709. *Cyclic Amidines. Part X.*[1] *2-Aminoquinazoline Derivatives.*

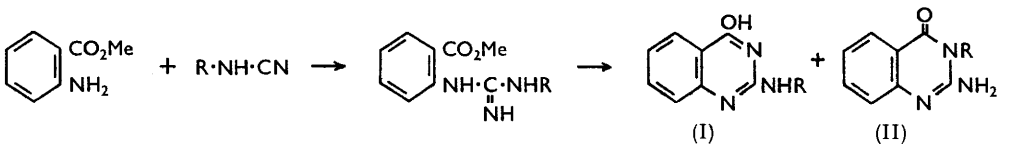
By R. J. Grout and M. W. Partridge.

2-(Substituted amino)- and 3-substituted 2-amino-quinazolines have been produced by interaction of a urea, an arenesulphonyl chloride, and methyl anthranilate.

Rearrangements of 3-substituted 2-amino-3,4-dihydro-4-oxoquinazolines to their 2-(substituted amino)-isomers, aminolyses, alkylations, and transalkylations of quinazoline derivatives have been examined. None of the compounds reported was of therapeutic interest.

Guanidines have been prepared from cyanamides, formed in pyridine, by interaction of a urea with an arenesulphonyl chloride.[2] The production of their cyclic analogues, 2-aminoquinazolines, is now described; the cyanamide, without isolation, is brought into reaction with methyl anthranilate.

The scope of this procedure was examined by the preparation of a series of 2-aminoquinazolines from seven alkyl-, an aralkyl-, and four aryl-ureas. As expected, the usual product was a mixture of the two isomers (I) and (II), resulting from the cyclisation, in both possible ways, of an intermediate guanidine derivative. These products were readily separable by exploiting the alkali-solubility of the 4-hydroxyquinazoline (I). When R was isopropyl, cyclohexyl, or *o*- or *p*-tolyl, the method afforded only the 4-hydroxy-



quinazoline (I). For confirmation of the structure (II), assigned to the alkali-insoluble isomers, certain examples were converted into the corresponding, known 2-hydroxyquinazolines. The properties of the unidentified material obtained by Deck and Dains [3] by interaction of *S*-methylphenylthiourea and anthranilic acid are in agreement with its being an analogous mixture of two isomers.

Methylphenylcyanamide, prepared from the urea, similarly furnished 4-hydroxy-2-*N*-methylanilinoquinazoline, but from 2-diethylaminoethyl-*p*-methoxyphenylcyanamide no recognisable product was obtained. In spite of the reported reactivity of 2-chloroquinazolines with alkylanilines,[4] and of a successful preparation of 4-ethoxy-2-*N*-methylanilinoquinazoline from 2-chloro-4-ethoxyquinazoline and methylaniline, *NN*-diethyl-*N'*-*p*-methoxyphenylethylenediamine could not be brought into reaction with 2-chloro-4-ethoxyquinazoline.

The production, from the corresponding urea, of *o*-methoxycarbonylphenylcyanamide for reaction with an amine salt did not appear to be a useful, alternative route to 2-aminoquinazolines, since, in addition to the required cyanamide (28%), its benzenesulphonyl derivative and 2,4-dihydroxyquinazoline were formed.

2-Amino-3,4-dihydro-3-methyl-4-oxoquinazoline (II; R = Me) is reported [5] to be unaffected by acids and alkalis, whereas we found that with alkali, but not with acid, it was almost quantitatively isomerised to the 2-methylaminoquinazoline (I; R = Me). The analogues (II; R = Et, Pr^n, Ph, *p*-MeO·C$_6$H$_4$) behaved similarly, whereas the 3-benzyl

[1] Part IX, *J.*, 1959, 2396.
[2] Partridge and Turner, *J. Pharm. Pharmacol.*, 1953, **5**, 103.
[3] Deck and Dains, *J. Amer. Chem. Soc.*, 1933, **55**, 4986.
[4] Curd, Landquist, and Rose, *J.*, 1947, 775.
[5] Griess, *Ber.*, 1880, **13**, 977.

analogue (II; R = Ph·CH_2) afforded only a low yield of its isomer (I; R = Ph·CH_2). Since thermal rearrangements have not been effected in this series,[6] it is suggested that the foregoing rearrangement involved intermediate formation of an *o*-guanidinobenzoate anion. Isomerisations which are formally similar have previously been encountered with pyridine,[7] glyoxaline,[8] pyrimidine,[9] and triazole [10] derivatives.

