Tetrahedron, 1957, Vol. 1, pp. 38–44. Pergamon Press Ltd., London

SYNTHESES IN THE QUINAZOLONE SERIES—VI
THE SYNTHESIS OF 1:2:3:4-TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES

T. A. KILROE SMITH and HENRY STEPHEN
The Department of Chemistry and Chemical Engineering, The University of the Witwatersrand Johannesburg, South Africa

(*Received* 5 *February* 1957)

Abstract—An investigation of the isomeric change of N^2-arylideneorthanilamides has led to the synthesis of a new series of 1:2:3:4-tetrahydro-4-oxoquinazolines from which the corresponding quinazol-4-ones have been obtained by oxidation. Based on the present investigation, a new synthesis of 2-(*o*-aminophenyl)-3*H*-quinazol-4-one (VI) is also reported.

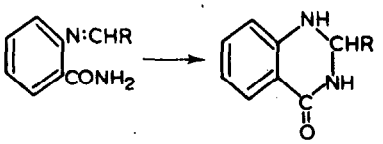
N^2-ARYLIDENEORTHANILAMIDES (I), which are readily prepared by condensing aromatic aldehydes with anthranilamide (Table 1), are characterised by the ease with which they isomerise to give 1:2:3:4-tetrahydro-2-aryl-4-oxoquinazolines (II) (Table 3). Isomerisation (Table 2) is readily effected in most cases by treating arylideneorthanilamides with dilute (8%) sodium hydroxide. In some instances dilute hydrochloric acid brought about the change, but this was invariably accompanied by partial hydrolysis of the orthanilamide. Heating under reduced pressure above the melting-point was sufficient in some instances to bring about isomerisation, which could be readily observed, since the oxoquinazolines have a higher melting-point than the corresponding arylideneorthanilamides. It is of interest to note that during the isomerisation of N^2-(*m*-nitrobenzylidene)- and N^2-(*p*-nitrobenzylidene)-orthanilamides under reduced pressure at the melting-point, oxidation takes place with the formation of 2-*m*-nitrophenyl-3*H*- and 2-*p*-nitrophenyl-3*H*-quinazol-4-one respectively. N^2-(*o*-nitrobenzylidene)-orthanilamide isomerises at the melting-point without oxidation and yields 1:2:3:4-tetrahydro-2-(*o*-nitrophenyl)-4-oxoquinazoline. A number of tetrahydro-4-oxoquinazolines have been oxidised with potassium permanganate in acetone to give the corresponding quinazol-4-ones, and the latter were identified by comparing with the same compounds already prepared by Stephen and Wadge.[1] The ease with which the hydrogen atoms in positions 1 and 2 in the tetrahydro-4-oxoquinazolines are removed by oxidation is indicated in the case of 1:2:3:4-tetrahydro-2-styryl-4-oxoquinazoline, the styryl radical remaining intact during oxidation.

The intermediate arylideneorthanilamides from the condensations of benzaldehyde *p*-methylbenzaldehyde, and piperonal with anthranilamide could not be isolated, since they isomerised rapidly to the corresponding 4-oxoquinazolines during their preparation.

In a previous communication[2] it has been shown that the condensation of 4-chloroquinazoline with methyl anthranilate gives methyl *N*-4-quinazolinyl-anthranilate (III), which with hydrogen chloride cyclises with elimination of methanol to quinazo-[4,3-*b*]quinazol-8-one (IV), and the latter has also been obtained by hydrolysis of 3-4′-quinazolinylquinazol-4-one (V).[3] Further hydrolysis of (IV) gives 2-(*o*-aminophenyl)-3*H*-quinazol-4-one (VI), the structure of which has now been confirmed by the

