806. *Syntheses in the Quinazolone Series. Part II.* Synthesis of Quino- and Quinazo-quinazolones.*

By (Mrs.) T. Stephen and Henry Stephen.

The synthesis of quinazolones has now been extended to the condensation of methyl anthranilate and of ammonium anthranilate with cyclic imidoyl chlorides, *i.e.*, compounds containing –N:CCl– as part of a ring structure, *viz.*, 2-chlorolepidine and its derivatives and 4-chloro- and 4-chloro-2-phenylquinazoline.

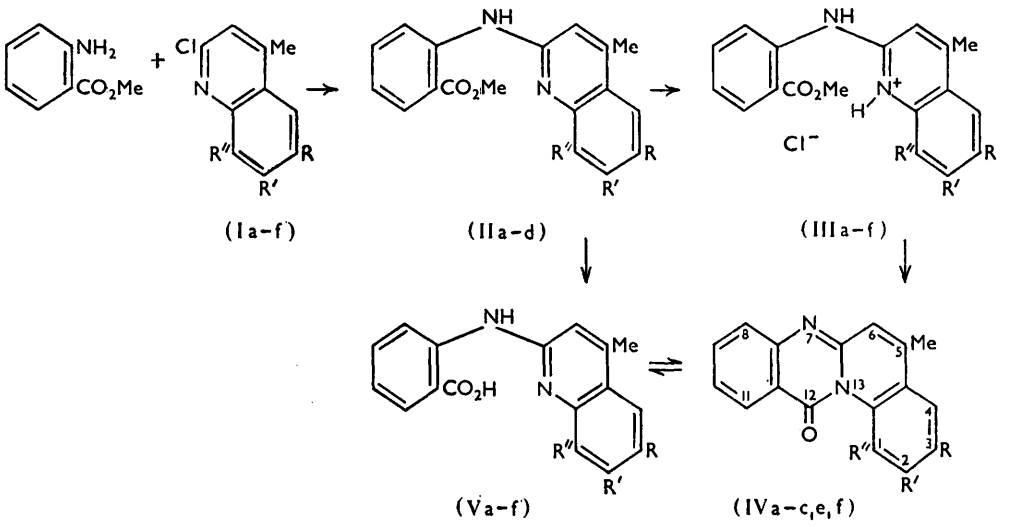
Methyl anthranilate condenses with 2-chlorolepidine (Ia) in two stages, giving at 140° an 80% yield of methyl *N*-2′-lepidylanthranilate but at 170—200° a quantitative yield of 5-methylquino[2,1-*b*]quinazol-12-one (IV) (Ring Index No. 2658). The latter product arises by conversion of the ester (II), by the hydrogen chloride liberated during the condensation, into the hydrochloride (III), the cation of which cyclises. Similarly, at 140° 2-chloro-4 : 6- (Ib), -4 : 7- (Ic) and -4 : 8-dimethylquinoline (Id) condense with methyl anthranilate, yielding respectively the esters (IIb—d). The chlorine atoms in 2-chloro-6-methoxy- (Ie) and -ethoxy-lepidine (If) are less reactive, since these compounds do not condense with methyl anthranilate at 140° : however, at 170° condensation takes place, and the products are mixtures of the esters and the quinoquinazolones; at 200° only the latter are obtained (95% yield). Likewise, 2-chlorolepidine and its 6- and 7-methyl derivatives (Ia and b) with methyl anthranilate at 200° give excellent yields of the corresponding quinazolones, (IVa—c). The product (IVa) is identical with that described by Bose and Sen [1] and Seide and Tschelencev.[2] Condensation of 2-chloro-4 : 8-dimethylquinoline (Id) with methyl anthranilate at its b. p. gives only *N*-(4 : 8-dimethyl-2-quinolyl)-anthranilic acid (Vd), produced by the action of hydrogen chloride on the ester (IId). Failure to effect cyclisation of the acid (Vd) or its ester (IId) is probably due to steric hindrance by the 8-methyl group. All the esters (II) are readily hydrolysed by alcoholic sodium hydroxide to the corresponding acids. Further, *N*-(6-methoxy-2-lepidyl)- (Ve) and *N*-(6-ethoxy-2-lepidyl)-anthranilic acid (Vf) were obtained by alkaline hydrolysis of the quinoquinazolones (IVe and f). All the acids except (Vd), when heated above the m. p. or boiled with acetic anhydride, are converted into the quinoquinazolones.