Direct alkylation of 2-amino-4-hydroxyquinazoline was inefficient for the production of its 3-n-butyl and 3-benzyl derivatives, and during alkylation with 2-chloroethyl acetate the deacetylated product, 2-amino-3,4-dihydro-3-2′-hydroxyethyl-4-oxoquinazoline (II; R = CH_2·CH_2·OH), was obtained.

Because of the low reactivity of certain 2-chloroquinazolines with aliphatic amines,[11] other routes to 2-alkylaminoquinazolines were investigated; *e.g.*, although 4-hydroxy-2-mercaptoquinazoline did not react with 2-diethylaminoethylamine, the 2-methylthio-derivative readily gave 2-2′-diethylaminoethylamino-4-hydroxyquinazoline, previously prepared from 2-chloro-4-hydroxyquinazoline.[12] Reaction of 2-amino-4-hydroxyquinazoline with aniline was slow, and with *o*-toluidine failed to yield a pure product, whereas with ethanolamine it gave the required 4-hydroxy-2-2′-hydroxyethylamino- together with 2,4-di-2′-hydroxyethylamino-quinazoline. Formation of the latter amine recalls similar replacements in quinolines [13] and naphthyridines.[14] For a similar reaction with a simple alkylamine, a mixture of the amine and its salt was used.

Transalkylation, known to occur with 2,4-dialkoxyquinazolines [15] and alkoxyamino-pyrimidines,[16] appeared to offer a prospect of a route to 4-alkoxy-2-aminoquinazolines. Thus 2-anilino-4-benzyloxy-, -4-butoxy-, and -4-pentyloxy-quinazoline were prepared in this way from 2-anilino-4-ethoxyquinazoline. The butyl ether was also produced by alkylation of 2-anilino-4-hydroxyquinazoline and unequivocally from 2-anilino-4-chloro-quinazoline and sodium butoxide. In contrast, the sodium derivative of ethanolamine with 2-anilino-4-ethoxyquinazoline afforded the 4-hydroxyethylamino-derivative, an authentic specimen of which was obtained from 2-chloro-4-2′-hydroxyethylamino-quinazoline [4] and aniline.

Many of the foregoing compounds were examined for schistosomicidal, molluscicidal, and viricidal activity; none was detected. The spasmolytic action observed at 1 : 100,000 especially in 3-alkyl-2-amino-3,4-dihydro-4-oxoquinazolines was too weak to be of practical significance.

Experimental

2-Ethylamino-4-hydroxy- and 2-Amino-3-ethyl-3,4-dihydro-4-oxo-quinazolines.—Ethylurea (8·8 g.), suspended in dry pyridine (30 ml.), was treated during 10 min. at 0° with benzenesulphonyl chloride (17·7 g., 1 mol.) and kept at 0° overnight. Methyl anthranilate (15·1 g., 1 mol.) was added and the mixture was heated on a steam-bath for 4 hr. The *4-hydroxyquinazolinium chloride* (6·1 g.) which separated crystallised from 2-ethoxyethanol as needles, m. p. 293° (decomp.) (Found: N, 19·8; Cl, 8·0. $2C_{10}H_{11}N_3O$,HCl requires N, 20·3; Cl, 8·5%). The *base* crystallised from acetone as prisms, m. p. 232°, $\lambda_{max.}$ 228, 267, and 322 mμ (ε 32,800, 14,200, and 3280) [Found: C, 60·5; H, 6·5; N, 21·3; H_2O (Karl Fischer), 4·4. $C_{10}H_{11}N_3O$,0·5H_2O requires C, 60·6; H, 6·1; N, 21·2; H_2O, 4·6%]. Its *picrate* (needles from acetic acid) had m. p. 274—275° (decomp.) (Found: C, 46·0; H, 3·2. $C_{16}H_{14}N_6O_8$ requires

[6] Wheeler, Johnson, and McFarland, *J. Amer. Chem. Soc.*, 1903, **25**, 787.
[7] Tschitschibabin and Kirssanow, *Ber.*, 1928, **61**, 1223.
[8] Johnson and Nicolet, *J. Amer. Chem. Soc.*, 1915, **37**, 2416.
[9] Carrington, Curd, and Richardson, *J.*, 1955, 1858; Brown, Hoerger, and Mason, *ibid.*, p. 4035.
[10] Dimroth, *Annalen*, 1909, **364**, 183.
[11] Bunnett, *J. Amer. Chem. Soc.*, 1946, **68**, 1327.
[12] Curd, Hoggarth, Landquist, and Rose, *J.*, 1948, 1766.
[13] Curd, Raison, and Rose, *J.*, 1947, 899.
[14] Oakes and Rydon, *J.*, 1958, 204.
[15] Lange and Sheibley, *J. Amer. Chem. Soc.*, 1932, **54**, 1994, 4305.
[16] Rose and Tuey, *J.*, 1946, 81.

