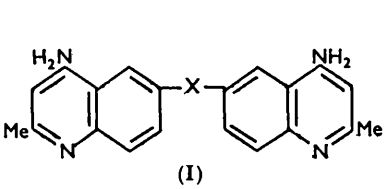
153. *A Search for New Trypanocides. Part IV.* Some Derivatives of 4-Amino-6-aminomethylquinaldine and 1 : 2-Di-(4-aminoquinald-6-yl)ethylene.*

By J. N. Ashley and M. Davis.

NN'-Di-(4-aminoquinald-6-ylmethyl)urea (Id), 1 : 3-di-[(4-aminoquinald-6-ylmethyl)amino]propane (Ie), 2-amino-4 : 6-di-[(4-aminoquinald-6-ylmethyl)amino]-1 : 3 : 5-triazine (If), 4-amino-6-[(4-aminoquinald-6-ylmethyl)-amino]quinaldine (Ig), 1 : 2-di-(4-aminoquinald-6-yl)ethylene (Ih), 2 : 3-di-(4-aminoquinald-6-yl)but-2-ene (Ii), and several of their derivatives and quaternary salts have been prepared as potential trypanocides.

In recent years, trypanocidal activity has been reported for many symmetrical quinoline derivatives of type (I) in which two 4-aminoquinaldine residues are joined at the 6-position by various chains or cyclic groups. Compounds most extensively examined include αω-di-(4-aminoquinald-6-ylamino)alkanes (Ia), αω-di(4-aminoquinald-6-yloxy)alkanes (Ib),

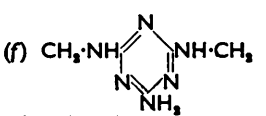


(I)

X

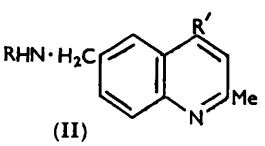
(*a*) NH·[CH$_2$]$_n$·NH
(*b*) O·[CH$_2$]$_n$·O
(*c*) NH·CO·[CRR']$_n$·CO·NH
(*d*) CH$_3$·NH·CO·NH·CH$_2$
(*e*) CH$_3$·NH·[CH$_2$]$_3$·NH·CH$_3$

X



(*f*)

(*g*) CH$_3$·NH
(*h*) CH = CH
(*i*) CMe = CMe



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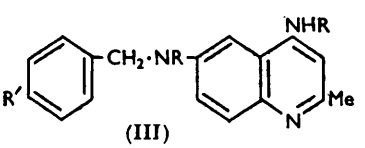

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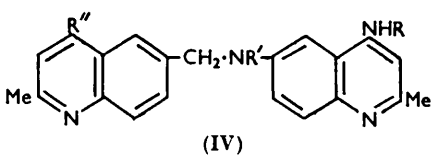

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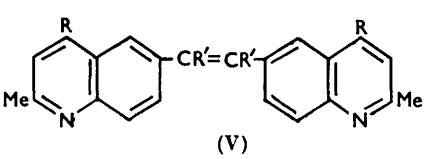

(V)

and the diamides (Ic) of 4 : 6-diaminoquinaldine with various dicarboxylic acids.[1] Many derivatives of 4-aminoquinaldine joined in the 6-position to heterocyclic compounds such as 2 : 4 : 6-triamino-1 : 3 : 5-triazine or 2 : 4-diamino-6-methylpyrimidine have exhibited high trypanocidal activity,[2] and symmetrical azo-compounds, ureas, thioureas, and

* Part III, *J.*, 1956, 3739.

[1] Jensch, *Z. angew. Chem.*, 1937, **50**, 891; Pratt and Archer, *J. Amer. Chem. Soc.*, 1948, **70**, 4065; Goble, *J. Pharmacol.*, 1950, **98**, 49.

[2] Barrett, Curd, and Hepworth, *J.*, 1953, 50.

guanidines derived from 4 : 6-diaminoquinoline, and linked through the 6-position, have been studied by Keneford *et al.*[3]

We have sought to extend this work and have prepared a number of compounds containing two 4-aminoquinaldine nuclei connected in the 6-position by various linkages. The 2-methyl group in the quinoline nucleus has been retained in all the compounds synthesised since it has been shown to be essential for high activity.[4] In one series of compounds derived from 1 : 2-di-(4-aminoquinald-6-yl)ethylene (Ih) the effect of replacing the 4-amino-group by other substituents has also been examined.

It was decided at first to synthesise several homologues of known trypanocides employing 4-amino-6-aminomethylquinaldine in place of 4 : 6-diaminoquinaldine. The required quinaldine was readily obtained by the Conrad–Limpach method from *N*-4-aminobenzylacetamide, which was prepared by catalytic reduction of the known *N*-4-nitrobenzylacetamide. The resulting 6-acetamidomethyl-4-hydroxyquinaldine (II; R = Ac, R′ = OH) was methylated to give the 4-methoxy-compound (cf. Pratt and Archer [1]) and this was fused with ammonium acetate yielding, after hydrolysis, 4-amino-6-aminomethylquinaldine (II; R = H, R′ = NH_2). The diamino-derivative reacted normally with carbonyl chloride, trimethylene dibromide, and 2-amino-4 : 6-dichloro-1 : 3 : 5-triazine, forming respectively *NN*′-di-(4-aminoquinald-6-ylmethyl)urea (Id), 1 : 3-di[(4-aminoquinald-6-ylmethyl)amino]propane (Ie), and 2-amino-4 : 6-di-[(4-aminoquinald-6-ylmethyl)amino]-1 : 3 : 5-triazine (If). With methyl dichloroacetate, the dichloroacetyl derivative (II; R = $CO{\cdot}CHCl_2$, R′ = NH_2) was formed. In the presence of sodium carbonate, methyl iodide gave the bisquaternary compound, 4-amino-6-dimethylaminomethylquinaldine bismethiodide. The monoquaternary salt, 4-amino-6-aminomethylquinaldine methiodide was produced when the 6-acetyl derivative was treated with methyl iodide and then hydrolysed with hydriodic acid.