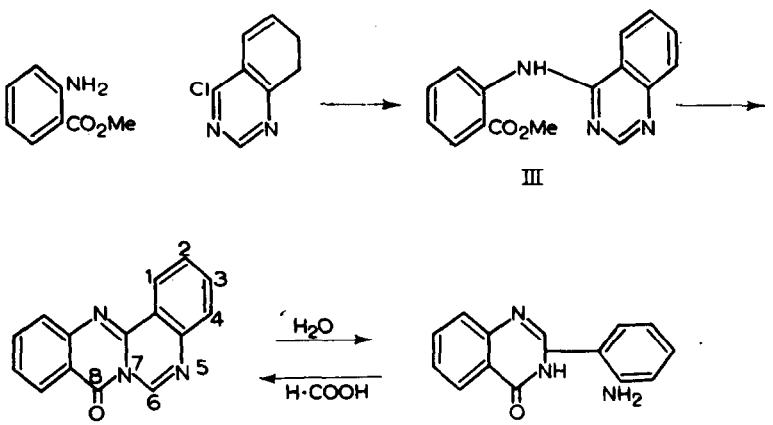
[1] H. Stephen and G. Wadge *J. Chem. Soc.* 4420 (1956).

preparation of N^2-(*o*-nitrobenzylidene)orthanilamide (VII), which as stated above is isomerised to give 1:2:3:4-tetrahydro-2-(*o*-nitrophenyl)-4-oxoquinazoline (VIII), and the latter on oxidation gives 2-(*o*-nitrophenyl)-3*H*-quinazol-4-one, which on reduction is converted into 2-(*o*-aminophenyl)-3*H*-quinazol-4-one identical with (VI), and on treatment with anhydrous formic acid yields (IV).



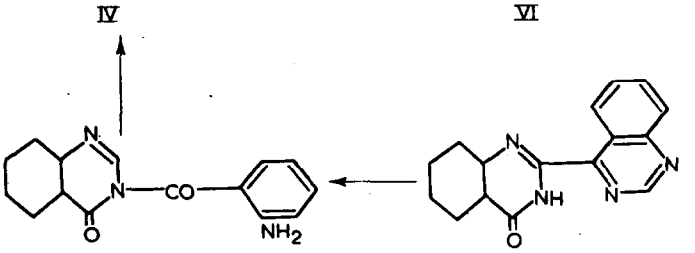
I II

In the preliminary stages of the present investigation it was intended to prepare methyl arylideneanthranilates with the object of their conversion to 1:2:3:4-tetrahydro-4-oxoquinazolines by the action of ammonia. Attempts to condense benzaldehyde with methyl anthranilate in ethanol in presence of hydrogen chloride gave a mixture of



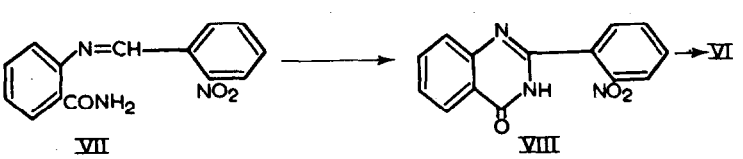
III

IV VI



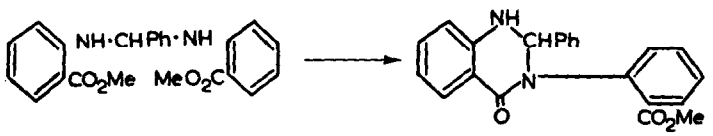
V

Intermediate compound not isolated

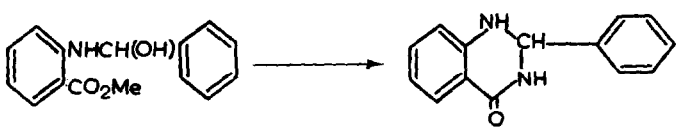


VII VIII

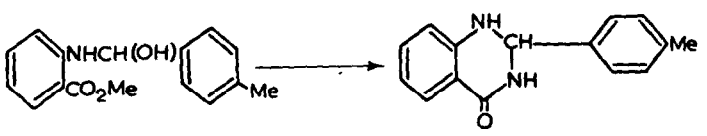
[di-(*o*-methoxycarbonylanilino)methyl] benzene (IX) and 1:2:3:4-tetrahydro-3-*o*-methoxy-carbonylphenyl-4-oxo-2-phenylquinazoline (X). In absence of hydrogen chloride, methyl anthranilate in ethanol combined with benzaldehyde and *p*-methylbenzaldehyde to give respectively methyl *N*-(α-hydroxybenzyl)orthanilate (XI) and methyl *N*-(α-hydroxy-4-methylbenzyl)orthanilate (XII), which on treatment with ammonia gave 1:2:3:4-tetrahydro-2-phenyl-4-oxoquinazoline (XIII), and 1:2:3:4-tetrahydro-2-*p*-tolyl-4-oxoquinazoline (XIV) respectively. These reactions are very slow, requiring from two to three weeks.