Attempts to condense 2-chlorolepidine and derivatives with ammonium anthranilate were unsuccessful. At room temperature there is no reaction and at higher temperatures ammonium anthranilate dissociates into ammonia and anthranilic acid, which then condenses with 2-chlorolepidine to give 5-methylquino[2,1-*b*]quinazol-12-one (IVa). This had previously been obtained by the same reaction by Ephraim [3] who designated it

* Part I, Levy and Stephen, *J.*, 1956, 985.

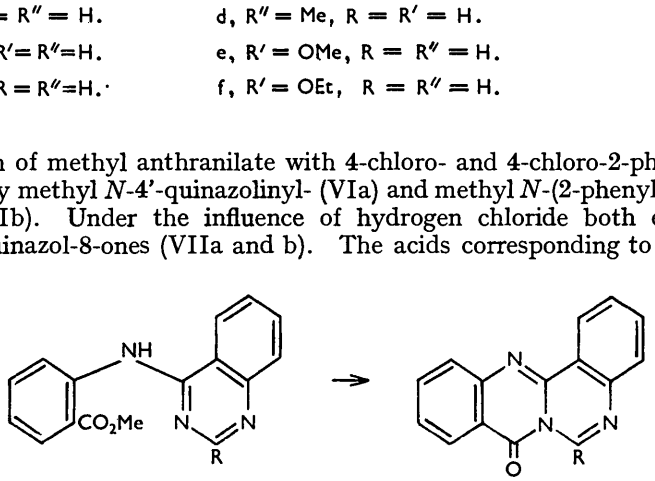
[1] Bose and Sen, *J.*, 1931, 2840.
[2] Seide and Tschelencev, *J. Gen. Chem. Russ.*, 1937, **7**, 2314.
[3] Ephraim, *Ber.*, 1892, **25**, 2710.

N-2-lepidylanthranil, and Backeberg [4] repeating Ephraim's experiment obtained the same compound and accepted the anthranil structure. Bose and Sen [1] had already shown that the compound is a quinazolone, and this structure was later confirmed by Bose [5] and by Seide and Tschelencev.[2]



a, R = R′ = R″ = H. d, R″ = Me, R = R′ = H.
b, R = Me, R′ = R″ = H. e, R′ = OMe, R = R″ = H.
c, R′ = Me, R = R″ = H. f, R′ = OEt, R = R″ = H.

Condensation of methyl anthranilate with 4-chloro- and 4-chloro-2-phenyl-quinazoline gave respectively methyl *N*-4′-quinazolinyl- (VIa) and methyl *N*-(2-phenyl-4-quinazolinyl)-anthranilate (VIb). Under the influence of hydrogen chloride both esters cyclise to quinazo[4,3-*b*]quinazol-8-ones (VIIa and b). The acids corresponding to (VI) are readily



(VI) a: R = H
b: R = Ph

(VII) a: R = H
b: R = Ph

obtained by condensing 4-chloro- and 4-chloro-2-phenyl-quinazoline with ammonium anthranilate in acetone at 0°. Both acids cyclise in refluxing acetic anhydride to the quinazolones (VII). Aggarawal and Ray [6] claim to have obtained the compound (VIIb) by condensing 2-phenylquinazol-4-one with anthranilic acid in phosphorus trichloride and give the m. p. 241—242°, whereas the m. p. of our product is 292°. Their product has been shown to have been a mixture of 2-phenylquinazol-4-one and *N*-(2-phenyl-4-quinazolinyl)anthranilic acid.