Another compound prepared (Ig) consisted of a 4-amino-6-methylquinaldine and a 4 : 6-diaminoquinaldine linked together through the 6-position. It is thus related to both the known trypanocides of type (Ia) and the homologous compound (Ie) described above. Condensation of 4-nitrobenzyl chloride with 4 : 6-diaminoquinaldine gave 4-amino-6-4′-nitrobenzylaminoquinaldine (III; R = H, R′ = NO_2) which was acetylated and then reduced catalytically to 4-acetamido-6-(*N*-4-aminobenzylacetamido)quinaldine (III; R = Ac, R′ = NH_2). Application of the Conrad–Limpach reaction to the latter base afforded 4-acetamido-6-[*N*-(4-hydroxyquinald-6-ylmethyl)acetamido]quinaldine (IV; R = R′ = Ac, R″ = OH). The corresponding 4-chloro-compound (IV; R = R′ = Ac, R″ = Cl) showed unusual stability. Thus, the 4-chloro-group was unaffected during the hydrolysis of the acetyl groups by 2N-hydrochloric acid at 100°, whilst treatment with alcoholic ammonia at 120° resulted only in the loss of one acetyl group, giving probably (IV; R = H, R′ = Ac, R″ = Cl). However, replacement of the chloro-group was readily effected by heating the compound with ammonia in phenol.[5] Hydrolysis of the product then gave the dihydrochloride of the required 4-amino-6-[(4-aminoquinald-6-ylmethyl)amino]-quinaldine (Ig).

In the aromatic diamidine series, high trypanocidal activity is retained when a central chain $\cdot O\cdot[CH_2]_n\cdot O\cdot$ is replaced by the unsaturated linkage, $\cdot CH{:}CH\cdot$.[6] We therefore investigated the corresponding quinaldine (Ih). To this end, 4 : 4′-diaminostilbene was submitted to the usual Conrad–Limpach condensation and the resulting 1 : 2-di-(4-hydroxyquinald-6-yl)ethylene (V; R = OH, R′ = H) was methylated and then fused with ammonium acetate, yielding 1 : 2-di-(4-aminoquinald-6-yl)ethylene (Ih). In order to study the effect of substitution in the amino-groups, the 4 : 4′-dichloro-compound (V; R = Cl, R′ = H) was condensed with a number of primary and secondary amines to form the

[3] Keneford, Lourie, Morley, Simpson, Williamson, and Wright, *J.*, 1952, 2595.
[4] Jensch, *Annalen*, 1950, **568**, 73.
[5] Backenberg and Marais, *J.*, 1942, 381; Albert, Brown, and Duewell, *J.*, 1948, 1284.
[6] Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103.

corresponding secondary and tertiary bases (see Table), most of which were converted into quaternary salts.

It has also been demonstrated in the diamidine series that replacement of the central CH:CH linkage by CMe:CMe causes a marked increase in activity against *T. congolense*.[7] The related quinaldine (Ii) was therefore similarly prepared from acetoacetic ester and 2 : 3-di-(*p*-aminophenyl)but-2-ene,[8] the final amination being effected in this case by ammonia–phenol treatment of the chloro-compound (V; R = Cl, R′ = Me).

1 : 2-*Di*-(4-R-*quinald*-6-*yl*)*ethylenes*.

No.	R	Derivative	Conditions	Yield (%)	M. p.	Form
1	NHMe	Base [a]	150°; 16 hr.	100	340° *	Rect. plates
2	—	2HCl	—	—	—	—
3	—	$2Me_2SO_4$	3 hr.	74	—	—
4	NHEt	Base [a]	150—160°; 20 hr.	79	320—325 *	Prisms
5	—	2HCl	—	—	—	—
6	—	$2Me_2SO_4$ [a]	9 hr.	52	>340	Blades
7	NEt_2	Base [b]	185°; 20 hr. Cu bronze added	74	152—154	Prisms
8	—	2HCl [a]	—	—	316—320 *	Prisms
9	—	$2Me_2SO_4$	2 hr.	64	—	—
10	$NH\cdot[CH_2]_2\cdot NEt_2$	Base [c]	160°; 20 hr. Cu bronze added	79	224—226	—
11	—	4HCl	—	—	—	—
12	—	$4Me_2SO_4$	3 hr.	78	—	—
13	Piperidino	Base [a]	185°; 7 hr.	80	242	Prisms
14	—	2HCl	—	—	—	—
15	—	$2Me_2SO_4$	3 hr.	76	150—152	Plates
16	Piperazino	Base [d]	185°; 20 hr.	71	Softens >240°	—
17	—	4HCl	—	—	—	—

