3-AMINOALKYL- AND 3-BENZYL-4(3H)-QUINAZOLINONES

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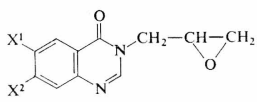
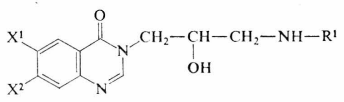
Reaction of 3-(2,3-epoxypropyl)-4(3*H*)-quinazolinone and/or its 6,7-dichloro- and 7-bromo--6-chloro derivatives (*Ib*, *Ic*) with 5-diethylamino-2-pentylamine, 3-diethylaminomethyl-4-hydroxyaniline, 3,4-methylenedioxyaniline and 4-dimethylaminoaniline gave the corresponding substituted 4(3*H*)-quinazolinones, *IIa*, *IIIb*, *IVb*, *Vc* and *VIc*. Reactions of 3-(2-chloroethyl)-4(3*H*)--quinazolinones with the substituted anilines, pyridine and pyrrolidine gave rise to 3-(2-aminoethyl)-4(3*H*)-quinazolinones *VIIIa*–*VIIIj*, *IX* and *X*. The piperidine derivative *XI* was obtained by the action of 1-(2-chloroethyl)piperidine on 4(3*H*)-quinazolinone. Reactions of 2-chlorobenzyl chloride 4-chlorobenzylchloride and 3,4,5-trimethoxybenzoyl chloride with 4(3*H*)-quinazolinone afforded 3-(2-chlorobenzyl)-, 3-(4-chlorobenzyl)-4(3*H*)-quinazolinone and 3-(3,4,5-trimethoxybenzoyl)-4(3*H*)-quinazolinone (*XII*, *XIII*, *XIV*). All the compounds were screened for coccidiostatic and antihelmintic activity.

Since the alkaloid febrifugin is known to have both the coccidiostatic and the antimalaric effects, we have extended our previous study of 4(3*H*)-equinazolinones[1] by further 3-(2-hydroxypropyl)-4(3*H*)-quinazolinones, of which three have 5-diethylamino-2-pentylamino or 3-diethylaminomethyl-4-hydroxyanilino grouping in the side chain. These substituents are typical of a number of the synthetic antimalarics. In their preparation we adhered to the method described previously[1]; the action of 1-chloromethyloxirane on 4(3*H*)-quinazolinone and its 6,7-dihalogeno derivatives gave rise to the corresponding 3-(2,3-epoxypropyl)-4(3*H*)-quinazolinones *Ia*, *Ib* and *Ic*, whose reactions with 5-diethylamino-2-pentylamine and 3-diethylaminomethyl-4-hydroxyaniline afforded the products *IIIb*, *IVb* and *VIc*. Analogously, the reactions of 3-(2,3-epoxypropyl)-4(3*H*)-quinazolinone with 4-dimethylaminoaniline, and of 7-bromo-6-chloro-3-(2,3-epoxypropyl)-4(3*H*)-quinazolinone with 3,4-methylenedioxyaniline gave the compounds *IIa* and *Vc*, respectively.

Further we investigated the effect of shortening the aliphatic bridge between $N_{(3)}$ of the quinazolinone ring and the nitrogen of the basic side chain or the aromatic ring on the coccidiostatic and antihelmintic efficacy. For this purpose we synthetized compounds of the type 3-(2-anilinoethyl)-4(3*H*)-quinazolinone, *VIIIa*–*VIIIj*, and analogous compounds with a pyridine, pyrrolidine or piperidine residue as the basic component (*IX*–*XI*). With the exception of compound *XI* their syntheses started from 4(3*H*)-quinazolinone; its reaction with 2-chloroethanol gave 3-(2-hydro-





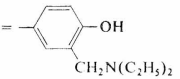
Ia, $X^1 = X^2 = H$

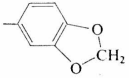
Ib, $X^1 = X^2 = Cl$

Ic, $X^1 = Cl$, $X^2 = Br$

IIa, $X^1 = X^2 = H$; $R^1 = -C_6H_4N(CH_3)_2$-4

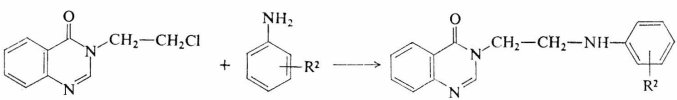
IIIb, $X^1 = X^2 = H$; $R^1 = -CH(CH_3)(CH_2)_3N(C_2H_5)_2$