[4] Backeberg, *J.*, 1933, 390.
[5] Bose, *Current Sci.*, 1934, **2**, 430.
[6] Aggarawal and Ray, *J. Indian Chem. Soc.*, 1929, **6**, 785.

Experimental

In the condensation of 2-chlorolepidine and its derivatives with methyl anthranilate, it was found that if equimolecular proportions of the reactants were used the yield of condensation product was 10—30% lower than if one mol. excess of methyl anthranilate was used. The condensation in all cases was carried out as follows :

2-Chlorolepidine or its derivative (1 mol.) was heated with methyl anthranilate (2 mol.) in an oil-bath and the temperature of condensation recorded. When separation of methyl anthranilate hydrochloride was considered complete, the mixture was made alkaline with ammonia, and steam-distilled in order to remove excess of methyl anthranilate and any unchanged lepidine (which distils in steam slowly without decomposition after all the methyl anthranilate has been removed).

Methyl N-2′-*Lepidylanthranilate* (IIa).—2-Chlorolepidine (1·7 g.) and methyl anthranilate (2·7 g.) were heated at 130° for 10 min. The product, m. p. 133—138° (1·5 g.), readily crystallised from ethanol in cream-coloured needles, m. p. 149° (Found : C, 74·35; H, 5·6; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%).

5-*Methylquino*[2,1-b]*quinazol*-12-*one* (IVa).—2-Chlorolepidine (1·7 g.) and methyl anthranilate (2·7 g.), heated together at 170° for 15 min., gave 100% yield of the quinazolone (IVa), which crystallises from ethanol in yellow needles, m. p. 213°, in agreement with Bose and Sen.[1] The product readily forms a hydrochloride, soluble in ethanol. Addition of platinic chloride to this solution gives a buff *platinichloride* [Found : Pt, 20·6. $(C_{17}H_{12}ON_2)_2,H_2PtCl_6$ requires Pt, 20·9%]. The ester (IIa) is readily soluble in concentrated hydrochloric acid but from boiling acid the hydrochloride of (IVa) separates. This on treatment with water and neutralisation liberates the base (IVa), m. p. 213°.

N-2′-*Lepidylanthranilic Acid* (Va).—An alcoholic solution of the ester (IIa) was refluxed with 10% sodium hydroxide solution for ½ hr., cooled, and acidified with acetic acid. The precipitated acid (Va) crystallised from ethanol in yellow needles, m. p. 203—204° (Found : C, 73·4; H, 4·9; N, 9·9. Calc. for $C_{17}H_{14}O_2N_2$: C, 73·4; H, 5·0; N, 10·1%).

Methyl N-(4 : 6-*Dimethyl*-2-*quinolyl*)*anthranilate* (IIb).—2-Chloro-4 : 6-dimethylquinoline (1 g.) and methyl anthranilate (1·6 g.) at 140° (½ hr.) gave a 50% yield of the ester (IIb), and 2-chloro-4 : 6-dimethylquinoline (0·4 g.) was recovered during steam-distillation. The *product* (IIb) crystallises from 75% dioxan in almost white needles, m. p. 162·5° (Found : C, 74·5; H, 6·0; N, 9·2. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9; N, 9·15%). Several attempts were made to improve the yield, but condensation for a longer period at 140° or at 140—150° gave mixtures of (IIb) and the quinazolone (IVb). When the reactants were refluxed for several hours in dry dioxan, they were recovered unchanged.

Methyl N-(4 : 7-*Dimethyl*-2-*quinolyl*)*anthranilate* (IIc).—2-Chloro-4 : 7-dimethylquinoline (1 g.) and methyl anthranilate (1·6 g.) at 140° (½ hr.) gave 80% of the *ester* (IIc) which crystallised from 75% dioxan in almost white needles, m. p. 172° (Found : C, 74·3; H, 6·0. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·9%). Condensation at 170—190° gave an inseparable mixture of the quinazolone (IVc) and the ester (IIc), which was entirely converted into the quinazolone (IVc) by boiling concentrated hydrochloric acid or hydrolysed to the acid (Vc) by sodium hydroxide.