		Found (%)					Required (%)				
No.	Formula	C	H	N	Cl	H_2O	C	H	N	Cl	H_2O
1	$C_{24}H_{24}N_4,H_2O$	74·5	7·2	14·1	—	—	74·6	6·8	14·5	—	—
2	$C_{24}H_{24}N_4,2HCl,H_2O$	—	—	12·25	15·85	—	—	—	12·2	15·45	—
3	$C_{28}H_{36}O_8N_4S_2$	—	—	8·9	—	—	—	—	9·0	—	—
4	$C_{26}H_{28}N_4,0·5H_2O$	76·7	7·2	13·8	—	1·7	77·0	7·2	13·8	—	2·2
5	$C_{26}H_{28}N_4,2HCl,H_2O$	—	—	11·6	14·6	—	—	—	11·5	14·6	—
6	$C_{30}H_{40}O_8N_4S_2$	—	—	8·8	—	—	—	—	8·6	—	—
7	$C_{30}H_{36}N_4$	79·4	8·0	12·2	—	—	79·4	8·0	12·4	—	—
8	$C_{30}H_{36}N_4,2HCl$	—	—	10·9	13·35	—	—	—	10·7	13·5	—
9	$C_{34}H_{48}O_8N_4S_2$	—	—	8·2	—	—	—	—	8·0	—	—
10	$C_{34}H_{46}N_6$	76·1	8·5	15·7	—	—	75·9	8·5	15·6	—	—
11	$C_{34}H_{46}N_6,4HCl$	—	—	12·4	20·75	—	—	—	12·3	20·8	—
12	$C_{42}H_{70}O_{16}N_6S_4$	—	—	8·3	—	—	—	—	8·1	—	—
13	$C_{32}H_{36}N_4,H_2O$	77·95	8·15	11·3	—	3·4	78·0	7·8	11·4	—	3·7
14	$C_{32}H_{36}N_4,2HCl,H_2O$	—	—	9·6	12·9	—	—	—	9·9	12·5	—
15	$C_{36}H_{48}O_8N_4S_2$	—	—	7·8	—	—	—	—	7·7	—	—
16	$C_{30}H_{34}N_6,H_2O$	72·8	7·1	16·2	—	—	72·6	7·1	16·9	—	—
17	$C_{30}H_{34}N_6,4HCl,3H_2O$	—	—	12·4	21·0	—	—	—	12·3	21·1	—

[a] Recryst. from EtOH. [b] Recryst. from light petroleum (b. p. 40—60°). [c] Recryst. from C_6H_6. [d] Recryst. from $CHCl_3$. [e] Recryst. from dimethylformamide. * With decomp.

These compounds were examined in our Biological Research Laboratories, and it was found that, although some of the compounds effected cures in mice infected with *T. rhodesiense* and one or two were active against *T. congolense*, none was as active as any of the usually employed trypanocidal agents.

Experimental

N-4-*Nitrobenzylacetamide* (cf. Amsel and Hofman [9]) —*N*-Benzylacetamide (190 g.) was slowly added to fuming nitric acid (*d* 1·5; 475 ml.) which was stirred and cooled in a freezing

[7] Fulton and Yorke, *Ann. Trop. Med. Parasitol.*, 1942, **36**, 131; 1943, **37**, 80, 152; Wien, *Brit. J. Pharmacol.*, 1946, **1**, 65.
[8] Allen and Corwin, *J. Amer. Chem. Soc.*, 1950, **72**, 114.
[9] Amsel and Hofmann, *Ber.*, 1886, **19**, 1284.

mixture, so that the temperature did not exceed 35°. The solution was kept for 10 min., ice (950 g.) was added, and concentrated aqueous ammonia was introduced slowly, the temperature being kept at <25°, until the mixture was alkaline to phenolphthalein. The precipitate was filtered off and recrystallised from water (charcoal), giving 128 g. (52%) of product, m. p. 130—131°.

N-4-*Aminobenzylacetamide*.—*N*-4-Nitrobenzylacetamide (41 g.) in methanol containing platinum oxide (1·5 g.) was reduced catalytically. The filtered solution was evaporated, and the residue was triturated with ether–light petroleum (b. p. 40—60°), to give N-4-*aminobenzylacetamide* (34·1 g., 98%; m. p. 90—96°) which separated from benzene or from chloroform–ether in plates, m. p. 99—101° (Found: N, 17·1. $C_9H_{12}ON_2$ requires N, 17·2%).

Ethyl γ-p-*Acetamidomethylanilinocrotonate*.—*N*-4-Aminobenzylacetamide (56 g.) and ethyl acetoacetate (56 g.) in ethanol (280 ml.) containing a few drops of concentrated hydrochloric acid were refluxed on the steam-bath overnight and then set aside. The *crotonate* (19·1 g.) which separated crystallised from ethyl acetate and aqueous methanol in needles, m. p. 113° (Found: C, 65·35; H, 7·1; N, 10·3. $C_{15}H_{20}O_3N_2$ requires C, 65·25; H, 7·3; N, 10·15%). Evaporation of the original mother-liquors and repeated crystallisation of the residue from methanol and from ethyl acetate gave a further quantity of the crotonate (total yield 39·9 g.), m. p. >110°. It is important that the crotonate be reasonably pure before any attempt is made to cyclise it.

