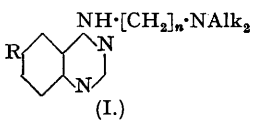
170. *Synthetic Antimalarials. Part XX. Cinnolines. Part XIII. Synthesis and Antimalarial Action of 4-Aminoalkylaminocinnolines.*

By J. R. KENEFORD and J. C. E. SIMPSON.

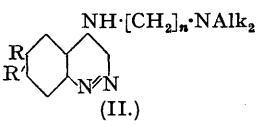
The preparation of a series of 6- and 7-substituted 4-aminoalkylaminocinnolines is described, and their antimalarial activities are recorded.

THE cinnoline ring-system is one which has obvious potentialities as a vehicle for the production of chemotherapeutic agents. As a result of earlier work (*J.*, 1942, 353; 1943, 447; 1945, 512, 520; 1946, 673; this vol., pp. 227, 232) having as its objective the consolidation of routes leading to different types of 4-substituted cinnolines, we were in a position to investigate the chemotherapeutic possibilities which this field appeared to offer, and we decided first to attempt to prepare compounds having antimalarial activity. Our interest in this problem was given additional stimulus by the fact that, when the work was begun, the bulk of the published synthetic work relating to the chemotherapy of malaria was restricted to derivatives of acridine and quinoline, although a few aminoalkylaminoquinazolines of type (I; R = Cl or NO_2) had been synthesised by Magidson and Golovchinskaya (*J. Gen. Chem. Russia*, 1938, **8**, 1797; *Chem. Abs.*, 1939, **33**, 4993); these compounds, however, were stated to be devoid of antimalarial activity.

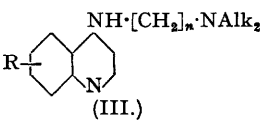
Preliminary results with cinnoline derivatives of type (II; R = H or OMe; R′ = H) (Simpson and Schofield, *Nature*, 1946, **157**, 439) suggested that activity might be expected in suitably substituted compounds, and in this paper we describe the preparation of a series of derivatives of type (II) substituted at C_6 and C_7. In choosing these positions of nuclear substitution we were guided partly by the accessibility of intermediates and partly by the fact that antimalarial activity is recorded for 4-aminoalkylaminoquinolines substituted in the same positions (III; R at C_6 or C_7) (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; B.P. Appl. 27673/38).



(I.)



(II.)

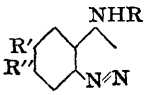


(III.)

The compounds listed in Table III were prepared by conversion of the requisite 4-hydroxycinnoline (*J.*, 1945, 520; this vol., pp. 227, 232) into the 4-chloro- and thence into the 4-phenoxy-derivative, followed by condensation of the latter with the appropriate amine; the use of phenoxy- instead of chloro-compounds for this reaction was more convenient, as most 4-chlorocinnolines decompose on storage, whereas the phenoxy-compounds can be kept indefinitely. The yield of 7-chloro-4-hydroxycinnoline was raised from 30% (this vol., p. 232) to 90% by the use of concentrated hydrochloric acid for the final stage, and we have found that this modification is of general applicability to the preparation in high yield of 4-hydroxycinnolines which do not contain an electron-attractive group in positions 6 or 8.

The compounds (I) were tested against *P. gallinaceum* in chicks at the Blackley laboratories of Imperial Chemical Industries Limited by the method of Curd, Davey, and Rose (*Ann. Trop. Med. Parasit.*, 1945, **39**, 139), and the results [including, for purposes of comparison, those of Simpson and Schofield (*loc. cit.*)] are shown in Table I. Inspection of these results leads to the following conclusions: (*a*) Combination of the side-chain characteristic of mepacrine and

TABLE I.