C, 45·9; H, 3·4%). The *acetyl derivative* separated as prisms, m. p. 121—122, from benzene–light petroleum (Found: N, 18·6. $C_{12}H_{13}N_3O_2$ requires N, 18·2%).

The pyridine mother-liquor from the isolation of the foregoing chloride was evaporated to dryness *in vacuo* and the residue, after being co-distilled with aqueous ammonia (130 ml.), dissolved in chloroform, and dried (K_2CO_3), furnished the *4-oxoquinazoline* (3 g.) which crystallised from water as prisms, m. p. 186—187°, $\lambda_{max.}$ 227, 268, and 329 mμ (ε 32,000, 13,200, 3800) (Found: C, 63·7; H, 5·8; N, 22·5. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·9; N, 22·2%). Its *picrate* formed prisms, m. p. 282—284° (decomp.) (from acetic acid) (Found: C, 45·9; H, 3·1%). Its *acetyl derivative* crystallised from benzene–light petroleum as prisms, m. p. 158—159° (Found: C, 62·3; H, 5·7. $C_{12}H_{13}N_3O_2$ requires C, 62·3; H, 5·7%).

Quinazolines listed in the Table were prepared analogously.

n-Pentylurea.—n-Pentylamine (17·4 g.) in concentrated hydrochloric acid (20 ml.) and water (50 ml.) was treated with sodium cyanate (13 g.) in water (100 ml.). After being concentrated to 100 ml., the solution gave the *urea* (17·5 g.), m. p. 99·5° (from ethyl acetate) (Found: N, 21·3. $C_6H_{14}N_2O$ requires N, 21·5%).

Methylphenylcyanamide.—*N*-Methyl-*N*-phenylurea (15 g.) was refluxed for 3 hr. with benzenesulphonyl chloride (17·7 g.) in dry benzene (50 ml.) containing triethylamine (30 g.). Solvent was removed from the filtered mixture, and the cyanamide (6·5 g.) was recovered from a steam-distillate of the residue by extraction with ether. It had b. p. 137—139°/17 mm. and gave an oxime, m. p. and mixed m. p. 102°.[19]

4-Hydroxy-2-N-methylanilinoquinazoline.—An aqueous alkaline solution of the product of interaction of methylphenylcyanamide (3 g.) and *o*-methoxycarbonylanilinium toluene-*p*-sulphonate (7·4 g.) at 210° for 2 hr. furnished, after being washed with ether and neutralised,

Quinazolines (I) *and* (II).