6-*Acetamidomethyl-4-hydroxyquinaldine*.—Ethyl *p*-acetamidomethylanilinocrotonate (46 g.) was added during several minutes to stirred boiling Dowtherm (300 ml.), and boiling was continued for a further 10 min. After being cooled, the mixture was filtered, and the product was washed with benzene and purified by trituration with a little warm alcohol, cooling, and dilution with ether (yield 68%); it was pure enough for methylation. The pure *product* crystallised from ethanol in plates, m. p. 277° (Found: N, 12·15. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

6-*Acetamidomethyl-4-methoxyquinaldine*.—Finely powdered 6-acetamidomethyl-4-hydroxyquinaldine (17 g.) and methyl sulphate (10·2 g.) were stirred under reflux in boiling dry toluene (100 ml.) for 3 hr. After being cooled, the toluene was decanted and the residue washed with ether, dissolved in hot water (100 ml.), and basified with 2N-sodium hydroxide. The 6-*acetamidomethyl-4-methoxyquinaldine* was filtered off and recrystallised from boiling water (charcoal) in needles (11·85 g., 66%), m. p. 170—172° (Found: N, 11·3. $C_{14}H_{16}O_2N_2$ requires N, 11·5%).

6-*Acetamidomethyl-4-aminoquinaldine*.—The 4-methoxy-compound (11·85 g.) and ammonium acetate (60 g.) were heated at 140° for 3 hr. The clear solution was diluted with a little water and basified with concentrated sodium hydroxide solution, and the precipitate was filtered off and washed with water. Recrystallisation from water (charcoal) gave 6-*acetamidomethyl-4-aminoquinaldine* (9·1 g., 82%) in plates, m. p. 239—240° (Found: C, 67·9; H, 6·6; N, 17·9. $C_{13}H_{15}ON_3$ requires C, 68·0; H, 6·6; N, 18·3%). The methiodide, prepared by using methyl iodide in boiling methanol, crystallised from methanol in prisms, m. p. 264—266° (decomp.) (Found: N, 11·3; I, 33·8. $C_{14}H_{18}ON_3I$ requires N, 11·3; I, 34·2%).

4-*Amino*-6-*aminomethylquinaldine*.—6-Acetamidomethyl-4-aminoquinaldine (9·1 g.) was heated with concentrated hydrochloric acid (70 ml.) in water (30 ml.) on the steam-bath overnight. The solution was cooled and the *dihydrochloride* (9·5 g., 92%) was filtered off and washed with alcohol; it crystallised from dilute hydrochloric acid–acetone in needles, m. p. >360° (Found: N, 15·7; Cl, 26·4; H_2O, 1·8. $C_{11}H_{13}N_3,2HCl,0{\cdot}25H_2O$ requires N, 15·9; Cl, 26·8; H_2O, 1·7%). The free *base* crystallised from chloroform in prisms, m. p. 215—216° (Found: C, 70·6; H, 6·8; N, 22·3. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·0; N, 22·45%). The 6-*dichloroacetyl derivative* was prepared by boiling a solution of the base with methyl dichloroacetate in alcohol for 1 hr.; recrystallised from chloroform, it had m. p. 215—217° (Found: N, 14·3; Cl, 23·1. $C_{13}H_{13}ON_3Cl_2$ requires N, 14·1; Cl, 23·8%).

4-*Amino*-6-*aminomethylquinaldine Methiodide Hydriodide*.—6-Acetamidomethyl-4-aminoquinaldine methiodide (2 g.) was heated with 25% hydriodic acid (15 ml., freshly distilled) on the steam-bath for 20 hr., then cooled and filtered, and the residue washed with acetone. The *methiodide hydriodide* crystallised from methanol in narrow prisms, m. p. 279—281° (Found: N, 8·7; I, 53·4. $C_{12}H_{16}N_3I,HI,H_2O$ requires N, 8·8; I, 53·4%).

Methylation of 4-*Amino*-6-*aminomethylquinaldine*.—The base (1·12 g.) was boiled with methyl iodide (30 ml.) and sodium carbonate (0·636 g.) in methanol (30 ml.) for 22 hr. The precipitate (2·55 g.) was filtered off and crystallised from methanol, yielding 4-*amino*-6-*dimethylaminomethylquinaldine dimethiodide* (2·2 g.), m. p. 276—278° (Found: C, 34·8; H, 4·5; N, 7·9; I,

50·8; *N*-Me, 11·2. $C_{15}H_{23}N_3I_2,H_2O$ requires C, 34·8; H, 4·9; N, 8·1; I, 49·1; *N*-Me, 11·6%). In absence of sodium carbonate, methylation was incomplete.