IX X



XI XII



XIII XIV

EXPERIMENTAL

Preparation of N²*-arylideneorthanilamides.* Anthranilamide (1 mol) and aromatic aldehyde (1 mol) were mixed and dissolved in ethanol, and after refluxing the solution for a few minutes the condensation product crystallised on cooling (Table 1), and was purified by recrystallisation from ethanol.

Isomerisation of arylideneorthanilamides to 1:2:3:4*-tetrahydro-2-aryl-4-oxoquinazolines.* (a) Refluxing the orthanilamide with *N* hydrochloric acid for ½ hour was sufficient in most cases to effect partial isomerisation, which was usually accompanied by hydrolysis of some of the amide. (b) Refluxing with 2 N sodium hydroxide solution with addition of ethanol to increase solubility of the amide brought about isomeric change usually in good yield. In those instances in which hydroxyl is present in the aryl radical, the oxoquinazoline is precipitated by addition of acetic acid. (c) Heating above the melting-point under reduced pressure resulted in rapid isomerisation in a few cases in good yield.

[2] T. Stephen and H. Stephen *J. Chem. Soc.* 4174 (1956).
[3] T. Stephen and H. Stephen *J. Chem. Soc.* 4178 (1956).

TABLE 1.—N^2-ARYLIDENEORTHANILAMIDES

Ar	Found (%)						Required (%)	
	Yield (%)	m.p.	Form	C	H	Formula	C	H
o-$C_6H_4(OH)$	81	165	orange needles	70·28	5·18	$C_{14}H_{12}O_2N_2$	70·0	5·04
o-$C_6H_4(OMe)$	77	159	pale yellow needles	70·66	5·7	$C_{15}H_{14}O_2N_2$	70·87	5·51
m-$C_6H_4(OH)$	70	146	yellow needles	70·28	5·39	$C_{14}H_{12}O_2N_2$	70·0	5·04
p-$C_6H_4(OH)$	70	160	yellow needles	70·4	5·22	do	do	do
p-$C_6H_4(OMe)$	61	158	pale yellow needles	70·78	5·64	$C_{15}H_{14}O_2N_2$	70·87	5·51
2:4-$C_6H_3(OH)_2$	90	190	orange needles	N,9·16,9·45			N,9·27	
2:4-$C_6H_3(OMe)_2$	88	160	yellow needles	67·42	5·69	$C_{16}H_{16}O_2N_2$	67·61	5·73
2:4-$C_6H_3(OEt)_2$	87	177	yellow needles	69·2	6·62	$C_{18}H_{20}O_2N_2$	69·23	6·46
2:4-$C_6H_3(OEt)(OH)$	72	180	yellow needles	67·43	6·86	$C_{16}H_{16}O_2N_2$	67·61	5·73
2:4-$C_6H_3(OH)(OEt)$	66		see Note (a)					
3:4-$C_6H_3(OH)(OMe)$	50	153	yellow needles	see Note (b)				
3:4-$C_6H_3(OMe)(OH)$	81	187	yellow needles	see Note (c)				
3:4-$C_6H_3(OEt)(OH)$	97	187	pale yellow needles	67·44	5·52	$C_{16}H_{16}O_2N_2$	67·61	5·73
3:4-$C_6H_3(OMe)_2$	84	165	yellow needles	67·72	5·86	do	67·61	5·73
3:4-$C_6H_3(OEt)(OMe)$	60	152	pale yellow needles	68·41	6·34	$C_{17}H_{18}O_2N_2$	68·46	6·09
2:3-$C_6H_3(OH)(OMe)$	81	168	red needles	66·55	5·36	$C_{15}H_{14}O_2N_2$	66·67	5·19
o-$C_6H_4(NO_2)$	86	174	yellow needles	62·48	4·17	$C_{14}H_{11}O_3N_3$	62·45	4·09
m-$C_6H_4(NO_2)$	95	199	yellow prisms	62·56	4·26	do	do	do
p-$C_6H_4(NO_2)$	93	191	yellow prisms	62·38	4·17	do	do	do
Ph·CH:CH	90	210	white needles	N,11·29		$C_{16}H_{14}ON_2$	N,11·20	
2:3:4-$C_6H_2(CO_2H)(OMe)_2$	96	208	white needles	62·15	5·14	$C_{17}H_{16}O_5N_2$	62·19	4·88