R	M. p.	Yield (%)	Formula	Found (%) C	H	N	Reqd. or Calc. (%) C	H	N
			Compounds (I)						
Me [a]	276°	7	$C_9H_9N_3O$	61·9	5·2	24·3	61·7	5·2	24·0
picrate	294 *		$C_{15}H_{12}N_6O_8$	44·7	3·2		44·6	3·0	
acetyl	196		$C_{11}H_{11}N_3O_2$			19·3			19·4
Pr[a]	198·5—200	34	$C_{11}H_{13}N_3O$	64·7	6·2		65·0	6·5	
0·5HCl	292·5—293·5		$2C_{11}H_{13}N_3O,HCl$	Cl, 7·8		19·1	Cl, 8·0		19·0
picrate	252 *		$C_{17}H_{16}N_6O_8$	47·0	3·8		47·2	3·7	
acetyl	118—119		$C_{13}H_{15}N_3O_2$			17·1			17·1
Pr[i]	212—213	45	$C_{11}H_{13}N_3O$	65·3	6·3	20·9	65·0	6·5	20·7
picrate	264 *		$C_{17}H_{16}N_6O_8$	47·3	3·9		47·2	3·7	
acetyl	129—130		$C_{13}H_{15}N_3O_2$			17·1			17·1
Bu[n] [b]	187—188	39	$C_{12}H_{15}N_3O$	66·4	7·0	19·5	66·3	7·0	19·3
0·5HCl	258—259		$2C_{12}H_{15}N_3O,HCl$	Cl, 8·0		18·2	Cl, 7·5		17·8
picrate	240 *		$C_{18}H_{18}N_6O_8$	48·1	3·9		48·4	4·1	
acetyl	111—112		$C_{14}H_{17}N_3O_2$	65·1	6·3		64·8	6·6	
$CH_3{\cdot}[CH_2]_4$	157·5—159	40	$C_{13}H_{17}N_3O$	67·4	7·0	18·1	67·5	7·4	18·2
0·5HCl	235		$2C_{13}H_{17}N_3O,HCl$	Cl, 8·0		16·7	Cl, 7·1		16·8
picrate	215—216		$C_{19}H_{20}N_6O_8$			18·1			18·3
acetyl	60—62		$C_{15}H_{19}N_3O_2$	66·2	6·9		65·9	7·0	
Cyclohexyl	209—210	58	$C_{14}H_{17}N_3O$	69·1	7·3	17·0	69·1	7·0	17·3
0·5HCl	283		$2C_{14}H_{17}N_3O,HCl$	Cl, 7·1			Cl, 6·8		
picrate	267 *		$C_{20}H_{20}N_6O_8$			17·9			17·8
acetyl	204—205		$C_{16}H_{19}N_3O_2$			14·8			14·7
Ph·CH_2	213·5—214·5	49	$C_{15}H_{13}N_3O$	71·6	5·1	17·0	71·7	5·2	16·7
picrate	236		$C_{21}H_{16}N_6O_8$	52·4	3·3	17·2	52·5	3·4	17·5
acetyl	124—125		$C_{17}H_{15}N_3O_2$			14·1			14·3
Ph [c]	261	19	$C_{14}H_{11}N_3O$	71·2	4·9	17·8	70·9	4·7	17·7
picrate	268 *		$C_{20}H_{14}N_6O_8$	51·4	3·2	17·8	51·5	3·0	18·0
acetyl	202—204		$C_{16}H_{13}N_3O_2$	68·5	4·8	15·1	68·8	4·7	15·1
p-C_6H_4Me	268—269	32	$C_{15}H_{13}N_3O$	71·9	4·9	16·8	71·7	5·2	16·7
semipicrate	285 *		$C_{36}H_{29}N_9O_9$	58·8	4·0	17·3	59·1	4·0	17·2
acetyl	209		$C_{17}H_{15}N_3O_2$			14·3			14·3
o-C_6H_4Me	287—289 *	41	$C_{15}H_{13}N_3O$			16·6			16·7
picrate	255—256 *		$C_{21}H_{16}N_6O_8$			17·2			17·5
acetyl	154—156		$C_{17}H_{15}N_3O_2$			14·5			14·3
p-MeO·C_6H_4 [d]	271—272	36							
acetyl	204—205		$C_{17}H_{15}N_3O_3$	65·7	4·5		66·0	4·9	

TABLE. (*Continued.*)

R	M. p.	Yield (%)	Formula	Found (%) C	Found (%) H	Found (%) N	Reqd. or Calc. (%) C	Reqd. or Calc. (%) H	Reqd. or Calc. (%) N
			Compounds (II)						
Me [e]	242°	46	$C_9H_9N_3O$	62·0	4·8	23·9	61·7	5·2	24·0
picrate	282—283 *		$C_{15}H_{12}N_6O_8$			20·6			20·8
acetyl	156—157		$C_{11}H_{11}N_3O_2$	60·9	4·9	19·6	60·8	5·1	19·4
Pr^n	186—188	16·5	$C_{11}H_{13}N_3O$	65·0	6·2	21·0	65·0	6·5	20·7
picrate	261		$C_{17}H_{16}N_6O_8$	46·8	3·8		47·2	3·7	
acetyl	151—152		$C_{13}H_{15}N_3O_2$	63·8	6·2		63·7	6·2	
Bu^n [f]	192	11	$C_{12}H_{15}N_3O$	66·0	6·7	19·3	66·3	7·0	19·3
picrate	228—229		$C_{18}H_{18}N_6O_8$	48·4	4·1		48·4	4·1	
acetyl	140—141		$C_{14}H_{17}N_3O_2$	64·6	6·4		64·8	6·6	
$CH_3{\cdot}[CH_2]_4$	177	16	$C_{13}H_{17}N_3O$	67·3	6·9	18·6	67·5	7·4	18·2
picrate	250		$C_{19}H_{20}N_6O_8$			18·4			18·3
acetyl	96		$C_{15}H_{19}N_3O_2$	66·1	6·8		65·9	7·0	
Ph·CH_2 [g]	202—204	9	$C_{15}H_{13}N_3O$	71·8	4·9	16·9	71·7	5·2	16·7
picrate	270 *		$C_{21}H_{16}N_6O_8$	52·9	3·6	17·6	52·5	3·4	17·5
acetyl	189—190		$C_{17}H_{15}N_3O_2$			13·9			14·3
Ph [h]	252	23	$C_{14}H_{11}N_3O$	71·2	4·5	17·8	70·9	4·7	17·7
HCl	291—292		$C_{14}H_{11}N_3O$,HCl	61·7	4·6	15·3	61·4	4·4	15·4
picrate	268—269 *		$C_{20}H_{14}N_6O_8$	51·5	3·4	17·7	51·5	3·0	18·0
diacetyl	209		$C_{18}H_{15}N_3O_3$	67·4	5·0	13·2	67·3	4·7	13·1
p-MeO·C_6H_4	234—236	5	$C_{15}H_{13}N_3O_2$	67·1	5·1	15·6	67·4	4·9	15·7
toluene-*p*-sulphonate	258—259		$C_{22}H_{21}N_3O_5S$	59·9	4·9		60·1	4·8	
picrate	271—272		$C_{21}H_{16}N_6O_9$	50·9	3·4	16·9	50·8	3·3	16·9
diacetyl	206—208		$C_{19}H_{17}N_3O_4$			12·2			12·0