1 : 3-*Di*-[(4-*aminoquinald*-6-*ylmethyl*)*amino*]*propane*.—4-Amino-6-aminomethylquinaldine (1·55 g.) and trimethylene dibromide (0·84 g.) were heated in alcohol (20 ml.) in a sealed tube at 120° for 3 hr. The contents of the tube were evaporated and the residue treated with aqueous sodium hydroxide. The gummy base which separated slowly hardened. It was filtered off, washed with water, and dissolved in alcohol, the resulting solution (after clarification with charcoal) being acidified with dilute hydrochloric acid and then evaporated to dryness under reduced pressure. Trituration of the residue with warm alcohol gave the hygroscopic 1 : 3-*di*-[(4-*aminoquinald*-6-*ylmethyl*)*amino*]*propane tetrahydrochloride*, decomp. >265° (Found: N, 12·2; Cl, 20·4; H_2O, 18·1. $C_{25}H_{30}N_6,4HCl,7H_2O$ requires N, 12·2; Cl, 20·7; H_2O, 18·4%). The amorphous free *base* had m. p. 90—110° (Found: C, 66·7; H, 7·5; N, 18·35. $C_{25}H_{30}N_6,2H_2O$ requires C, 66·6; H, 7·6; N, 18·6%).

NN′-*Di*-(4-*aminoquinald*-6-*ylmethyl*)*urea*.—Carbonyl chloride was passed for 1·25 hr. through a solution of 4-amino-6-aminomethylquinaldine (1·5 g.) and sodium acetate (1·5 g.) in hot water (50 ml.). The clear solution was then cooled and basified with ammonia, and the *urea* filtered off and washed with water. Recrystallisation from a large volume of water gave needles (0·93 g.), decomp. >255° (Found: C, 55·9; H, 6·3; N, 17·5. $C_{23}H_{24}ON_6,5H_2O$ requires C, 56·3; H, 7·0; N, 17·1%). The *dihydrochloride* formed hygroscopic needles, m. p. >360°, from a large volume of alcohol (Found: N, 17·0; Cl, 14·9; H_2O, 3·7. $C_{23}H_{24}ON_6,2HCl,H_2O$ requires N, 17·1; Cl, 14·5; H_2O, 3·7%).

2-*Amino*-4 : 6-*di*-[(4-*aminoquinald*-6-*ylmethyl*)*amino*]-1 : 3 : 5-*triazine*.—2-Amino-4 : 6-dichloro-1 : 3 : 5-triazine (0·495 g.) was added to a solution of 4-amino-6-aminomethylquinaldine (1·12 g.) in nitrobenzene (10 ml.) at 160°. A precipitate commenced to separate almost immediately and, after being kept for 45 min. at 150—160°, the suspension was cooled, diluted with ether, and filtered, and the 2-*amino*-4 : 6-*di*-[(4-*aminoquinald*-6-*ylmethyl*)*amino*]-1 : 3 : 5-*triazine dihydrochloride* was recrystallised from alcohol, to yield 1·1 g., m. p. 270—280° (Found: N, 22·0; Cl, 11·1; H_2O, 14·9. $C_{25}H_{26}N_{10},2HCl,5H_2O$ requires N, 22·2; Cl, 11·3; H_2O, 14·3%).

4-*Amino*-6-4′-*nitrobenzylaminoquinaldine*.—4 : 6-Diaminoquinaldine (20 g.) and 4-nitrobenzyl chloride (20 g.) in dry alcohol (200 ml.) were boiled under reflux for 6 hr. The solution was treated with water (400 ml.), 2N-hydrochloric acid (100 ml.), and charcoal, and then boiled. The insoluble residue left after filtration of the hot mixture was re-extracted with boiling water. Treatment of the combined extracts with 2N-sodium hydroxide and crystallisation of the precipitate from methanol gave 4-*amino*-6-4′-*nitrobenzylaminoquinaldine* (15·75 g.), orange rhombs, m. p. 199° (decomp.) (from chloroform) (Found: C, 62·0; H, 5·5; N, 17·2; H_2O, 7·0. $C_{17}H_{16}O_2N_4,1·25H_2O$ requires C, 61·7; H, 5·6; N, 16·9; H_2O, 6·9%). The *hydrochloride* crystallised from aqueous alcohol in yellow plates, m. p. 265—270° (decomp.) (Found: Cl, 10·6. $C_{17}H_{16}O_2N_4,HCl$ requires Cl, 10·35%). The *diacetyl derivative* crystallised from chloroform–benzene in pale yellow prisms, m. p. 234—236° (Found: C, 65·1; H, 5·1. $C_{21}H_{20}O_4N_4$ requires C, 64·3; H, 5·15%).

4-*Amino*-6-4′-*aminobenzylaminoquinaldine*.—The above nitro-compound (2 g.) was reduced over platinum oxide in methanol at atmospheric temperature and pressure. Evaporation of the solution and crystallisation of the residue from chloroform gave the amine (1 g.) as colourless plates, m. p. 205—206° (Found: C, 73·2; H, 6·6. $C_{17}H_{18}N_4$ requires C, 73·4; H, 6·5%).

4-*Acetamido*-6-N-4′-*aminobenzylacetamidoquinaldine*.—4-Acetamido-6-*N*-4′-nitrobenzylacetamidoquinaldine (15·65 g.) was reduced over platinum oxide in methanol, at atmospheric temperature and pressure, and the residue obtained on evaporation of the solvent was repeatedly extracted with hot ethyl acetate. Concentration of the extracts gave 4-*acetamido*-6-N-4′-*aminobenzylacetamidoquinaldine* (10·1 g., m. p. >214°), colourless prisms, m. p. 221° (effervesces and loses solvent at 120—124°), from ethyl acetate [Found (after drying): C, 70·0; H, 6·4; N, 15·45. $C_{21}H_{22}O_2N_4$ requires C, 69·7; H, 6·1; N, 15·5%].