Compounds of type 

Ref. No.	R.	R′.	R″.	Dose (mg./kg.).	Activity.*
3309	CHMe·$[CH_2]_3$·NEt_2	H	H	250	++
				120	+
6022	,,	H	Cl	80	++
				40	++
5655	,,	Cl	H	160	+ to ++
				80	—
5654	,,	Br	H	160	+ to ++
				80	—
4404	,,	OMe	H	80	—
5656	,,	Cl	Cl	160	++
				80	+ to ++
				40	
				20	—
5659	,,	Cl	Me	160	+ to ++
				80	+
3602	$[CH_2]_2$·NEt_2	H	H	200	±
				120	—
6024	,,	H	Cl	80	+
5853	,,	Cl	Cl	80	—
6023	$[CH_2]_3$·NEt_2	H	Cl	80	++
				40	+
5852	,,	Cl	Cl	80	+
6021	$[CH_2]_3$·NMe_2	H	Cl	80	+ to ++
				40	+
5657	,,	Cl	Cl	160	+ to ++
				80	±
5658	,,	Cl	Me	160	+ to ++
				80	+
6025	$[CH_2]_3$·NBu^{α}_2	H	Cl	80	+
5854	,,	Cl	Cl	80	—
6026	$[CH_2]_3$·N·C_5N_{10}	H	Cl	80	+
5855	,,	Cl	Cl	80	—

* Activity is shown as marked (++), slight (+), doubtful (±), or inactive (−).

pamaquin with a suitably substituted nucleus results in considerably greater activity than does the combination of other side-chains with the same nuclei (compare, *e.g.*, 3309, 6022, 5656 with 3602, 6024, 5853); (*b*) substitution at C_7, *ceteris paribus*, increases the antimalarial activity; (*c*) substitution at C_6 exerts a pronounced dystherapeutic effect. These conclusions are meant to apply only to the range of compounds studied; a discussion of their possible significance is held over pending the accumulation of further data.

The following compounds were tested for prophylactic activity against *P. gallinaceum* in chicks by the method of Davey (*Ann. Trop. Med. Parasit.*, 1946, **40**, 52) but found to be inactive; 5654, 5659, 6022, 6023, and 6024 at 80 mg./kg., and 6024, 6025, and 6026 at 160 mg./kg.

A paper by Leonard and Boyd (*J. Org. Chem.*, 1946, **11**, 419), which appeared after completion of this work, describes the preparation of 6023 and of 6-bromo-4-γ-diethylaminopropyl-

TABLE II.

4-Phenoxycinnolines.

Substituent at					Analysis. Found, %.			Analysis. Required, %.		
6.	7.	M. p.	Formula.	Crystalline form.	C.	H.	N.	C.	H.	N.
H	H	94—95°	$C_{14}H_{10}ON_2$	Colourless needles or leaflets [1]	75·5	4·45	12·9	75·6	4·55	12·6
H	Cl	127—128	$C_{14}H_9ON_2Cl$	Colourless needles [2]	65·4	3·7	—	65·5	3·55	—
Cl	H	128—129	$C_{14}H_9ON_2Cl$	,, [2]	65·2	3·45	—	65·5	3·55	—
Br	H	151·5—152	$C_{14}H_9ON_2Br$	,, [2]	55·6	3·2	—	55·8	3·0	—
OMe	H	108—109	$C_{15}H_{12}O_2N_2$	,, [3]	71·0	4·45	—	71·4	4·8	—
Cl	Me	154—155	$C_{15}H_{11}ON_2Cl$	,, [2]	66·2	3·95	10·6	66·5	4·1	10·35

[1] From ether–ligroin (b. p. 40—60°). [2] From alcohol. [3] From aqueous alcohol.

TABLE III.

4-Aminoalkylaminocinnolines.

