72. *Synthetic Antimalarials. Part V. 2-Naphthylamino-4-aminoalkylamino-6-methylpyrimidines.*

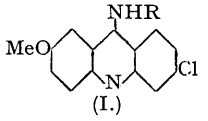
By F. H. S. Curd, C. G. Raison, and F. L. Rose.

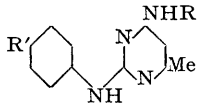
Some of the structural variations which have been introduced into the mepacrine molecule are considered in relation to their effect on antimalarial activity and taken as a basis for extending the investigation of the 2-substituted-anilino-4-dialkylaminoalkylamino-6-methylpyrimidines described in Parts I and II (this vol., pp. 343, 351) to include a number of analogous naphthylamino compounds. High antimalarial activity is shown by 2-(6′-*bromo*-β-*naphthylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* and several related compounds.

The formal planar similarity of mepacrine (I; R = CHMe·$[CH_2]_3$·NEt_2) and 2-*p*-chloroanilino-4-β-diethylaminoethylamino-6-methylpyrimidine (II; R = $[CH_2]_2$·NEt_2, R′ = Cl) to riboflavin (Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, in the press) and the inhibition of the antibacterial activity of the first two compounds for *Lactobacillus casei* by the vitamin (Madinaveitia, *Biochem. J.*, in the press) led to the belief that there might be some connection between mepacrine and the pyrimidine antimalarials of type (II) (Parts I and II, *loc. cit.*), the activity of both types of compound possibly being due to an interference with the function of a riboflavin-

containing enzyme system in the malaria parasite. It was therefore thought that important results might be obtained if some of the modifications in the mepacrine molecule investigated by other workers, excluding simple changes in substituents, were taken as a guide for further variations in the 2-substituted-anilino-4-dialkylaminoalkylamino-6-methylpyrimidine structure (II).

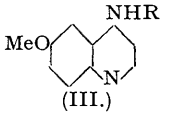
Magidson and Rubtsov (*J. Gen. Chem. Russ.*, 1937, **7**, 1896) and Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) have found that 4-dialkylaminoalkylamino derivatives of 6-methoxyquinoline (III) have antimalarial activity;


(I.)


(II.)

the 7-halogeno-substituted-4-dialkylaminoalkylaminoquinolines (IV) of D.R.P. 683,692 are also known to be active. That these compounds represent portions of the mepacrine molecule (I; R = CHMe·$[CH_2]_3$·NEt_2) can be seen from the appended formulæ, and it is therefore possible that they owe their activity to this relationship and act in a similar manner to mepacrine.

E.P. 481,874 relates to benzoquinoline derivatives, carrying an aminoalkylamino group in the 4-position, which are stated to possess plasmodicidal activity. The permissible variations include not only derivatives of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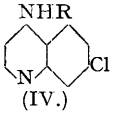
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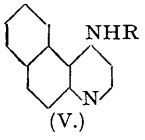
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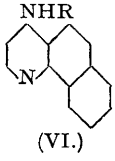
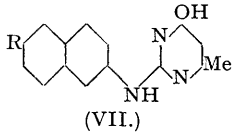
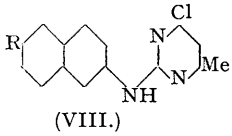
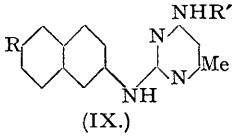

(VI.)

(R = dialkylaminoalkyl group.)

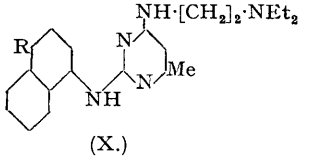
5 : 6-benzoquinoline (V) but also of 7 : 8-benzoquinoline (VI). The former may be regarded as derived from those of type (III), the third ring of mepacrine being attached to the benzene nucleus instead of the pyridine nucleus, so that the 6-methoxy group of (III) is replaced by a fused benzene nucleus in the 5 : 6-position. The latter are similarly related to type (IV), the 7-chlorine atom being replaced by a benzene ring fused in the 7 : 8-position. A corresponding variation of the 2-*p*-substituted-anilino-4-aminoalkylamino-6-methylpyrimidines (II) was therefore indicated, and a series of 2-β-naphthylamino-4-aminoalkylamino-6-methylpyrimidines (IX; R = H, R′ = alkylene·N(alkyl)$_2$) has now been prepared.