Ethyl γ-p-[N-(4-*Acetamidoquinald*-6-*yl*)*acetamidomethyl*]*anilinocrotonate*.—The foregoing amino-compound (4·5 g.), ethyl acetoacetate (2 g.), and concentrated hydrochloric acid (1 drop), in alcohol (80 ml.), were heated under reflux for 18 hr. After distillation of the solvent, the residue was heated on the steam-bath for 1 hr., then extracted several times with boiling benzene (total 500 ml.), and the combined extracts were cooled and chromatographed over alumina. Elution with benzene gave the *crotonate* (3·15 g.; m. p. >135°), which formed colourless plates, m. p. 142—144°, from ethyl acetate–light petroleum (b. p. 40—60°) (Found: C, 68·3; H, 6·25;

N, 11·9. $C_{27}H_{30}O_4N_4$ requires C, 68·3; H, 6·4; N, 11·8%). Further elution of the column with chloroform and acetone and purification of the original benzene-insoluble residue gave unchanged amino-compound (1·2 g.).

4-Acetamido-6-[N-(4-hydroxyquinald-6-ylmethyl)acetamido]quinaldine.—The above crotonate (7 g.) was slowly added with stirring to boiling Dowtherm (80 ml.). After 10 min. the solution was cooled, diluted with light petroleum (b. p. 40—60°), and filtered. The amorphous hydroxyquinaldine could not be obtained crystalline. The *picrate* formed needles, m. p. 160—162°, from methanol (Found : N, 15·1. $C_{25}H_{24}O_3N_4,C_6H_3O_7N_3$ requires N, 14·9%).

4-Acetamido-6-[N-(4-chloroquinald-6-ylmethyl)acetamido]quinaldine.—The crude amorphous hydroxy-compound (from 7 g. of crotonate) was boiled with phosphorus oxychloride (30 ml.) for 15 min. and the solution was then evaporated under reduced pressure. The residue was extracted thrice with hot water, then filtered (charcoal), and the combined extracts were basified with 2N-sodium hydroxide. The amorphous *chloro-compound* (3·5 g.) which separated was purified by dissolving it in alcohol and slowly precipitating it with ether (Found : N, 12·4; Cl, 7·9. . $C_{25}H_{23}O_2N_4Cl$ requires N, 12·5; Cl, 7·95%). The *picrate*, m. p. 210° (decomp.), was sparingly soluble in alcohol (Found : N, 15·7. $C_{25}H_{23}O_2N_4Cl,2C_6H_3O_7N_3$ requires N, 15·5%). Evaporation of the alcohol–ether mother-liquors and hydrolysis of the residue with hydrochloric acid gave the hydrochloride of (IV; R = R′ = H, R″ = Cl) (1·1 g.) (see below).

Reaction of 4-Acetamido-6-[N-(4-chloroquinald-6-ylmethyl)acetamido]quinaldine with Alcoholic Ammonia.—The 4-chloro-compound (1·2 g.) and saturated alcoholic ammonia (30 ml.) were heated for 7 hr. at 120° in a sealed tube. The resulting solution was evaporated and the residue crystallised from methanol, giving the *chloro-amine* (0·35 g.), pale yellow needles, m. p. 256° (Found : C, 65·2; H, 5·6; N, 13·25; Cl, 8·3; H_2O, 5·0. $C_{23}H_{21}ON_4Cl,H_2O$ requires C, 65·4; H, 5·5; N, 13·25; Cl, 8·4; H_2O, 4·3%). Some starting material was recovered from the mother-liquors.

4-Amino-6-[(4-chloroquinald-6-ylmethyl)amino]quinaldine.—The diacetyl compound (IV; R = R′ = Ac, R″ = Cl) (1·5 g.) in 2N-hydrochloric acid (60 ml.) was heated on the steam-bath for 1 hr., then concentrated and cooled. The *dihydrochloride*, which separated, was recrystallised from N-hydrochloric acid; it had m. p. >360° (Found : C, 55·6; H, 5·2; N, 12·1; total Cl, 23·25; Cl^-, 15·6. $C_{21}H_{19}N_4Cl,2HCl,H_2O$ requires C, 55·6; H, 5·2; N, 12·1; total Cl, 23·5; Cl^-, 15·6%).

4-Amino-6-[(4-aminoquinald-6-ylmethyl)amino]quinaldine.—A solution of the crude diacetyl compound (IV; R = R′ = H, R″ = Cl) (4·45 g.) in phenol (25 g.) was heated at 185—195° for 3 hr., while a rapid stream of ammonia was passed through the solution. After being cooled, the solution was mixed with concentrated hydrochloric acid (20 ml.) and steam-distilled to remove phenol and to complete hydrolysis. The *dihydrochloride*, which separated on cooling, was recrystallised by dissolution in boiling water (100 ml.) cooling, and addition of concentrated hydrochloric acid. The yield was 2 g. (Found : C, 58·1; H, 6·7; N, 16·3; Cl, 16·5. $C_{21}H_{21}N_5,2HCl,H_2O$ requires C, 58·0; H, 5·8; N, 16·1; Cl, 16·3%).