* With decomp.

[a] Griess [5] records no m. p. for this compound. [b] The same compound (57%) was obtained as the amphoteric product, when 2-amino-4-hydroxyquinazoline, n-butylamine (1 mol.), and n-butylamine toluene-*p*-sulphonate (1 mol.) were heated together at 210° for 16 hr. [c] Mixed [15] m. p. 261°. [d] Mixed [4] m. p. 271—272°. [e] Griess [5] records no m. p. for this compound; 1,2,3,4-tetrahydro-3-methyl-2,4-dioxoquinazoline (90%), m. p. and mixed [17] m. p. 234—236°, was obtained by addition of sodium nitrite to a boiling solution in 2N-hydrochloric acid. [f] 2-Amino-4-hydroxyquinazoline alkylated with n-butyl bromide in ethanolic sodium ethoxide gave the same compound (11%). [g] Benzylation of 2-amino-4-hydroxyquinazoline gave 28% of this compound. [h] Wheeler, Johnson, and McFarland [6] record m. p. 237—238°; 1,2,3,4-tetrahydro-2,4-dioxo-3-phenylquinazoline (70%), m. p. and mixed [18] m. p. 280—281°, was obtained by the addition of sodium nitrite to a boiling solution in 2N-hydrochloric acid.

the *quinazoline* (1·3 g.), which crystallised from ethanol as prisms, m. p. 197·5—198·5° (Found: C, 71·8; H, 5·1; N, 16·9. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%). Its *toluene*-p-*sulphonate* (prisms from ethanol–ether) had m. p. 173—174° (Found: N, 9·7. $C_{22}H_{21}N_3O_4S$ requires N, 9·9%).

(2-*Diethylaminoethyl*)-p-*methoxyphenylcyanamide.*—*p*-Methoxyphenylcyanamide [20] (9·8 g.) and 2-diethylaminoethyl chloride hydrochloride (11·4 g.), when refluxed in ethanol (150 ml.) containing sodium (3 g.) for 1 hr., furnished the *cyanamide* (11·3 g.), m. p. 31—33°, b. p. 184°/4 mm. (Found: N, 16·8. $C_{14}H_{21}N_3O$ requires N, 17·0%), and tri-*p*-methoxyphenylisomelamine (1·4 g.), m. p. 212° (Found: C, 64·4; H, 5·4; N, 19·3. Calc. for $C_{24}H_{24}N_6O_3$: C, 64·9; H, 5·4; N, 18·9%); King and Tonkin [20] recorded m. p. 218°.

4-*Ethoxy*-2-N-*methylanilinoquinazoline*, formed when 2-chloro-4-ethoxyquinazoline [21] and methylaniline were boiled in ethanol for 1 hr., crystallised from light petroleum as prisms, m. p. 87—88° (Found: C, 73·4; H, 5·7; N, 15·0. $C_{17}H_{17}N_3O$ requires C, 73·1; H, 6·1; N, 15·0%). Its *picrate* separated from ethanol as prisms, m. p. 189—190° (decomp.) (Found: N, 16·2. $C_{23}H_{20}N_6O_8$ requires N, 16·5%).