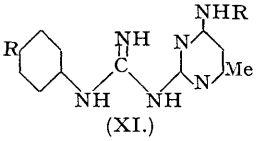

(VII.)


(VIII.)


(IX.)

Condensation of 4-hydroxy-2-methylthio-6-methylpyrimidine with β-naphthylamine at 130—135° gave 2-β-*naphthylamino*-4-*hydroxy*-6-*methylpyrimidine* (VII; R = H), with elimination of methylthiol, and conversion into the corresponding *chloro*-compound (VIII; R = H) was effected by boiling with phosphoryl chloride. Like 4-chloro-2-*p*-chloroanilino-6-methylpyrimidine and similar compounds, 4-chloro-2-β-naphthylamino-6-methylpyrimidine reacted readily with bases such as β-diethylaminoethylamine on heating at 120—130°. In this way the following have been prepared: 2-β-*naphthylamino*-4-β-*diethylaminoethylamino*- (IX; R = H R′ = $[CH_2]_2$·NEt_2), 2-β-*naphthylamino*-4-γ-*diethylaminopropylamino*- (IX; R = H, R′ = $[CH_2]_3$·NEt_2), 2-β-*naphthylamino*-4-δ-*diethylaminobutylamino*- (IX; R = H, R′ = $[CH_2]_4$·NEt_2), 2-β-*naphthylamino*-4-δ-*diethylamino*-α-*methylbutylamino*- (IX; R = H, R′ = CHMe·$[CH_2]_3$·NEt_2), and 2-β-*naphthylamino*-4-(p-β-*diethylaminoethoxyphenylamino*)-6-*methylpyrimidine* (IX; R = H, R′ = *p*-C_6H_4O·$[CH_2]_2$·NEt_2).


(X.)


(XI.)

The above compounds were most conveniently isolated for biological testing as their crystalline dihydrochlorides, which are colourless and soluble in water.

All the compounds of type (IX) exhibited antimalarial activity when tested against *P. gallinaceum* in chicks, although none was outstandingly active. Since they can be regarded as 3 : 4-disubstituted aniline derivatives, they are related to the compounds of this type described in Part II (*loc. cit.*) which were also active and were investigated on account of their closer similarity to riboflavin than compounds of type (II).

For comparison with compounds of type (IX), 2-α-naphthylamino-4-β-diethylaminoethylamino-6-methyl-

pyrimidine (X; R = H) was prepared but was without demonstrable activity; this type was not further investigated. In (X; R = H) neither of the points of attachment of the second benzene nucleus in the naphthylamino residue corresponds to the *para* position of the anilino residue in the prototype (II). In order, therefore, to explore this relationship further, the synthesis of the corresponding 4-chloro-α-naphthylamino compound (X; R = Cl) was undertaken, and it was found that antimalarial activity had been largely restored.

The above results were taken to support the belief that the mode of action of the 2-β-naphthylamino compounds of type (IX) was not fundamentally different from that of the simple anilino derivatives of type (II), probably involving a riboflavin antagonism. For this reason it appeared unlikely that further substitution in the β-naphthylamino residue of compounds of type (IX) would lead to an increase in antimalarial activity. Nevertheless this elaboration appeared to offer considerable possibilities for other reasons.

It was noted that in many of the examples quoted in E.P. 481,874 the fused benzene ring of the benzoquinolines carried an additional substituent, particularly halogen or methoxyl, so that it appeared as if, in passing from the compounds of types (III) and (IV) to the corresponding benzoquinoline types (V) and (VI), transfer of the substituent to the additional nucleus of the latter might be important for high activity. Further, the formal resemblance of compounds of type (IX) to the planar formulation of compounds of type (XI)

TABLE I.

Antimalarial Activities.

Activity is expressed as in Part I. The compounds were given orally. Full biological result will be published elsewhere.