Table 1. *Substituted quino*[2,1-*b*]*quinazol*-12-*ones* (IV).

	Condensation					Found (%)			Required (%)		
Product [a]	Temp.	Time (min.)	Yield (%)	M. p.	Formula	C	H	N	C	H	N
IVb	170°	15	93	199°	$C_{18}H_{14}ON_2$	78·6	5·3	10·0	78·8	5·1	10·2
IVc	200—220	—	100	194·5	,,	78·6	5·4	10·1	78·8	5·1	10·2
IVe	,,	10	96	230	$C_{18}H_{14}O_2N_2$	74·5	4·9	9·8	74·5	4·8	9·65
IVf	,,	10	95	193	$C_{19}H_{16}O_2N_2$	75·0	5·4	9·3	75·0	5·3	9·2

[a] All yellow needles from dioxan, except (IVb) which was crystallised from ethanol. *Platinichlorides*, B_2,H_2PtCl_6, were obtained as orange needles from (IVc) (Found : Pt, 20·0. Reqd. : Pt, 20·3%), (IVe) (Found : Pt, 19·5. Reqd. : Pt, 19·6), and (IVf) (Found : Pt, 19·1%. Reqd. : Pt, 19·5). The base (IVb) gave a buff *salt*, $B_2,H_2PtCl_6,2(B,HCl)$ (Found : Pt, 12·3. Reqd. : Pt, 12·3%).

Methyl N-(4 : 8-*Dimethylquinolyl*)*anthranilate* (IId).—Condensation of 2-chloro-4 : 8-dimethylquinoline (1 g.) with methyl anthranilate (1·6 g.) at 140° for 10 min. gave 80% of the

ester (IId), crystallising from ethanol in almost white needles, m. p. 170° (Found: C, 74·4; H, 6·0; N, 9·0. $C_{19}H_{18}O_2N_2$ requires C, 74·5; H, 5·8; N, 9·15%).

Analogous Products.—Table 1 records the *quinoquinazolones* prepared as above.

Table 2 records the N-*quinolylaminoanthranilic acids* (V) prepared from the ester (II) and/or the quinoquinazolone (IV) by hydrolysis with sodium hydroxide in boiling aqueous dioxan for

TABLE 2. *Substituted* N-*quinolylaminoanthranilic acids* (V).

Product[a]	Starting material	Time of hydrol. (hr.)	M. p.[b]	Formula	Found (%) C	H	N	Required (%) C	H	N
Vb	IIb	0·5	236°	$C_{18}H_{16}O_2N_2$	73·6	5·7	9·5	74·0	5·5	9·6
Vc	IIc, IVc	0·5	242	,,	73·5	5·6	—	74·0	5·5	—
Ve	IVe	1	218	$C_{18}H_{16}O_3N_2$	70·1	5·15	9·2	70·1	5·2	9·1
Vf	IVf	1	188	$C_{19}H_{18}O_3N_2$	70·7	5·7	8·6	70·8	5·6	8·7

[a] All yellow needles from dioxan, except that (IVc) was crystallised from 75% dioxan. [b] With evolution of CO_2.

the time stated. These acids, except (Vf), were converted into quinoquinazolones when sublimed or boiled with acetic anhydride.

The following notes record additional information about these compounds.

Bose and Sen [1] condensed 2-chloro-4 : 7-dimethylquinoline with anthranilic acid and claim to have obtained (IVc), crystallising from acetone in colourless needles, m. p. 150°. On hydrolysis of this compound they claim to have obtained the acid (Vc), m. p. 226°. The only evidence Bose and Sen [1] put forward in support of the constitution of these compounds is analyses for nitrogen.

No condensation occurred between 2-chloro-6-ethoxylepidine and methyl anthranilate below 150°, or when the components were refluxed in solvents such as toluene or xylene for 2—4 hr. Condensation at 150—170° resulted in mixtures which could either be converted into the quinazolone (IVf) by boiling with hydrochloric acid, or hydrolysed to the acid (Vf) by sodium hydroxide.