2-p-*Anisidino*-4-*ethoxyquinazoline.*—2-Chloro-4-ethoxyquinazoline (2·3 g.) and *p*-anisidine (1·2 g.) were boiled in ethanol (20 ml.) for 1 hr. and the *base* (2·9 g.), liberated with sodium carbonate, crystallised from light petroleum as prisms, m. p. 98—99° (Found: C, 69·1; H, 5·5.

[17] Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2052.
[18] Pawlewski, *Ber.*, 1905, **38**, 130.
[19] von Braun and Schwarz, *Ber.*, 1903, **36**, 3660.
[20] King and Tonkin, *J.*, 1946, 1063.
[21] Lange, Roush, and Ashbeck, *J. Amer. Chem. Soc.*, 1930, **52**, 3696.

$C_{17}H_{17}N_3O_2$ requires C, 69·1; H, 5·8%). Its *picrate* formed prisms, m. p. 179—180°, from acetone (Found: C, 52·4; H, 3·9. $C_{23}H_{20}N_6O_9$ requires C, 52·7; H, 3·8%).

Interaction of Methyl o-Ureidobenzoate and Benzenesulphonyl Chloride.—Benzenesulphonyl chloride (17·7 g.) was slowly added at 0° to methyl *o*-ureidobenzoate [17] (19·4 g.), suspended in pyridine (30 ml.), and the mixture was kept at 0° overnight. The water-insoluble residue obtained by removal of the solvent furnished, as an alkali-soluble fraction, methyl *o*-cyanamidobenzoate, m. p. and mixed m. p. 105—106° [22] (4·9 g.), and 2,4-dihydroxyquinazoline (3·5 g.), m. p. and mixed m. p. 349—350° (Found: C, 59·1; H, 3·7; N, 16·8. Calc. for $C_8H_6N_2O_2$: C, 59·3; H, 3·7; N, 17·3%). The alkali-insoluble fraction yielded *methyl o-benzenesulphonylcyanamidobenzoate* (8·1 g.) which crystallised from propan-2-ol as prisms, m. p. 108° (Found: C, 57·0; H, 4·3; N, 8·8. $C_{15}H_{12}N_2O_4S$ requires C, 57·0; H, 3·8; N, 8·9%).

Rearrangement of 3-Substituted 2-Amino-3,4-dihydro-4-oxoquinazolines.—2-Amino-3,4-dihydro-4-oxo-3-phenylquinazoline (1 g.) was boiled with 10N-sodium hydroxide (20 ml.) for 8 hr. Decomposition of the resulting sodium salt with acetic acid gave 2-anilino-4-hydroxyquinazoline (1 g.), m. p. 261°, undepressed on admixture with a specimen prepared by Lange and Sheibley's method.[15] Its acetyl derivative had m. p. and mixed m. p. 202—204°.

The same product was formed (74%) when 2-amino-4-hydroxyquinazoline was boiled with aniline (10 mol.) for 24 hr.

The following compounds were similarly produced by analogous rearrangements and identified by comparison of the base and appropriate derivatives with specimens already described: 4-hydroxy-2-methylaminoquinazoline (95%); 2-ethylamino-4-hydroxyquinazoline (75%); 4-hydroxy-2-n-propylaminoquinazoline (50%); 2-benzylamino-4-hydroxyquinazoline (11%); 4-hydroxy-2-*p*-methoxyanilinoquinazoline (100%), also produced by boiling 4-ethoxy-2-*p*-methoxyanilinoquinazoline with 3N-hydrochloric acid for 5 hr.

2-Guanidino-4-hydroxyquinazoline.—Dicyandiamide (8·4 g.), *o*-methoxycarbonylanilinium toluene-*p*-sulphonate (32·3 g.) and toluene-*p*-sulphonic acid (19 g.), when boiled together in water (200 ml.) for 3 hr. and cooled, gave the *toluene*-p-*sulphonate* (15·3 g.) which crystallised from dilute aqueous toluene-*p*-sulphonic acid as needles, m. p. 291—292° (Found: C, 51·1; H, 4·4; N, 18·4. $C_{16}H_{17}N_5O_4S$ requires C, 51·2; H, 4·6; N, 18·7%). The base liberated from this salt had m. p. 310—311° (decomp.), undepressed on admixture with a sample prepared by Cohn's method; [23] Cohn recorded m. p. above 280° and regarded this compound as 3-amidino-2-amino-3,4-dihydro-4-oxoquinazoline, although it is soluble in aqueous alcoholic alkali without decomposition.