Ref. No.	Formula of base.	Dose, mg./kg.	Activity.
3301	IX; R = H, R′ = $[CH_2]_2$·NEt_2	200	++
		80	+ to ++
		40	±
3581	IX; R = H, R′ = $[CH_2]_3$·NEt_2	80	+
		40	+
3582	IX; R = H, R′ = $[CH_2]_4$·NEt_2	160	+
		80	−
3583	IX; R = H, R′ = CHMe·$[CH_2]_3$·NEt_2	120	+
		80	−
3584	IX; R = H, R′ = *p*-C_6H_4O·$[CH_2]_2$·NEt_2	160	+
		80	−
3501	IX; R = OCH_3, R′ = $[CH_2]_2$·NEt_2	80	++
		40	++
		20	+
3502	IX; R = Br, R′ = $[CH_2]_2$·NEt_2	80	++
		40	++
		20	+
4009	IX; R = Br, R′ = $[CH_2]_2$·NMe_2	40	++
		20	±
4008	IX; R = Br, R′ = $[CH_2]_3$·NMe_2	40	++
		20	+
4007	IX; R = Br, R′ = $[CH_2]_3$·NEt_2	80	++
		40	+
4466	IX; R = Br, R′ = $[CH_2]_3$·NBu^{α}_2	160	+
		40	−
4605	IX; R = Br, R′ = $[CH_2]_3$·$NMePr^{\beta}$	80	++
		40	+
4977	IX; R = Br, R′ = CHMe·$[CH_2]_3$·NEt_2	40	±
3585	X; R = H	80	−
3764	X; R = Cl	80	+
		40	+

described in Part IV (this vol., p. 362), and the importance of the 4-substituent in the phenyl nucleus of the latter for antimalarial activity, suggested the introduction of substituents into the corresponding position of type (IX). The introduction of substituents into the 6-position of the β-naphthylamino residue of (IX) was also suggested by application of the original concept (see Part I, *loc. cit.*) of the possible oxidation, under biological conditions, of the 2-anilino-4-dialkylaminoalkylamino-6-methylpyrimidine structure to give a compound of quinone-like character which might interfere with the function of some biological system responsible for oxygen or hydrogen transfer in a similar manner to the inhibitions investigated by Fildes (*Lancet*, 1940, i, 955). In compounds of type (IX) such an oxidation, if it occurred, might be expected to be facilitated by substitution in the 6-position of the β-naphthylamino residue.

By application of the same synthetic method as used for the unsubstituted β-naphthylamino compounds we therefore prepared 2-(6′-*bromo*-β-*naphthylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IX; R = Br, R′ = $[CH_2]_2$·NEt_2) by way of (VII; R = Br) and (VIII, R = Br) and 2-(6′-*methoxy*-β-*naphthylamino*)-4-β-*diethylaminoethylamino*-6-*methylpyrimidine* (IX; R = OMe, R′ = $[CH_2]_2$·NEt_2) through (VII; R = OMe) and (VIII; R = OMe). The high activity of these two compounds (see Table I) naturally led to an examination of the effect of varying the side chain, and the β-diethylaminoethylamino residue of (IX; R = Br, R′ = $[CH_2]_2$·NEt_2) was replaced by a number of other side chains of similar type. No enhancement of activity resulted.

Experimental.

2-β-Naphthylamino-4-hydroxy-6-methylpyrimidine (VII; R = H).—An intimate mixture of 4-hydroxy-2-methylthio-6-methylpyrimidine (93·6 g.) and β-naphthylamine (280·8 g.) was stirred and heated at 130—135° for 60 hours. Methylthiol was evolved. After cooling, the solid was ground, boiled with alcohol (1 l.), filtered at 50°, and the residue washed thoroughly with alcohol. *2-β-Naphthylamino-4-hydroxy-6-methylpyrimidine* remained as a brown crystalline powder (yield, 86%) which crystallised from β-ethoxyethanol (charcoal) in faintly pink needles, m. p. 244—245° (Found: C, 71·8; H, 5·6; N, 16·4. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