IVb, $X^1 = X^2 = Cl$; $R^1 =$ 

Vc, $X^1 = Cl$, $X^2 = Br$; $R^1 =$ 

VIc, $X^1 = Cl$, $X^2 = Br$; $R^1 = -CH(CH_3)(CH_2)_3N(C_2H_5)_2$

xyethyl)-4(3*H*)-quinazolinone, which was chlorinated to 3-(2-chloroethyl)-4(3*H*)--quinazolinone. This was used for alkylation of a number of variously substituted anilines in hot xylene. Replacement of xylene by pyridine invariably resulted in N[2-(4(3*H*)-quinazolinone-3-yl)ethyl]pyridinium chloride (*IX*). 3-(2-Piperidinoethyl)-4(3*H*)-quinazolinone (*XI*), in the form of dihydrochloride, was prepared earlier by Sen and Singh[2] from 3-(2-chloroethyl)-4(3*H*)-quinazolinone and piperidine, its m.p. was 180°C. We have synthetized compound *XI* in a reverse way and 4(3*H*)--quinazolinone was treated with 1-(2-chloroethyl)piperidine. The product obtained melted at 242–247°C.

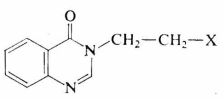


VII *VIII*

a, $R^2 = 2\text{-Cl}$
b, $R^2 = 3\text{-Cl}$
c, $R^2 = 4\text{-Cl}$
d, $R^2 = 2\text{-OCH}_3$
e, $R^2 = 3\text{-OCH}_3$
f, $R^2 = 4\text{-OCH}_3$

g, $R^2 = 2\text{-CH}_3$
h, $R^2 = 3\text{-CH}_3$
i, $R^2 = 4\text{-CH}_3$
j, $R^2 = 3,4\text{-OCH}_2O$–

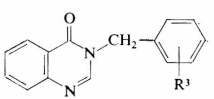
Of the group of substances having a one-carbon bridge on the $N_{(3)}$ atom of the quinazolinone ring, three compounds were prepared: 3-(2-chlorobenzyl)-, 3-(4-chlorobenzyl)- and 3-(3,4,5-trimethoxybenzoyl)-4(3*H*)-quinazolinone (*XII*–*XIV*). The first two were obtained by reaction of 2- and/or 4-chlorobenzyl chloride with 4(3*H*)-quinazolinone in dimethylformamide in the presence of potassium carbonate. The amide *XIV* was formed by acylation of 4(3*H*)-quinazolinone by 3,4,5-trimethoxybenzoyl chloride in pyridine.



IX, X = —N(CH₃)₂

X, X = —N⟨ ⟩

XI, X = —N⟨ ⟩



XII, R^3 = 2-Cl

XIII, R^3 = 4-Cl

The compounds prepared were tested for both coccidiostatic and antihelmintic activity. The coccidiostatic efficacy was assessed on chickens invaded by *Eimeria tenella*, the battery test[3] being used. It appeared that the attachment of the 5-diethylamino-2-pentylamino and 3-diethylaminomethyl-4-hydroxyanilino residues to position 3 of the 2-hydroxypropyl bridge of 3-(2-hydroxypropyl)-4(3*H*)-quinazolinone did not lead to an increase in coccidiostatic efficacy, compared to the compounds prepared previously[1]. An appreciable effect was observed with the compound *VIc* only. The shortening of the three-carbon bridge on $N_{(3)}$ and removal of the alcoholic or ketonic group resulted in a practical disappearance of coccidiostatic efficacy. The antihelmintic efficacy was assessed on rats invaded by *Nippostrongylus brasiliensis* and on mice invaded by the tapeworm *Hymenolepis nana*[3]. Significant antihelmintic effects were observed with compounds *VIIIa*, *VIIIc* and *VIIIf* against *N. brasiliensis*, and *XIII* and *XIV* against *H. nana*. However, the results do not allow of deriving any relations between structure and biological activity.

EXPERIMENTAL

The melting points were determined on the Kofler block in a Boetius apparatus.

3-[3-(4-Dimethylaminoanilino)-2-hydroxypropyl]-4(3*H*)-quinazolinone (*IIa*)

To a solution of 4(3*H*)-quinazolinone (14·6 g, 0·1 mol) in methanol (35 ml) containing sodium (2·1 g) 1-chloromethyloxirane (30 ml) was added dropwise under stirring. After 4 h the separated NaCl was filtered off and the filtrate distilled *in vacuo*. The oily residue was mixed with 4-di-

methylaminoaniline (13·6 g, 0·1 mol) and heated to 85°C, at which temperature an exothermic reaction occurred. The mixture was heated to 100°C for 1 h. The solidified melt was crystallized from methanol (800 ml); yield 7·0 g (20·7%), m.p. 181—182°C.