3-*Methoxy*-5-*methylquino*[2,1-b]*quinazol*-12-*one* (IVe).—2-Chloro-6-methoxylepidine (2 g.) and methyl anthranilate (2·7 g.) did not condense below 150°. Reaction at 150—160° (½ hr.) gave mixtures of probably the expected ester and the quinazolone (IVe), which could not be separated, but when boiled with concentrated hydrochloric acid gave only quinazolone (IVe). Hydrolysis with alcoholic sodium hydroxide converted the mixture into the acid (Ve). Condensation of 2-chloro-6-methoxylepidine with methyl anthranilate at 200—220° for 10 min. resulted in a 96% yield of the quinoquinazolone (IVe). It crystallised from dioxan in canary-yellow needles, m. p. 230° (Found: C, 74·5; H, 4·9; N, 9·8%).

N-(4 : 8-*Dimethyl*-2-*quinolyl*)*anthranilic Acid* (Vd).—When 2-chloro-4 : 8-dimethylquinoline (1 g.) and excess of methyl anthranilate were heated to the b. p. (approx. 250°) until all signs of reaction had ceased, the product was the acid (Vd). In this condensation, the ester (IId) first formed failed to undergo ring closure but the hydrogen chloride present hydrolysed the ester group. The *acid* crystallised from dioxan in yellow needles, m. p. 240° (Found: C, 73·6; H, 5·55; N, 9·5. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). All attempts to bring about ring closure by heating it above the m. p. or boiling it with acetic anhydride failed. The ester (IId) in dioxan on hydrolysis with 10% sodium hydroxide yielded the acid (Vd), m. p. 240°. On boiling the acid (Vd) with concentrated hydrochloric acid, pale cream-coloured crystals separated. These contained ionisable chlorine and analysed as the *hydrochloride* of the acid (Vd) (Found: *M*, by titration, 331·5. $C_{18}H_{16}O_2N_2$,HCl requires *M*, 328·5).

Methyl N-4′-*Quinazolinylanthranilate* (VIa).—To 4-chloroquinazoline (3 g., 1 mol.) in dry acetone methyl anthranilate (2 mols., 5·6 g.) was added. After a few min. the temperature rose from 18° to 28° and a copious white precipitate separated. After 1 hr. this was filtered off and dried (5·6 g., m. p. 195° with effervescence). The acetone filtrate and washings on evaporation yielded unchanged methyl anthranilate (2·5 g.). The precipitate contained ionisable chlorine, was completely soluble in cold water, and addition of aqueous ammonia precipitated the *base* (VIa) which crystallised from dioxan in white needles, m. p. 211° (Found: C, 68·5; H, 4·6; N, 15·3. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·65; N, 15·05%). The *hydrochloride* had m. p. 195° (Found: *M*, 308·3; N, 13·3%. $C_{16}H_{13}O_2N_3$,HCl requires *M*, 315·5; N, 13·3%).

Quinazo[4,3-b]*quinazol*-8-*one* (VIIa).—The ester (VIa) was heated at its m. p. until effervescence ceased. The *product* crystallised from ethanol in pale cream-coloured needles, m. p. 197° (Found: C, 72·3; H, 3·85; N, 16·9. $C_{15}H_9ON_3$ requires C, 72·8; H, 3·6; N, 17·0%).

N-4′-*Quinazolinylanthranilic Acid.*—To a solution of 4-chloroquinazoline (1 mol., 2 g.) in acetone (20 c.c.) at 0°, ammonium anthranilate (1 mol., 2 g.) in acetone (200 c.c.) at 0° was added. There was an immediate precipitate of ammonium chloride. After an hour this was filtered off and the filtrate evaporated under reduced pressure, leaving a yellow solid which did not crystallise from any organic solvents. The *acid* was purified by dissolution in hot sodium carbonate solution and reprecipitation by acetic acid, then being a pale yellow solid, m. p. 248° (decomp.) (Found: C, 67·7; H, 4·3; N, 15·9. $C_{15}H_{11}O_2N_3$ requires C, 67·9; H, 4·15; N, 15·8%). The *platinichloride* was obtained by treating a solution in acetone containing concentrated hydrochloric acid with platinic chloride [Found: C, 20·6. $(C_{15}H_{11}O_2N_3)_2,H_2PtCl_6$ requires Pt, 20·7%]. Heating the acid at 250° until effervescence ceased converted it into the quinazolone (VIIa), m. p. 197°.