N^2-(2-Hydroxy-4-ethoxy-benzylidene) orthanilamide (a), N^2-(3-hydroxy-4-methoxy-benzylidene) orthanilamide (b), N^2-(3-ethoxy-4-hydroxy-benzylidene) orthanilamide (c) isomerise during recrystallisation from ethanol to the corresponding 4-oxoquinazolines. For identification and analysis (a) was ethylated and converted into 1:2:3:4-tetrahydro-2-(2′:4′-diethoxyphenyl)-4-oxoquinazoline, (b) and (c) were methylated and converted into 1:2:3-tetrahydro-2-(3′:4′-dimethoxyphenyl)-4-oxoquinazoline and 1:2:3:4-tetrahydro-2-(3-ethoxy-4-methoxy-phenyl)-4-oxoquinazoline respectively.

All compounds in Table 1 are new.

Table 2 summarises the results of isomerisation of arylideneorthanilamides by acid, alkali and heating. The numbers in parentheses indicate the percentage conversion to 1:2:3:4-tetrahydro-2-aryl-4-oxoquinazoline. Hy indicates hydrolysis.

Oxidation of 1:2:3:4-*tetrahydro-2-aryl-4-oxoquinazolines to 2-aryl-quinazol-4-ones.* The 4-oxoquinazoline dissolved in dry acetone was treated with potassium permanganate in dry acetone, which was added during 2–3 hours. Excess potassium permanganate was removed by addition of solid sodium bisulphite and the mixture filtered, and after evaporation of the acetone the residue consisting of the quinazol-4-one was recrystallised from ethanol or methanol. Table 4 gives details of the compounds prepared.

TABLE 2

	Acid	Alkali	Heat
Arylideneorthanilamide from			
o-hydroxy-benzaldehyde	(82) Hy	—	decomp.
o-methoxy-benzaldehyde	Hy	(88)	—
m-hydroxy-benzaldehyde	Hy	(100)	—
p-hydroxy-benzaldehyde	(70) Hy	—	—
p-methoxy-benzaldehyde	(62)	—	—
2-hydroxy-3-methoxy-benzaldehyde	(87) Hy	—	—
3-methoxy-4-hydroxy-benzaldehyde	(92) Hy	—	—
3:4-dimethoxy-benzaldehyde	Hy	(100)	—
4-methoxy-3-hydroxy-benzaldehyde	Hy	(100)	—
3-ethoxy-4-hydroxy-benzaldehyde	—	(100)	—
2-hydroxy-4-ethoxy-benzaldehyde	—	—	(100)
2:4-dimethoxy-benzaldehyde	Hy	(100)	—
2:4-diethoxy-benzaldehyde	Hy	(94)	—
3-ethoxy-4-methoxy-benzaldehyde	Hy	(80)	—
o-nitro-benzaldehyde	Hy	(96)	—
m-nitro-benzaldehyde	—	—	(96)
p-nitro-benzaldehyde	—	—	(90)
opianic acid	—	(100)	(100)
cinnamaldehyde	Hy	(58)	—

Footnotes to Table 3.

[a] Also obtained by methylating 1:2:3:4-tetrahydro-2-*p*-hydroxyphenyl-4-oxoquinazoline.