3-[3-(5-Diethylamino-2-pentylamino)-2-hydroxypropyl]-6,7-dichloro-4(3*H*)-quinazolinone (*IIIb*)

A mixture of the compound *Ib* (ref.[1], 2·4 g, 8·8 mmol) and 5-diethylamino-2-pentylamine[4] (4·3 g, 27 mmol) was heated in a bath to 100°C for 3/4 h. The melt was dissolved in a little chloroform, discoloured with active carbon and the filtrate was diluted with light petroleum until it turned turbid; yield 1·7 g (45%), m.p. 105—112°C. The analytical sample melted at 125—128°C (benzene–light petroleum 1 : 3). For $C_{20}H_{30}Cl_2N_4O_2$ (429·4) calculated: 55·94% C, 7·04% H, 16·52% Cl, 13·05% N; found: 56·06% C, 7·10% H, 16·48% Cl, 13·32% N.

3-[3-(3-Diethylaminomethyl-4-hydroxyanilino)-2-hydroxypropyl]-6,7-dichloro-4(3*H*)-quinazolinone (*IVb*)

3-Diethylaminomethyl-4-hydroxyaniline dihydrochloride[5] (8·0 g, 30 mmol) was decomposed with an equimolar amount of sodium ethoxide, the separated NaCl was removed by filtration, the filtrate was distilled *in vacuo*, and again after an addition of benzene (20 ml). The oily residue was mixed with *Ib* (2·71 g, 10 mmol) and heated to 100°C for 1/2 h. The melt was dissolved in benzene (50 ml) and allowed to crystallize. The crude product (2·8 g, 60%, m.p. 102—105°C) was dissolved in benzene (50 ml), the solution was shaken with ammonia (5 ml) and concentrated *in vacuo*. The analytical sample melted at 122—123°C (ethanol). For $C_{22}H_{26}Cl_2N_4O_3$ (465·4) 56·78% C, 5·63% H, 15·24% Cl, 12·04% N; found: 56·50% C, 5·75% H, 15·23% Cl, 11·74% N.

3[3-(3,4-Methylenedioxyanilino)-2-hydroxypropyl]-7-bromo-6-chloro-4(3*H*)-quinazolinone (*Vc*)

A mixture of *Ic* (ref.[1] 3·15 g, 10 mmol) and 3,4-methylenedioxyaniline (1·5 g, 12 mmol) was heated to 100°C for 1 h. The solidified melt was crystallized from ethanol; yield 3·0 g (66·4%), m.p. 213—215°C. For $C_{18}H_{15}BrClN_3O_4$ (452·7) calculated: 47·75% C, 3·34% H, 17·65% Br, 7·83% Cl, 9·28% N; found: 47·30% C, 3·35% H, 17·59% Br, 7·83% Cl, 9·54% N.

3-[3-(5-Diethylamino-2-pentylamino)-2-hydroxypropyl]-7-bromo-6-chloro-4(3*H*)-quinazolinone (*VIc*)

A mixture of *Ic* (ref.[1] 3·15 g, 10 mmol) and 5-diethylamino-2-pentylamine[4] (2·4 g, 10 mmol) was stirred and heated to 100°C for 1 h. The melt, while still warm, was dissolved in benzene (8 ml), discoloured with active carbon and filtered. Light petroleum was added to the filtrate until a crystalline substance separated. After 2 days of standing in a refrigerator the product was collected on a filter and recrystallized from hexane; yield 3·2 g (67·5%), m.p. 120°C. For $C_{20}H_{30}$·$BrClN_4O_2$ (473·8) calculated: 50·70% C, 6·38% H, 16·87% Br, 7·48% Cl, 11·82% N; found: 50·41% C, 6·54% H, 16·55% Br, 7·34% Cl, 11·85% N.

3-(2-Anilinoethyl)-4(3*H*)-quinazolinones *VIIIa—VIIIj*

A mixture of 3-(2-chloroethyl)-4(3*H*)-quinazolinone[2] (20 mmol), the corresponding aniline (40 mmol) and xylene (25—30 ml) was refluxed for 5—12 h. The xylene was distilled off *in vacuo* and the residue was freed from the used aniline hydrochloride by stirring up in water. The insoluble part of the residue was crystallized from ethanol or methanol to a constant m.p. (Table I).