Methyl N-(2-*Phenyl*-4-*quinazolinyl*)*anthranilate* (VIb).—4-Chloro-2-phenylquinazoline (1 mol., 2 g.) and methyl anthranilate (2 mols., 2·7 g.) were refluxed in toluene for 2 hr. The mixture was made alkaline with aqueous ammonia and steam-distilled. After the excess of methyl anthranilate had been removed, the residue was slowly volatile in steam, giving cream-coloured needles, m. p. 179°. The bulk of the product crystallised from dioxan to give the same *compound*, m. p. 179° (Found: C, 74·45; H, 4·8; N, 12·0. $C_{22}H_{17}O_2N_3$ requires C, 74·4; H, 4·8; N, 12·2%).

6-*Phenylquinazo*[4,3-b]*quinazol*-8-*one* (VIIb).—The ester (VIb), heated under reflux with acetic anhydride for 1 hr., gave, on cooling, pale cream needles, m. p. 292°, of the cyclised *compound* (Found: C, 77·9; H, 4·2; N, 13·1. $C_{21}H_{13}ON_3$ requires C, 78·0; H, 4·0; N, 13·0%).

N-(2-*Phenyl*-4-*quinazolinyl*)*anthranilic Acid.*—The ester (VIb) (0·5 g.) was boiled in dioxan (25 c.c.) and 10% aqueous sodium hydroxide (25 c.c.) under reflux for ½ hr. The *acid* was precipitated with acetic acid, and crystallised from aqueous dioxan in bright yellow needles, m. p. 255° (decomp.) (Found: C, 73·5; H, 4·55; N, 12·6. $C_{21}H_{15}O_2N_3$ requires C, 73·9; H, 4·4; N, 12·7%).

A solution of 2-phenyl-4-chloroquinazoline (1·2 g.) in acetone (50 c.c.) at 0° was added to a solution of ammonium anthranilate (0·8 g.) in acetone (50 c.c.) at 0°. There was an immediate precipitate of ammonium chloride which was filtered off after 1 hr., and the acetone filtrate was evaporated under reduced pressure. The resulting compound was boiled with water to remove anthranilic acid, and then treated with cold aqueous ammonia to separate the acid from 2-phenylquinazol-4-one. Acidification of the ammoniacal solution with acetic acid gave the acid, m. p. 255° (from dioxan). Heating the acid at 255—260° until effervescence ceased gave a mixture, m. p. 220—245°, showing that it does not readily cyclise, probably owing to steric hindrance by the 2-phenyl group. Boiling the acid with acetic anhydride for 1 hr. gave a clear solution, from which after cooling, cream needles, m. p. 292°, identical with the quinazolone (VIIb) were obtained.

4-Chloro-2-phenylquinazoline (0·6 g.) and anthranilic acid (0·7 g.) were boiled under reflux in toluene (20 c.c.) for 1 hr. The toluene was removed under reduced pressure, and the residue boiled with water until free from anthranilic acid. Crystallisation from aqueous dioxan gave a compound, m. p. 240—245° (cf. m. p. 241—242° given for the acid by Aggarawal and Ray [6]). The product was treated with cold aqueous ammonia, and the insoluble portion identified as 2-phenylquinazol-4-one, m. p. 236°. The ammoniacal solution, on acidification with acetic acid, deposited the acid, which after crystallising from dioxan had m. p. and mixed m. p. 255°.

One of us (T. S.) acknowledges with thanks a grant from the South African Council for Scientific and Industrial Research.

THE UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG, SOUTH AFRICA.

[*Received, January 16th*, 1956.]