2-Amino-4-hydroxyquinazoline.—(i) 2-Guanidino-4-hydroxyquinazoline (2 g.), when boiled for 2 hr. with potassium hydroxide (4 g.) in ethylene glycol (20 ml.), diluted with water, and neutralised, gave the aminoquinazoline (1·3 g.) which crystallised from water or ethanol as needles, m. p. 315° (decomp.) (Found: N, 25·8. Calc. for $C_8H_7N_3O$: N, 26·1%). Its *picrate* (needles from aqueous acetic acid) had m. p. 258—260° (decomp.) (Found: C, 43·2; H, 2·7. $C_{14}H_{10}N_6O_8$ requires C, 43·1; H, 2·6%). The *acetyl derivative* crystallised from 2-ethoxyethanol as prisms, m. p. 277—280° (Found: N, 20·7. $C_{10}H_9N_3O_2$ requires N, 20·7%).

(ii) Anthranilic acid (137 g.) in concentrated hydrochloric acid (93 ml.) and water (1 l.) was kept for 7 weeks with cyanamide prepared from calcium cyanamide (400 g.). The product was completely precipitated with ammonia, dissolved in aqueous sodium hydroxide, recovered (86 g.) by the addition of carbon dioxide, and recrystallised from glacial acetic acid (1·9 l.).

2-Amino-3,4-dihydro-3-2′-hydroxyethyl-4-oxoquinazoline.—2-Amino-4-hydroxyquinazoline (6·4 g.) and 2-chloroethyl acetate (5·4 g.) were boiled for 45 min. in ethanol (100 ml.) containing sodium (0·92 g.) and sodium iodide (0·6 g.). Next day, the suspension was filtered and evaporated to dryness. The alkali-insoluble residue yielded the *3-2′-hydroxyethyl derivative* (0·8 g.) as prisms, m. p. 224°, on crystallisation from ethanol (Found: C, 58·4; H, 5·0; N, 20·4; Ac, 0. $C_{10}H_{11}N_3O_2$ requires C, 58·5; H, 5·4; N, 20·5%). The *picrate* (prisms from ethanol) had m. p. 220—221° (Found: C, 44·7; H, 3·1. $C_{16}H_{14}N_6O_9$ requires C, 44·2; H, 3·3%). Ethylene chlorohydrin did not effect alkylation. Attempted alkylation of 2-acetamido-4-hydroxyquinazoline with 2-chloroethyl acetate gave only 2-amino-4-hydroxyquinazoline (93%).

2-2′-Diethylaminoethylamino-4-hydroxyquinazoline (4·1 g.) was formed when 4-hydroxy-2-methylthioquinazoline [24] (3·8 g.) and 2-diethylaminoethylamine (4·6 g.) were heated together

[22] McKee, *J. prakt. Chem.*, 1911, **84**, 821.
[23] Cohn, *J. prakt. Chem.*, 1911, **84**, 394.
[24] Douglass and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 719.

at 180° for 75 min. and it crystallised as needles, m. p. 94—96°, from aqueous ethanol; Curd, Hoggarth, Landquist, and Rose [12] record m. p. 96—98° [Found: C, 60·9; H, 7·8; H_2O (Karl Fischer), 6·9. Calc. for $C_{14}H_{20}N_4O,H_2O$: C, 60·4; H, 8·0; H_2O, 6·5%]. The *picrate* (needles from aqueous acetic acid) had m. p. 234—235° (decomp.) (Found: C, 49·1; H, 5·1. $C_{20}H_{23}N_7O_8$ requires C, 49·1; H, 4·7%). Its *methiodide* was formed when the tertiary base was kept in methyl iodide for 48 hr. and crystallised from aqueous acetone as needles, m. p. 191—192° (Found: C, 42·2; H, 6·1; I, 29·8; loss at 100°/vac., 6·3. $C_{15}H_{23}IN_4O,1\frac{1}{2}H_2O$ requires C, 42·0; H, 6·1; I, 29·6; H_2O, 6·3%). The *methopicrate* separated as needles, m. p. 194—196°, from water (Found: C, 50·0; H, 5·2; N, 19·5. $C_{21}H_{25}N_7O_8$ requires C, 50·1; H, 5·0; N, 19·5%).