[b] Prepared by ethylating (i) N^3-(2′-ethoxy-4′-hydroxybenzylidene)orthanilamide; (ii) N^3-(2′-hydroxy-4′-ethoxybenzylidene)orthanilamide.

[c] N^3-(2′-hydroxy-3′-methoxyphenyl)orthanilamide could not be isomerised satisfactorily to the correponding 4-oxoquinazoline by the action of sodium hydroxide or hydrochloric acid. The orthanilamide was refluxed in glacial acetic acid for ½ hr and the 4-oxoquinazoline precipitated by the addition of water, filtered, and crystallized from ethanol.

[d] was obtained by isomerisation of N^3-(3′-methoxy-4′-hydroxyphenyl)orthanilamide in glacial acetic acid, as in (c).

[e] Prepared by (i) methylating 1:2:3:4-tetrahydro-2-(3′-ethoxy-4′-hydroxyphenyl)-4-oxoquinazoline; (ii) ethylating 1:2:3:4-tetrahydro-2-(3′-hydroxy-4′-methoxyphenyl)-4-oxoquinazoline.

[f] was obtained by methylating (i) 1:2:3:4-tetrahydro-2-(3′-methoxy-4-hydroxyphenyl)-4-oxoquinazoline; (ii) 1:2:3:4-tetrahydro-2-(3′-hydroxy-4′-methoxyphenyl)-4-oxoquinazoline; (iii) N^3-(3′-methoxy-4′-hydroxybenzylidene)othanilamide; (iv) N^3-(3′-hydroxy-4′-methoxybenzylidene)orthanilamide.

[g] 1:2:3:4-tetrahydro-(*o*-nitrophenyl)-4-oxoquinazoline was also obtained by refluxing N^3-2-(*o*-nitrobenzylidene)orthanilamide (10 g) in water (50 c.c.) and ethanol (25 c.c.) and saturated sodium hydrogen carbonate solution (5 c.c.) for 1 hr. The 4-oxoquinazoline was deposited on cooling in ice, filtered, and crystallised from ethanol.

[h] Also prepared by refluxing cinnamaldehyde (3 g) and anthranilamide (3 g) in ethanol in presence of a flake of sodium hydroxide. The 4-oxoquinazoline separates as yellow plates or needles on cooling.

[i] 1:2:3:4-tetrahydro-2-(3′:4′-methylenedioxyphenyl)-4-oxoquinazoline was also prepared by allowing a mixture of piperonal (3 g) and methyl anthranilate (3 g) in ethanol to remain for 2 days at room temperature and then saturating with ammonia. After 4 weeks, concentrated aqueous ammonia was added and the precipitated compound was crystallised from methanol in white needles, m.p. 202°.

Ethylation and methylation were done at 0° in alkaline solution using ethyl and methyl sulphate respectively.

All compounds in Table 3 are new.

Methyl N-(α-*hydroxybenzyl*)*orthanilate* (XI). Methyl anthranilate (15·1 g) and benzaldehyde (10·6 g) were mixed in light petroleum (60–80°) and kept in an atmosphere of carbon dioxide in a refrigerator for 3 days. The addition product separated as a white solid (75%) which crystallised in needles from light petroleum (40–60°), m.p. 77° (Found: C, 70·44; H, 5·7. $C_{15}H_{15}O_3N$ requires C, 70·02; H, 5·88%). Methyl *N*-(α-hydroxy-4-methylbenzylorthanilate (XIII) was similarly prepared (65%) by addition of methyl anthranilate and *p*-methyl-benzaldehyde, crystallised in white needles, m.p. 79° (Found: C, 71·44; H, 6·16. $C_{16}H_{17}O_3N$ requires C, 70·85; H, 6·27%). Treatment of the above compounds in ethanol saturated with ammonia gave, respectively (after remaining in the refrigerator for two weeks), 1:2:3:4-tetrahydro-2-phenyl-4-oxoquinazoline (XII) (41%), m.p. 228°, and 1:2:3:4-tetrahydro-2-*p*-totyl-4-oxoquinazoline (XIV) (58%), m.p. 230°, identical in both cases with the compounds previously prepared (Table 3).