Ref. No.	Substituent at 4.	6.	7.	M. p.	Formula.	Reaction conditions.	Crystalline form.	Analysis. Found, %. C.	H.	N.	Cl.	Required, %. C.	H.	N.	Cl.
5655	NH·CHMe·[CH$_2$]$_3$·NEt$_2$	Cl	H	107—108°	$C_{17}H_{25}N_4Cl$	150°/2 hr.	Colourless micro-needles [1]	63·3	8·05	—	11·25	63·6	7·85	—	11·1
5654	,,	Br	H	97·5—98·5	$C_{17}H_{25}N_4Br$	,,	Colourless needles [1]	55·6	7·05	15·35	—	55·9	6·9	15·3	—
5656	,,	Cl	Cl	121·5—123	$C_{17}H_{24}N_4Cl_2$	130°/2½ hr.	Colourless micro-needles [1]	57·45	6·55	15·2	20·2	57·4	6·8	15·8	20·0
5659	,,	Cl	Me	120—121	$C_{18}H_{27}N_4Cl$	170°/2½ hr.	Colourless micro-needles [1]	64·75	8·25	16·7	—	64·55	8·1	16·7	—
6022	,,	H	Cl	123·5—124·5	$C_{17}H_{25}N_4Cl$	150°/2 hr.	Cream-coloured micro-needles [2]	63·65	7·8	17·2	—	63·6	7·9	17·5	—
5853	NH·[CH$_2$]$_2$·NEt$_2$	Cl	Cl	204—204·5	$C_{14}H_{18}N_4Cl_2$	130°/¼ hr.	Pale yellow glistening plates [3]	53·9	5·7	17·75	—	53·7	5·8	17·9	—
6024	,,	H	Cl	182·5—183·5	$C_{14}H_{19}N_4Cl$	,,	Cream-coloured hair-like needles [3]	60·4	6·65	19·7	—	60·3	6·9	20·1	—
5657	NH·[CH$_2$]$_3$·NMe$_2$	Cl	Cl	170—171	$C_{13}H_{16}N_4Cl_2$	,,	Small colourless blades [3]	52·45	5·4	18·75	23·85	52·2	5·4	18·7	23·7
5658	,,	Cl	Me	168—170	$C_{14}H_{19}N_4Cl$	,,	Colourless lustrous plates [4]	60·35	6·85	19·85	—	60·3	6·9	20·1	—
6021	,,	H	Cl	175—176	$C_{13}H_{17}N_4Cl$	,,	Long colourless needles [3]	59·1	6·65	20·75	—	58·95	6·5	21·2	—
5852	NH·[CH$_2$]$_3$·NEt$_2$	Cl	Cl	151·5—152·5	$C_{15}H_{20}N_4Cl_2$	,,	Dull micro-crystals [1]	55·35	6·15	17·1	—	55·0	6·2	17·1	—
6023	,,	H	Cl	162—163 [5]	$C_{15}H_{21}N_4Cl$	,,	Lustrous cream-coloured tablets [2]	61·45	7·4	18·9	—	61·5	7·2	19·1	—
5854	NH·[CH$_2$]$_3$·NBu$^{\alpha}$$_2$	Cl	Cl	153·5—154	$C_{19}H_{28}N_4Cl_2$	,,	Colourless micro-needles [3]	59·5	7·25	—	18·35	59·5	7·4	—	18·5
6025	,,	H	Cl	123—124	$C_{19}H_{29}N_4Cl$	,,	Cream-coloured micro-needles [6]	65·3	8·3	15·7	—	65·4	8·4	16·1	—
5855	NH·[CH$_2$]$_3$·N·C$_5$H$_{10}$	Cl	Cl	214—215	$C_{16}H_{20}N_4Cl_2$	,,	Lustrous prismatic needles [3]	56·95	6·05	—	21·3	56·6	5·95	—	20·9
6026	,,	H	Cl	180—181	$C_{16}H_{21}N_4Cl$	,,	Lustrous narrow plates [3]	62·55	7·1	18·15	—	63·0	6·95	18·4	—

[1] From ether. [2] From ethyl acetate. [3] From alcohol. [4] From benzene.
[5] Leonard and Boyd (*loc. cit.*) give m. p. 164—165°. [6] From benzene–ligroin (b. p. 60—80°).

aminocinnoline; these compounds, for which no antimalarial results are yet recorded, were made directly from the chlorocinnolines and the amine.

Experimental.

M. ps. are uncorrected Derivatives of 4-hydroxy- and 4-hydroxy-6-methoxy-cinnoline were prepared by Dr. K. Schofield. All the reactions could apparently be carried out on any desired scale without loss of yield.

Improved Preparation of 7-Chloro-4-hydroxycinnoline.—Diazotisation was effected in hydrochloric acid, followed by heating on the steam-bath at 60° (cf. this vol., p. 232). It was found that the yield of cinnoline increased with an increase in concentration of acid up to *ca.* 8·5N; the yield was then 90—95%, and no significant increase resulted with higher concentrations. The ratio amino-ketone : acid medium varied between 1 : 60 and 1 : 100.

Similar results were obtained in the preparation of 4-hydroxycinnoline (70—75% yield in 9—9·5N-hydrochloric acid; contrast *J.*, 1945 520); amino-ketone : acid medium = *ca.* 1 : 100.

In each set of experiments the acid concentrations were calculated after addition of the nitrite solution, and the time of reaction was 4—5 hours. The products were isolated by evaporation under reduced pressure (this gave 4-hydroxycinnoline as hydrochloride, but in the case of the 7-chloro-compound much free base crystallised from the reaction mixture).