4-Chloro-2-β-naphthylamino-6-methylpyrimidine (VIII; R = H).—The above hydroxypyrimidine (50·2 g.) and phosphoryl chloride (125 c.c.) were heated under reflux at 120—130° for 4 hours. Excess of phosphoryl chloride was then removed in a vacuum at 50—60° and the remaining solid added to ice-water. After stirring for an hour with cooling, the mixture was carefully basified with ammonia and extracted with ether. Removal of ether from the washed and dried (Na_2SO_4) extract left the *chloropyrimidine* as buff-coloured crystals (yield, 92·5%) which separated from alcohol as colourless thick prisms, m. p. 145—147° (Found: Cl, 12·6. $C_{15}H_{12}N_3Cl$ required Cl, 13·2%).

2-α-Naphthylamino-4-hydroxy-6-methylpyrimidine was prepared from 4-hydroxy-2-methylthio-6-methylpyrimidine and α-naphthylamine by the method described above for the isomeric β-naphthylamino compound (yield, 86%). Crystallised from β-ethoxyethanol it had m. p. 256—257° (Found: N, 16·6. $C_{15}H_{13}ON_3$ requires N, 16·7%).

4-Chloro-2-α-naphthylamino-6-methylpyrimidine.—A solution of the above hydroxypyrimidine (7·5 g.) in phosphoryl chloride (20 c.c.) was placed in an oil-bath preheated to 100—110° and stirred for 15 minutes, when bright yellow needles separated (if the period of heating exceeded one hour the needles redissolved and an intractable product was formed). After cooling, the mixture was poured on ice, basified with ammonia at 0—5°, and the product extracted with ether. The ether extract was washed, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from alcohol gave the *chloropyrimidine* as colourless transparent prisms, m. p. 131—132° (yield, 81%) (Found: Cl, 13·1. $C_{15}H_{12}N_3Cl$ requires Cl, 13·2%).

2-(4′-Chloro-α-naphthylamino)-4-hydroxy-6-methylpyrimidine was obtained when 4-hydroxy-2-methylthio-6-methylpyrimidine (39 g.), 4-chloro-α-naphthylamine (54 g.), and β-ethoxyethanol (75 c.c.) were refluxed with stirring in an oil-bath at 150—160° for 48 hours. When cold, the crystals which had separated were collected and washed, first with β-ethoxyethanol and then with alcohol (yield, 61%). The compound crystallised from β-ethoxyethanol in colourless needles, m. p. 298—301° (Found: N, 14·5; Cl, 12·8. $C_{15}H_{12}ON_3Cl$ requires N, 14·7; Cl, 12·4%).

Table II.

2-Naphthylamino-4-aminoalkylamino-6-methylpyrimidine Dihydrochlorides.