TABLE 3.—1:2:3:4-TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES
(For yields see Table 2)

Aryl	m.p.	Form	Solvent	Found (%)		Formula	Required (%)	
				C	H		C	H
Ph	228°	white needles	MeOH	75·34	5·6	$C_{14}H_{12}ON_2$	75·0	5·36
p-MeC_6H_4	230°	rhombic prisms	MeOH	75·58	6·0	$C_{15}H_{14}ON_2$	75·63	5·98
o-$C_6H_4(OH)$	300°	white needles	EtOH	69·75	5·16	$C_{14}H_{12}O_2N_2$	70·0	5·0
m-$C_6H_4(OH)$	209°	white needles	MeOH	69·76	5·21	$C_{14}H_{12}O_2N_2$	70·0	5·0
p-$C_6H_4(OH)$	332°	white needles	EtOH	—	—	—	—	—
o-$C_6H_4(OMe)$	181°	white needles	EtOH	70·75	5·68	$C_{15}H_{14}O_2N_2$	70·87	5·51
p-$C_6H_4(OMe)$[a]	195°	plates	MeOH	70·96	5·7	$C_{15}H_{14}O_2N_2$	70·87	5·51
2′:4′-$C_6H_3(OH)$-(OEt)	305°	white needles	EtOH					
2′:4′$C_6H_3(OEt)_2$[b]	149°	white needles	EtOH	69·01	6·63	$C_{18}H_{20}O_3N_2$	69·23	6·46
2′:4′-$C_6H_3(OMe)_2$	187°	white needles	EtOH	65·29	6·47	$C_{15}H_{16}O_3N_2$ + EtOH.	65·45	6·6
2′:3′-C_6H_3(OH)(OMe)[c]	279°	yellow needles	AcOH	N, 10·4%		$C_{15}H_{14}O_3N_2$	N, 10·37%	
3′:4-C_6H_3(OMe)(OH)[d]	224°	white needles	EtOH					
3′:4′-C_6H_3(OH)(OMe)	191°	white needles	EtOH					
3′:4′-C_6H_3(OEt)(OMe)[e]	89°	white needles	EtOH	68·31	6·21	$C_{17}H_{18}O_3N_2$	68·46	6·04
3′:4′-C_6H_3(OEt)(OH)	218°	white needles	EtOH					
3′:4′-C_6H_3-$(OMe)_2$[f]	226°	white needles	AcOH	67·66	5·86	$C_{16}H_{16}O_3N_2$	67·61	5·73
o-$C_6H_4NO_2$[g]	192°	yellow prisms	EtOH	62·50	4·12	$C_{14}H_{11}O_3N_2$	62·45	4·09
C_6H_5·CH:CH[h]	294°	yellow needles	EtOH	N, 11·11%		$C_{16}H_{14}ON_2$	N, 11·2%	
3′:4′-$C_6H_3(CH_2O_2)$[i]	202°	white needles	MeOH	67·64	4·72	$C_{15}H_{12}O_3N_2$	67·17	4·48
2′:3′:4′-$C_6H_2(CO_2H)(OMe)_2$	296°	white needles	EtOH	N, 8·54%		$C_{17}H_{16}O_5N_2$	N, 8·54%	

Reaction between methyl anthranilate and benzaldehyde in presence of hydrogen chloride. A solution of methyl anthranilate (10 g, 2 mol) and benzaldehyde (4 g, 1·1 mol) in ethanol (50 c.c.) was warmed with a trace of hydrogen chloride. The solution became orange in colour, and after refluxing for 40 min a white crystalline solid separated which was filtered hot (8·6 g), m.p. 265–275°. Extraction with acetone yielded an insoluble portion (6·9 g), m.p. 278–280° (Found: C, 73·68; H, 5·35. $C_{22}H_{18}O_3N_2$ requires C, 73·72; H, 5·06%, which corresponds with (X)). Evaporation of the acetone solution left a residue (1·7 g), m.p. 188–190° (Found: C, 70·46; H, 5·71. $C_{23}H_{22}O_4N_2$ requires C, 70·77; H, 5·64%, which corresponds with (IX)).