Preparation of 4-Chlorocinnolines.—The appropriate 4-hydroxycinnoline (1 mol.), phosphorus pentachloride (*ca.* 2 mols.), and phosphorus oxychloride (*ca.* 6 mols.) were heated on the steam-bath for 1 hour. The reaction was usually rapid; the hydroxycinnoline dissolved, and the chlorocinnoline crystallised from the hot solution. The mixture was poured on ice, made just alkaline with aqueous sodium hydroxide, and extracted with ether. The extract was washed with very dilute sodium hydroxide and water, dried, and concentrated (in the case of 4-hydroxycinnoline this was done under reduced pressure); yields of crude products were 80—90%. 4-Anilinocinnolines, by which the chlorocinnolines were occasionally characterised, were made by warming the reactants on the steam-bath for a few minutes, followed by crystallisation of the products from alcohol or ammoniacal alcohol.

4-Chlorocinnoline formed very pale yellow needles, m. p. 78—79°, from ether–ligroin (b. p. 40—60°); Busch and Klett (*Ber.*, 1892, **25**, 2847) and Leonard and Boyd (*loc. cit.*) give m. p. 79° and 76—77° respectively. The compound is unstable and decomposes very rapidly when warmed either alone or with acids. 4-Anilinocinnoline formed pale yellow silky needles, m. p. 229·5—230·5° (Busch and Klett, *loc. cit.*, give m.p. 232°) (Found : N, 19·0. Calc. for $C_{14}H_{11}N_3$: N, 19·0%). 4-Chloro-6-bromocinnoline, pale yellow needles, had m. p. 136—138° [Leonard and Boyd, *loc. cit.*, give 136—137° and 127—128° (interconvertible)]. 4 : 7-Dichlorocinnoline formed colourless polyhedra, m. p. 143—144° (Found : C, 48·3; H, 2·1; Cl, 35·4. Calc. for $C_8H_4N_2Cl_2$: C, 48·2; H, 2·0; Cl, 35·7%); Leonard and Boyd give m. p. 143—143·5°. The 4 : 6-isomer, soft pale yellow needles, had m. p. 111—112°, and 4 : 6-dichloro-7-methylcinnoline crystallised in small cream-coloured needles, m. p. 176—177°. *4-Chloro-6-methoxycinnoline* formed colourless hair-like needles, m. p. 149—151°, from ether (Found : Cl, 18·4. $C_9H_7ON_2Cl$ requires Cl, 18·25%), and yielded *4-anilino-6-methoxycinnoline* (pale yellow needles, m. p. 235·5—236°) (Found : C, 71·6; H, 5·25. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2%).

Preparation of 4-Phenoxycinnolines.—The chloro-compound (1 mol.) was added to a solution of powdered potassium hydroxide (1·2 mols.) in phenol (*ca.* 7·5 mols.), and the whole was heated on the steam-bath for 1 hour (the reaction with 4-chloro-6-methoxycinnoline was sluggish, and a reaction time of 6 hours was used). The mixture was poured into excess of aqueous sodium hydroxide and extracted with ether, after which the extract was repeatedly washed with sodium hydroxide solution and water, dried, and concentrated, giving the phenoxy-compounds (see Table II) in yields of 80—95%.

Preparation of 4-Aminoalkylaminocinnolines.—The phenoxy-compound (1 mol.) and aliphatic amine (*ca.* 2 mols.) were heated in an oil-bath, completion of the reaction being ascertained by examination of a sample of the material which (except in the reactions with δ-diethylamino-α-methylbutylamine) crystallised on cooling. The cold mixtures were filtered after addition of ether and the solid bases crystallised from the appropriate solvent (yields, 90—95%). The reactions in which δ-diethylamino-α-methylbutylamine was used were more sluggish than those with other amines, and the products from them were worked up by basification with aqueous sodium hydroxide and extraction with ether; the ethereal solutions were extracted with 33% aqueous acetic acid, the latter basified, and the products again taken into ether, which was washed, dried, and evaporated; excess of fatty amine was then removed at 90—110°/0·2—0·5 mm., and the residues recrystallised (yields were 65—75%). Distillation of the aminoalkylaminocinnolines was unsuccessful in the few cases tried owing to decomposition. 4404 was prepared by heating the chloro-compound and amine in phenol at 170°; 3602 was formed when 4-chlorocinnoline and the amine were heated at 130° without solvent under nitrogen, but was best prepared *via* the phenoxy-compound.

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