Ref. No.	Compound.	Formula.	M. p.	Analysis. Found (%). C.	H.	N.	Cl.†	Required (%). C.	H.	N.	Cl.
3301	IX; R = H, R′ = $[CH_2]_2$·NEt_2	$C_{21}H_{27}N_5,2HCl,H_2O$ (3)	252—254°	58·2	7·2	15·8	15·9	58·2	6·9	15·55	15·8
3581	IX; R = H, R′ = $[CH_2]_3$·NEt_2	$C_{22}H_{29}N_5,2HCl,H_2O$ (4)	259—260	57·7	7·2	—	15·4	58·1	7·3	—	15·6
3582	IX; R = H, R′ = $[CH_2]_4$·NEt_2	$C_{23}H_{31}N_5,2HCl,2H_2O$ (4)	262—263	56·7	7·7	—	14·4	56·8	7·6	—	14·6
3583	IX; R = H, R′ = CHMe·$[CH_2]_3$·NEt_2	$C_{24}H_{33}N_5,2HCl,0·5H_2O$ (4)	268—270	61·4	7·7	—	14·5	60·9	7·6	—	15·0
3584	IX; R = H, R′ = *p*-C_6H_4O·$[CH_2]_2$·NEt_2	$C_{27}H_{31}ON_5,2HCl,1·5H_2O$ (2)	269—271	59·8	6·7	—	12·4	59·9	6·65	—	13·1
3501	IX; R = OMe, R′ = $[CH_2]_3$·NEt_2	$C_{22}H_{29}ON_5,2HCl,1·5H_2O$ (3)	228—230	55·5	7·1	14·2	14·2	55·1	7·1	14·6	14·8
3502	IX; R = Br, R′ = $[CH_2]_2$·NEt_2	$C_{21}H_{26}N_5Br,2HCl,1·5H_2O$ (2)	290	47·9	5·9	13·3	12·8	47·7	5·9	13·3	13·4
4009	IX; R = Br, R′ = $[CH_2]_2$·NMe_2	$C_{19}H_{22}N_5Br,2HCl,0·5H_2O$ (2)	276—278	47·4	5·3	14·3	14·3	47·3	5·2	14·5	14·7
4008	IX; R = Br, R′ = $[CH_2]_3$·NMe_2	$C_{20}H_{24}N_5Br,2HCl,2·5H_2O$ (3)	234—236	45·0	6·0	13·2	13·0	45·1	5·8	13·2	13·35
4007	IX; R = Br, R′ = $[CH_2]_2$·NEt_2	$C_{22}H_{29}N_5Br,2HCl,H_2O$ (3)	259—260	50·0	5·9	13·5	13·6	49·6	6·0	13·1	13·3
4466	IX; R = Br, R′ = $[CH_2]_2$·NBu^{α}_2	$C_{26}H_{36}N_5Br,2HCl,2H_2O$ (4)	230—232	51·7	6·9	11·8	12·3	51·4	6·9	11·5	11·7
4605	IX; R = Br, R′ = $[CH_2]_3$·NMePrβ	$C_{22}H_{29}N_5Br,2HCl,3·5H_2O$ (5)	273	45·8	5·75	12·6	13·4	45·7	6·4	12·1	12·3
				45·7	5·9						
4977*	IX; R = Br, R′ = CHMe·$[CH_2]_3$·NEt_2	$C_{24}H_{32}N_5Br,2HCl,2H_2O$ (1)	275—276	49·6	6·3	12·2	12·5	49·6	6·55	12·1	12·9
3585	X; R = H, R′ = $[CH_2]_2$·NEt_2	$C_{21}H_{27}N_5,2HCl,H_2O$ (1)	275—276	57·0	6·9	—	16·2	57·3	7·0	—	16·1
3764	X; R = Cl, R′ = $[CH_2]_2$·NEt_2	$C_{21}H_{26}N_5Cl,2HCl,0·5H_2O$ (2)	294—295	54·3	5·9	14·7	15·3	54·15	6·2	15·0	15·3

* Prepared by Miss S. Everitt.

† In all cases except 3301 and 3501, ionic chloride was determined.

From: (1) alcohol; (2) aqueous alcohol; (3) slightly aqueous alcohol; (4) alcohol–ethyl acetate; (5) dilute hydrochloric acid.

All compounds melted with decomposition.

4-Chloro-2-(4′-chloro-α-naphthylamino)-6-methylpyrimidine.—The above hydroxypyrimidine (40 g.) was stirred with phosphoryl chloride (150 c.c.) at 120—130° for 1 hour. After cooling, the mixture was added to ice-water and stirred for a short time. The hydrochloride, which separated, was collected, stirred with methanol (150 c.c.), cooled in ice-water, and made alkaline by addition of ammonia. After dilution with water (200 c.c.), the *chloropyrimidine* was collected, washed, and dried in a vacuum (yield, 90%). It crystallised from acetone in long colourless needles, m. p. 170° (Found: N, 13·7; Cl, 22·3. $C_{15}H_{11}N_3Cl_2$ requires N, 13·8; Cl, 23·3%).