Condensation of 4 : 4′-Diaminostilbene with Acetoacetic Ester.—*trans*-4 : 4′-Diaminostilbene (13 g.) and acetoacetic ester (17 ml.) in methanol (100 ml.) containing concentrated hydrochloric acid (1 drop), were heated under reflux for 2 hr., then cooled and filtered to give the *crotonate*, 24·2 g. (90%), m. p. 177—184°, raised by recrystallisation from methanol to 184—185° (Found : C, 71·9; H, 7·0; N, 6·45. $C_{26}H_{30}O_4N_2$ requires C, 72·0; H, 6·9; N, 6·5%).

1 : 2-Di-(4-hydroxyquinald-6-yl)ethylene.—The foregoing crotonate (39·1 g.) was slowly added to stirred boiling Dowtherm (200 ml.). After 15 min. the suspension was cooled and filtered, and the crude quinaldine (33·05 g.) was washed with benzene and used without further purification.

1 : 2-Di-(4-methoxyquinald-6-yl)ethylene.—The crude hydroxy-compound (23 g.) and methyl sulphate (18·6 g.) were heated in dry toluene (80 ml.) for 3 hr. After being cooled, the product was filtered off, washed with benzene, and repeatedly extracted with boiling water (charcoal) until the extracts no longer gave a precipitate with alkali. The combined extracts were basified with concentrated aqueous sodium hydroxide and the precipitate was filtered off, washed with water, and crystallised from alcohol. The bright yellow *methoxy-compound* (8·8 g.) had m. p. 269—270° (Found : C, 77·5; H, 6·5; N, 7·5. $C_{24}H_{22}O_2N_2$ requires C, 77·8; H, 6·0; N, 7·6%). The yellow *dihydrochloride*, crystallised from N-hydrochloric acid and from aqueous alcohol, had m. p. >370° (Found : N, 5·9; Cl, 14·0. $C_{24}H_{22}O_2N_2,2HCl,3H_2O$ requires N, 5·65; Cl, 14·25%). The *bismetho(methyl sulphate)*, crystallised from methanol–ether, had m. p. 270° (decomp.) (Found : N, 4·55. $C_{24}H_{22}O_2N_2,2Me_2SO_4$ requires N, 4·5%).

1 : 2-*Di*-(4-*aminoquinald*-6-*yl*)*ethylene*.—1 : 2-Di-(4-methoxyquinald-6-yl)ethylene (3 g.) and anmonium acetate (30 g.) were heated together at 135—140° for 3 hr. The cooled mixture was dissolved in water, and excess of concentrated aqueous sodium hydroxide added. The *diamine* was filtered off, washed with water, and crystallised from alcohol (2·1 g.; m. p. >360°) (Found : C, 74·8; H, 6·3; N, 14·6. $C_{22}H_{20}N_4,C_2H_6O$ requires C, 74·6; H, 6·7; N, 14·5%). The *dihydrochloride* was purified by the addition of alcohol to its solution in the minimum quantity of hot water; it had m. p. >370° (Found : N, 11·5; Cl, 15·2. $C_{22}H_{20}N_4,2HCl,3·5H_2O$ requires N, 11·8; Cl, 14·9%). The *bismetho*(*methyl sulphate*), similarly purified from aqueous alcohol, was hygroscopic and had m. p. >295° (Found : N, 8·15. $C_{22}H_{20}N_4,2Me_2SO_4,5H_2O$ requires N, 8·2%).

1 : 2-*Di*-(4-*chloroquinald*-6-*yl*)*ethylene*.—The crude 1 : 2-di-(4-hydroxyquinald-6-yl)ethylene (14·5 g.) was boiled with phosphorus oxychloride (100 ml.) for 1 hr., excess of reagent then being distilled off *in vacuo*. The residue was cooled and cautiously treated with dilute sodium hydroxide solution until alkaline; the *chloro-compound* which separated crystallised from chloroform (charcoal) in pale yellow prisms, m. p. 274—276° (decomp.) (Found : N, 7·2; Cl, 19·2. $C_{22}H_{16}N_2Cl_2$ requires N, 7·4; Cl, 18·7%). The *dihydrochloride* (Found : N, 6·1; Cl, 31·3. $C_{22}H_{16}N_2Cl_2,2HCl$ requires N, 6·2; Cl, 31·4%) was almost insoluble in water and alcohol.

Condensation of 1 : 2-*Di*-(4-*chloroquinald*-6-*yl*)*ethylene with Amines*.—The chloro-compound was heated with a large excess of the amine (approx. 10 mol.) in a sealed tube under the conditions given in the Table. In the cases of methylamine and ethylamine, 33% solutions of the base in alcohol were used. The products were isolated by warming the contents of the tube with dilute sodium hydroxide solution, filtering off the solid, washing it thoroughly with water, drying it, and crystallising it from the appropriate solvent. In organic solvents all the 4-substituted amino-compounds thus obtained formed yellow solutions which exhibited a brilliant blue or violet fluorescence. The quaternary salts were prepared by boiling a solution or suspension of the base in toluene with a slight excess of methyl sulphate for the time stated in the Table. The yellow or green products were purified from alcohol or methanol–ether.