4-Hydroxy-2-2′-hydroxyethylaminoquinazoline (1·15 g.) separated when 2-amino-4-hydroxyquinazoline (3·2 g.) and ethanolamine (12·2 g.) were boiled together for 6 hr. and poured into water. It crystallised as needles, m. p. 249·5—250°, from water (Found: N, 20·1. $C_{10}H_{11}N_3O_2$ requires N, 20·5%). Its *picrate* separated as needles, m. p. 212—213°, from glacial acetic acid (Found: C, 44·5; H, 3·1; N, 18·9. $C_{16}H_{14}N_6O_9$ requires C, 44·2; H, 3·3; N, 19·4%). A basic water-soluble by-product (1·65 g.), possibly *2,4-di-(2-hydroxyethylamino)quinazoline*, crystallised from water as prisms, m. p. 162—163° (Found: C, 58·4; H, 6·6; N, 22·7. $C_{12}H_{16}N_4O_2$ requires C, 58·1; H, 6·5; N, 22·6%), and formed a *picrate* (prisms from ethanol), m. p. 226—229° (Found: C, 45·0; H, 4·3; N, 20·2. $C_{18}H_{19}N_7O_9$ requires C, 45·3; H, 4·0; N, 20·5%).

*n-Butylamine Toluene-*p*-sulphonate*, prepared in propan-2-ol, crystallised as needles, m. p. 122° from ethyl acetate (Found: C, 54·1; H, 7·8. $C_{11}H_{19}NO_3S$ requires C, 53·9; H, 7·8%).

2-Anilino-4-n-butoxyquinazoline.—(i) 2-Anilino-4-ethoxyquinazoline [15] (2·7 g.) was boiled for 1 hr. in n-butanol (30 ml.) containing sodium (0·23 g.) and poured into water. The *butyl ether* (2·4 g.) which separated crystallised from ethanol as prisms, m. p. 82—83° (Found: C, 73·8; H, 6·2; N, 14·1. $C_{18}H_{19}N_3O$ requires C, 73·7; H, 6·5; N, 14·3%). The *picrate* (prisms from ethanol) had m. p. 182—183° (Found: N, 16·3. $C_{24}H_{22}N_6O_8$ requires N, 16·1%).

(ii) Crude 2-anilino-4-chloroquinazoline (1·1 g.), formed from 2-anilino-4-hydroxyquinazoline and phosphoryl chloride, furnished the same compound (0·2 g.), m. p. and mixed m. p. 82—83°, when boiled for 16 hr. with butan-1-ol (25 ml.) containing sodium (0·1 g.).

(iii) 2-Anilino-4-hydroxyquinazoline (5 g.) afforded the butyl ether (2 g.) when refluxed for 16 hr. with n-butyl bromide (5 g.) in ethanol (60 ml.) containing sodium (0·5 g.).

The following ethers were obtained by transalkylation similar to that described above:

2-Anilino-4-n-pentyloxyquinazoline (70%), plates, m. p. 61—62°, from propan-2-ol (Found: 74·4; H, 6·6. $C_{19}H_{21}N_3O$ requires C, 74·2; H, 6·9%); *picrate*, m. p. 183—185° (Found: N, 15·5. $C_{25}H_{24}N_6O_8$ requires N, 15·7%).

2-Anilino-4-benzyloxyquinazoline (78%), needles, m. p. 118—119°, from propan-2-ol (Found: C, 76·9; H, 5·0. $C_{21}H_{17}N_3O$ requires C, 77·0; H, 5·2%); *picrate*, m. p. 215—216° (decomp.) (Found: N, 14·8. $C_{27}H_{20}N_6O_8$ requires N, 15·1%).

2-Anilino-4-2′-hydroxyethylaminoquinazoline.—(i) The precipitate formed when 2-anilino-4-ethoxyquinazoline (5·3 g.) was boiled for 1 hr. with ethanolamine (60 ml.) containing sodium (0·5 g.) and poured into water, afforded the *4-2′-hydroxyethylamino-derivative* (5 g.), which crystallised from toluene as needles, m. p. 147—149° (Found: N, 19·9. $C_{16}H_{16}N_4O$ requires N, 20·0%). Its *picrate* crystallised as prisms, m. p. 185°, from water (Found: C, 52·2; H, 3·7. $C_{22}H_{19}N_7O_8$ requires C, 51·9; H, 3·8%). At 20°, the reaction yield was 5·15 g. This compound was stable to alcoholic alkali and with nitrous acid at 10° gave its *nitrite* (needles from propan-2-ol), m. p. 163—165° (decomp.) (Found: N, 21·1. $C_{16}H_{17}N_5O_3$ requires N, 21·4%).

(ii) 2-Chloro-4-2′-hydroxyethylaminoquinazoline [4] (1 g.) and aniline (0·42 g.) in water (10 ml.) and hydrochloric acid (0·2 ml.) were boiled for 45 min. to yield, after basification, the same compound (1·14 g.), m. p. and mixed m. p. 148—149°.

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