2-(6′-Bromo-β-naphthylamino)-4-hydroxy-6-methylpyrimidine (VII; R = Br).—4-Hydroxy-2-methylthio-6-methylpyrimidine (78 g.), 6-bromo-β-naphthylamine (133 g.) (Franzen and Stäuble, *J. pr. Chem.*, 1921, **101**, 59) and β-ethoxyethanol (320 c.c.) were heated together at 150—160°, with stirring, for 60 hours. When cold, the separated *product* was filtered and washed, first with β-ethoxyethanol and then with alcohol (yield, 62%). It had m. p. 286—289°, unchanged by crystallisation from β-ethoxyethanol (Found: N, 12·8; Br, 24·2. $C_{15}H_{12}ON_3Br$ requires N, 12·7; Br, 24·25%). It was soluble in aqueous sodium hydroxide.

4-Chloro-2-(6′-bromo-β-naphthylamino)-6-methylpyrimidine (VIII; R = Br).—Prepared from the above hydroxy compound by a method similar to that used for the 4′-chloro-α-naphthylamino analogue, but prolonging the time of heating to 2 hours, the *compound* (yield, 93%) crystallised from alcohol in pale yellow needles, m. p. 152—154° (Found: 1 mg. ≡ 0·962 mg. Ag halides. $C_{15}H_{11}N_3ClBr$ requires 1 mg. ≡ 0·951 mg. Ag halides).

6-Methoxy-β-naphthylamine.—6-Bromo-2-methoxynaphthalene (53 g.) (Franzen and Stäuble, *J. pr. Chem.*, 1922, **103**, 352) was heated in an autoclave with aqueous ammonia (*d.* 0·880, 162·5 c.c.), alcohol (75 c.c.) and copper powder (1 g.) at 160—170° for 10 hours. The volatile constituents of the resulting mixture were removed with steam and the granular residue collected and dissolved in dilute hydrochloric acid, and the solution treated with decolourising carbon and filtered. Addition of sodium chloride to the filtrate precipitated the hydrochloride, which was filtered off, redissolved in hot water, and the solution made alkaline with sodium hydroxide. The precipitated base was collected, washed well with water, and dried (yield, 65%). Crystallised from methanol it had m. p. 150° (Found: C, 76·0; H, 6·1; N, 8·2. Calc. for $C_{11}H_{11}ON$: C, 76·3; H, 6·4; N, 8·1%). Windaus (*Ber.*, 1924, **57**, 1731) gives m. p. 139—140°; F.P. 646,576 gives m. p. 156—157°. The acetyl derivative separated from aqueous alcohol, m. p. 165—166° (Found: C, 72·7; H, 6·0. Calc. for $C_{13}H_{13}O_2N$: C, 72·6; H, 6·1%). Windaus (*loc. cit.*) gives m. p. 159—160°.

2-(6′-*Methoxy*-β-*naphthylamino*)-4-*hydroxy*-6-*methylpyrimidine* (VII; R = OMe) was obtained by using 6-methoxy-β-naphthylamine in the same manner as the 6-bromo-β-naphthylamino analogue (yield, 77%). After crystallisation from β-ethoxyethanol it had m. p. 238—239° (Found: N, 14·1. $C_{16}H_{15}O_2N_3$ requires N, 14·9%). It dissolved in aqueous sodium hydroxide.

4-*Chloro*-2-(6′-*methoxy*-β-*naphthylamino*)-6-*methylpyrimidine* (VIII; R = OMe), prepared from the hydroxypyrimidine by the method described above for the 4-chloro-α-naphthylamino analogue (yield, 92%), crystallised from alcohol in almost colourless prisms, m. p. 148—150° (Found: Cl, 12·1. $C_{16}H_{14}ON_3Cl$ requires Cl, 11·9%).

Condensation of 4-*Chloro*-2-*naphthylamino*-6-*methylpyrimidines with Aminoalkylamines.*—These reactions proceeded smoothly, giving good yields, when the chloropyrimidines (1 mol.) were heated with the appropriate aminoalkylamine (1·25 mols.) at 120—130° for 6—10 hours. The basified (NaOH) melts were extracted with ether or chloroform, from which the products were extracted with 5% acetic acid, isolation usually being carried out by making alkaline with sodium hydroxide and re-extracting with ether or chloroform. The bases were generally oils but formed crystalline dihydrochlorides, details of which are given in Table II.

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