1 : 2-*Di*-(4-*phenoxyquinald*-6-*yl*)*ethylene*.—The 4-chloro-compound (4 g.) and phenol (10 g.) were heated under reflux for 3 hr. The resulting solution was basified with excess of sodium hydroxide solution, and the precipitate filtered off, washed with water, and crystallised from alcohol (charcoal) (yield 3·55 g., 68%; m. p. 250—255°). Recrystallisation gave 1 : 2-*di*-(4-*phenoxyquinald*-6-*yl*)*ethylene* in brick-red prisms, m. p. 258—260° (Found : C, 81·4; H, 6·0; N, 5·8; H_2O, 1·4. $C_{34}H_{26}O_2N_2,0·5H_2O$ requires C, 81·1; H, 5·4; N, 5·6; H_2O, 1·8%). The *dihydrochloride* (Found : N, 5·0; Cl, 12·9. $C_{34}H_{26}O_2N_2,2HCl$ requires N, 4·8; Cl, 12·9%) formed a grey-green amorphous powder, soluble in cold water. The *bismetho*(*methyl sulphate*) (Found : N, 4·0. $C_{34}H_{26}O_2N_2,2Me_2SO_4$ requires N, 3·8%), prepared in the usual way, was a dark-blue solid, soluble in water to a mauve solution with a strong fluorescence.

Condensation of 2 : 3-*Di*-p-*aminophenylbut*-2-*ene with Acetoacetic Ester*.—A solution of the amine (3·45 g.) and acetoacetic ester (4·3 g.) in methanol (20 ml.) containing concentrated hydrochloric acid (1 drop) was refluxed for 4·5 hr., then cooled overnight. The *crotonate* (5·9 g., 88%), m. p. 125°, was filtered off and recrystallised from methanol. It had m. p. 138° (softens at 134°) (Found : C, 72·85; H, 7·4; N, 6·35. $C_{28}H_{34}O_4N_2$ requires C, 72·7; H, 7·4; N, 6·05%).

2 : 3-*Di*-(4-*hydroxyquinald*-6-*yl*)*but*-2-*ene*.—The foregoing crotonate (5·9 g.) was added to boiling Dowtherm (40 ml.). After 5 min. the suspension was cooled, diluted with benzene, and filtered and the crude quinaldine (4·65 g., 100%) washed with benzene and ether.

2 : 3-*Di*-(4-*chloroquinald*-6-*yl*)*but*-2-*ene*.—The crude hydroxy-compound (4·65 g.) and phosphorus oxychloride (30 ml.) were boiled for 30 min., excess of reagent then being distilled off *in vacuo*. The residue was cautiously treated with dilute aqueous sodium hydroxide, and the precipitate filtered off, washed, dried, and extracted with boiling benzene (charcoal). Evaporation of the extracts to a low bulk and addition of alcohol gave the *dichloro-compound* (1·75 g.), narrow plates, m. p. 232—234° (decomp.) (Found : N, 7·1; Cl, 17·0. $C_{24}H_{20}N_2Cl_2$ requires N, 6·9; Cl, 17·4%).

2 : 3-*Di*-(4-*aminoquinald*-6-*yl*)*but*-2-*ene*.—The chloro-compound (1·75 g.) in phenol (15 g.) was heated at 190° and dry ammonia bubbled through the solution for 5 hr. The mixture was then steam-distilled to remove phenol and basified with aqueous sodium hydroxide, and the base filtered off, washed, and crystallised from aqueous ethanol. 2 : 3-*Di*-(4-*aminoquinald*-6-*yl*)*but*-2-*ene* (1·35 g., 85%) formed prisms from chloroform or aqueous alcohol, decomp. approx. 308° (Found : C, 74·9; H, 6·4; N, 14·9. $C_{24}H_{24}N_4,H_2O$ requires C, 74·6; H, 6·8; N, 14·5%).

The *dihydrochloride* separated from hot water in prisms (Found: N, 12·4; Cl, 15·5. $C_{24}H_{24}N_4,2HCl,H_2O$ requires N, 12·2; Cl, 15·5%). The *bismetho(methyl sulphate)* formed prisms, decomposing above 350°, from aqueous alcohol (Found: N, 9·2. $C_{24}H_{24}N_4,2Me_2SO_4$ requires N, 9·0%).

2 : 3-*Di*-(4-*methoxyquinald*-6-*yl*)*but*-2-*ene*.—Crude 2 : 3-di-(4-hydroxyquinald-6-yl)but-2-ene (0·78 g.) and methyl sulphate (0·55 g.) in dry toluene (50 ml.) were boiled for 3 hr. then cooled. The solvent was decanted and the residual gum washed with ether, boiled with water (60 ml.) and charcoal, and filtered. 2 : 3-*Di*-(4-*methoxyquinald*-6-*yl*)*but*-2-*ene* was precipitated by basifying the aqueous extracts, and formed needles (from aqueous alcohol), m. p. 240—242° (decomp.) (Found: C, 76·9; H, 6·3; N, 7·1; H_2O, 1·4. $C_{26}H_{26}O_2N_2,0·33H_2O$ requires C, 77·1; H, 6·6; N, 6·9; H_2O, 1·5%).

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