.3)				13.25	1060
9a	R	67	192	$C_{14}H_{13}ClN_4O$			12.2	19.1	3300-2700, 1680, 1600
				(288.7)			12.3	19.4	
9c	S	36	187	$C_{14}H_{13}FN_4O$				20.4	3300-2650,[b] 1670, 1650
			(EtOAc)	(272.3)				20.6	
9d	R	81	242	$C_{14}H_{12}ClN_5O_3$			10.9	20.7	3300-2700, 1690, 1560,
			(BuOH)	(333.7)			10.6	21.0	1520, 1350
9f	R	68	205-6	$C_{15}H_{13}N_4O_3$	53.85	4.15	10.4	16.6	3320-2700,[c] 1660, 1600,
			(MeOH)	(332.7)	54.15	3.95	10.65	16.85	1560, 1240, 1020

[a] For Methods P-S, see text

[b] Intensive maximum at 3240 cm^{-1}

[c] Intensive maximum at 3200 cm^{-1}

Table 6: ^{1}H n.m.r. spectra of the 2-halomethyl-3-hetarylquinazolin-4(3H)-ones **7-9** in $CDCl_3$

7a: 2.05s (2xMe), 425.s (CH_2Cl), 6.0s (2x pyrrole H), 7.3-8.0 (3xArH), 8.35d (J≈9 Hz; 5-H)

7c: 2.0s (2xMe), 5.0d (J≈46 Hz; CH_2F), 5.95s (2x pyrrole H), 7.3-7.9m (3xArH), 8.3d (J≈9 Hz; 5-H)

8a: 2.2s + 2.35s (2xMe), 4.3s (CH_2Cl), 7.4-7.9m (3xArH), 8.35d (J≈9 Hz; 5-H)

8d: 2.15s + 2.4s (2xMe), 4.3s (CH_2Cl), 7.85d (J≈9 Hz; 8-H), 8.55dd (7-H), 8.95d (J≈2 Hz; 5-H)

8f: 2.15s + 2.3s (2xMe), 4.25s (CH_2Cl), 6.15s (OCH_2O), 7.1s + 7.55s (2xArH)

8h: 2.1s + 2.25s (2xMe), 5.0d (J≈48 Hz; CH_2F), 6.05s (OCH_2), 7.1s + 7.5s (2xArH)

9a: 2.1s (2xMe), 4.3s (CH_2Cl), 7.3-7.9m (3xArH), 8.3d (J≈9 Hz; 5-H), 10.15bs (NH)

9c: 2.1s (2xMe), 5.05d (J≈46 Hz; CH_2F), 7.4-7.9m (3xArH), 8.3d (J≈9 Hz; 5-H)

9d:* 2.1s (2xMe), 4.55s (CH_2Cl), 8.15d (J≈9 Hz; 8-H), 8.85dd (7-H), 9.05d (J≈2Hz; 5-H)

9f: 2.1s (2xMe), 4.25s (CH_2Cl), 6.1s (OCH_2O), 6.6bs (NH), 7.1s + 7.55s (2xArH)

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* In DMSO-d_6

In the **f** series part of the product separated in crystalline form when the mixture was allowed to cool; an equal amount of the same product was obtained by evaporation of the filtrate to dryness at reduced pressure. The combined crude fractions were purified by pouring their solution in CH_2Cl_2 (200 ml) through a Kieselgel G column (100 g). When the solvent benzene was replaced by dioxan in the **f** series, the same product was obtained in slightly lower yield.

(b) Mixtures of the benzoxazinones **12a**, **d** and **f**, respectively, (50 mmol), 4-amino-3,5-dimethylpyrazole[18] (50-55 mmol) and anhydrous dioxan (200 ml in the **a** and **f**, 60 ml in the **d** series) were stirred for 16 h at room temperature; almost clear solutions formed in the **a** and **f** series whereas, in the **d** series, crystallization of the product from the initially formed clear solution soon started. The small amounts of impurities were filtered off in the **a** and **f** series and the filtrates, as well as the mixture resulting in the **d** series (containing part of the product in crystalline form) were evaporated to dryness at reduced pressure. The residues were purified either by chromatography (**a** series; Kieselgel G; CH_2Cl_2 - acetone, 7:3) or trituration with CH_2Cl_2 (**d** series) or by recrystallization from methanol (**f** series). Alternatively, the residue was dissolved in CH_2Cl_2 (20 ml) and allowed to stand overnight whereby the product gradually crystallized (**a** series).