During the present investigation the following new arylidene orthanilic acids were prepared:

TABLE 4.—2-ARYLQUINAZOL-4-ONES PRODUCED BY OXIDATION OF 1:2:3:4—TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES

Aryl	Yield (%)	m.p.	Form	Solvent	Found (%)			Formula	Required (%)		
					C	H	N		C	H	N
Ph*	70	238°	white needles	AcOH	—	—	—	—	—	—	—
p-C_6H_4·Me*	73	241°	"	acetone	—	—	—	—	—	—	—
o-C_6H_4·OMe	50	208°	"	EtOH	—	—	11·32	$C_{15}H_{12}O_2N_2$	—	—	11·11
p-C_6H_4·OMe*	98	247°	"	"	—	—	—	—	—	—	—
o-C_6H_4·NO_2	95	237°	yellow needles	EtOH	—	—	15·7	$C_{14}H_9O_2N_3$	—	—	15·74
m-C_6H_4·NO_2	96	354°d	"	AcOH	—	—	15·73	$C_{14}H_9O_2N_3$	—	—	15·74
p-C_6H_4·NO_2	90	365°d	white needles	AcOH	—	—	15·74	$C_{14}H_9O_2N_3$	—	—	15·74
2′:4′-$C_6H_3(OMe)_2$*	75	207°	"	AcOH	67·8	5·17	—	$C_{16}H_{14}O_2N_2$	68·08	5·01	—
2′:4′-$C_6H_3(OEt)_2$	87	174°	"	EtOH	69·7	6·06	—	$C_{18}H_{18}O_2N_2$	69·68	5·86	—
3′:4′-$C_6H_3(OMe)_2$*	65	247°	"	AcOH	—	—	—	—	—	—	—
3′:4′-$C_6H_3(O_2H_2C)$	75	279°	"	AcOH	67·43	4·06		$C_{15}H_{10}O_3N_2$	67·67	3·79	—
3′:4′-C_6H_3(OEt)(OMe)	90	239°	"	acetone	68·66	5·59		$C_{17}H_{16}O_3N_2$	68·92	5·45	—
Ph·CH:CH*	44	252°	"	EtOH	—	—	11·35	$C_{16}H_{12}ON_2$	—	—	11·36

* Stephen and Wadge *J. Chem. Soc.* 4420 (1956).

N-(*2-hydroxy-4-ethoxybenzylidene*)*orthanilic acid* was obtained by refluxing a solution of 2-hydroxy-4-ethoxy-benzaldehyde (12·5 g) and anthranilic acid (10·3 g) in ethanol. A copious yellow crystalline deposit (19·8 g, 92%) of the condensation product was obtained which crystallised in yellow needles from ethanol, m.p. 206° (Found: C, 67·05; H, 5·01. $C_{16}H_{15}O_4N$ requires C, 67·21; H, 5·26%).

N-(*2-ethoxy-4-hydroxybenzylidene*)*orthanilic acid.* 2-ethoxy-4-hydroxy-benzaldehyde (1·66 g) and anthranilic acid (1·37 g) were mixed and dissolved in ethanol. After refluxing for 20 min and cooling, the condensation product separated as yellow needles (2·8 g, 97%) m.p. 211°, decomp. (Found: C, 66·95; H, 5·49. $C_{16}H_{15}O_4N$ requires C, 67·21; H, 5·26%).

N-(*3-methoxy-2-hydroxybenzylidene*)*orthanilic acid* was prepared by refluxing anthranilic acid (6·85 g) and 2-hydroxy-3-methoxybenzaldehyde (7·6 g) in benzene (80 c.c.). The condensation product (10·92 g, 80%) was deposited and crystallised from ethanol as orange needles, m.p. 119° (Found: C, 66·74; H, 5·01. $C_{15}H_{13}O_4N$ requires C, 66·41; H, 4·83%). The above compounds did not yield tetrahydro-4-oxoquinazolines on treatment with ammonia.

Acknowledgements—The authors thank Dr. R. S. Cahn for advice in connection with the nomenclature adopted in this paper.