Method S: By halogen exchange

Mixtures of the 3-hetarylbenzoxazinones **7a**, **8f** and **9a** (2-50 mmol), KF (3 mol-equivalent) and 1,2-ethanediol (3-5 ml for 10 mmol of the hetarylbenzoxazinone) were heated for 2 h at 165°C, allowed to cool and taken up in water and CH_2Cl_2. The aqueous phases were extracted with CH_2Cl_2, the combined CH_2Cl_2 solutions dried ($MgSO_4$) and evaporated to dryness. The residues were purified by column chromatography (**7c**, **9c**; Kieselgel G; CH_2Cl_2 - hexane, 7:3) or by recrystallization from benzene (**7c**), ethanol (**8h**) or ethyl acetate (**9c**).

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REFERENCES

1 Legrand, L.; Lozac'h, N. Bull. soc. chim. France **1961**, 1400, and earlier references cited; Bogert, M.T.; Gortner, R.A. J.Am. Chem. Soc. **1909**, 31, 943; Heller, G. Ber. dtsch. chem. Ges.**1915**, 48, 1182

2 Dymek, W.; Lubimowski, B. Diessertationes Pharm. **1964**, 16 247; Chem. Abstr. **1965**, 63, 11561c

3 Dymek, W.; Lubimowski, B.; Karwal, S. Diss. Pharm. Pharmacol.**1968**, 20 29; Chem. Abstr. **1968**, 69, 273p

4 Boltze, K.-H.; Dell, H.-D.; Lehwald, H.; Lorenz, D.; Rüberger-Schweer, M. Arzneimittelforsch. **1963**, 13, 688

5 Beri, M.L.; Narang, K.S.; Ray, J.N. J. Indian Chem. Soc. **1935**, 12, 395; Chem. Abstr. **1936**, 30, 463[8]

6 Gärtner, S. Liebigs Ann. Chem. **1904**, 336, 220

7 Imperial Chem. Ind., Ltd., Brit. 857.362 (Dec 29, 1960); Chem. Abtrs. **1961**, 55, 14487g

8 Abezgauz, F.I.; Sokolov, S.V.; Udilov, G.P. Zh. Obshch. Khim. **1964**, 34, 2965

9 Petersen, S.; Herlinger, H.; Tietze, E.; Stiefken, W. Angew. Chem. **1962**, 74, 855

10 Armarego, W.L.F. in Adv. Heterocyclic Chem., Vol. 1 (ed. A.R.Katritzky), Academic Press, New York and London, **1963** (a) p. 291, (b) p. 293

11 Amarego W.L.F. in The Chemistry of Heterocyclic Compounds (Series Editor A. Weissberger), Vol. 24,Part I (ed. D.J. Brown), Interscience, New York etc., **1967** (a) p. 79, (b) p. 84, (c) p. 337, (d) p. 338

12 Mamoli, E. Gazz. chim. ital. **1907**, 36I, 169

13 Heller, G. J. prakt. Chem. **1927**. 2 116, 1

14 Peet, N.T.; Sunder, S.; Creppe, R.J. J. Org. Chem. **1976**, 41, 2732

15 Mérour, J.Y. J. Heterocycl. Chem. **1982**, 19, 1425

16 Scheiner, P.; Frank, L.; Giusti, I.; Arwin, S.; Pearson, S.A.; Excellent, F.; Harper, A.R. J. Heterocycl. Chem. **1984**, 21, 1817

17 Morgan G.T.; Burgess, H. J. Chem. Soc. 1921, 119, 697

18 Morgan, G.T.; Akermann, J. ibid. **1923**, 123, 1310

19 Pawlevski,B.; Ber. dtsch. chem. Ges. **1905**, 38, 1684