3-(2-Pyridinioethyl)-4(3*H*)-quinazolinone Chloride (*IX*)

A mixture of 3-(2-chloroethyl)-4(3*H*)-quinazolinone[2] (4·2 g, 20 mmol) and pyridine (30 ml) was refluxed for 4 h. The separated product was collected on a filter and crystallized from ethanol; yield 5·6 g (97·5%), m.p. 255–256°C. For $C_{15}H_{14}ClN_3$ (287·7) calculated: 62·09% C, 4·90% H, 12·32% Cl, 14·60% N; found: 62·36% C, 5·00% H, 12·40% Cl, 14·70% N.

3-(2-Pyrrolidinoethyl)-4(3*H*)-quinazolinone Dihydrochloride (*X*)

A mixture of 3-(2-chloroethyl)-4(3*H*)-quinazolinone[5] (4·2 g, 20 mmol), pyrrolidine (7·1 g, 100 mmol) and benzene (30 ml) was refluxed for 6 h, shaken with 5M-NaOH (5 ml) and the benzene layer was evaporated. The residue was dissolved in a small amount of hydrochloric acid and taken to dryness *in vacuo*. The residue was dissolved in hot ethanol (10 ml), then benzene

TABLE I

3-(1-Anilinoethyl)-4(3*H*)-quinazolinones

Compound (yield)	M.p., °C (solvent)	Formula mol.mass	Calculated/Found			
			% C	% H	% N	% Cl
VIIIa	152–154	$C_{16}H_{14}ClN_3O$	64·11	4·70	14·01	11·83
(37)	(ethanol)	(299·8)	64·00	4·81	14·02	12·04
VIIIb	153–154	$C_{16}H_{14}ClN_3O$	64·11	4·70	14·01	11·83
(49)	(ethanol)	(299·8)	63·90	4·95	14·17	11·96
VIIIc	146–147	$C_{16}H_{14}ClN_3O$	64·11	4·70	14·01	11·83
(29)	ethanol)	(299·8)	64·27	4·87	14·25	11·75
VIIId	163–165	$C_{17}H_{17}N_3O_2$	69·13	5·80	14·23	—
(47)	(methanol)	(295·3)	68·71	5·98	14·12	—
VIIIe	119–122	$C_{17}H_{17}N_3O_2$	69·13	5·80	14·23	—
(44)	(methanol)	(295·3)	69·73	5·94	14·42	—
VIIIf	152–153	$C_{17}H_{17}N_3O_2$	69·13	5·80	14·23	—
(42)	(methanol)	(295·3)	69·41	6·06	14·32	—
VIIIg	178–180·5	$C_{17}H_{17}N_3O$	73·09	6·14	15·04	—
(45)	(methanol)	(279·3)	73·56	6·25	14·91	—
VIIIh	122–124	$C_{17}H_{17}N_3O$	73·09	6·14	15·04	—
(40)	(methanol)	(279·3)	72·84	6·19	15·08	—
VIIIi	141–142	$C_{17}H_{17}N_3O$	73·09	6·14	15·04	—
(43)	(methanol)	(279·3)	72·89	6·31	15·11	—
VIIIj	176–177	$C_{17}H_{15}N_3O_3$	66·01	4·89	13·59	—
(51)	(ethanol)	(309·3)	66·16	5·17	13·69	—

(20 ml) was added; yield 5·5 g (87%), m.p. 239–241°C. For $C_{14}H_{19}Cl_2N_3O$ (316·2) calculated: 53·17% C, 6·06% H, 22·19% Cl, 13·41% N; found: 53·20% C, 6·38% H, 22·19% Cl, 13·41% N.

3-(2-Piperidinoethyl)-4(3*H*)-quinazolinone Dihydrochloride (*XI*)

A mixture of 4(3*H*)-quinazolinone (5·84 g, 40 mmol), hydrochloride of 2-piperidinoethyl chloride (7·26 g, 30 mmol) potassium carbonate (11·05 g, 80 mmol) and water (30 ml) was refluxed for 6 h, distilled *in vacuo*, and the residue was extracted with hot dioxan. After the addition of an equivalent amount of hydrochloric acid the product separated; yield 6·6 g (50%), m.p. 242–247°C (dioxan); reported[2] m.p. 180°C.

3-(2-Chlorobenzyl) and 3-(4-Chlorobenzyl)-4(3*H*)-quinazolinones (*XII*, *XIII*)

A stirred mixture of 4-(3*H*)-quinazolinone (7·3 g, 50 mmol), sodium hydrogen carbonate (4·6 g, 55 mmol) and 2-chlorobenzyl chloride (8·05 g, 50 mmol) in dimethylformamide (30 ml) was heated to 70°C. After the evolution of carbon dioxide had ceased the mixture was distilled *in vacuo* and the residue was extracted into a small volume of hot benzene. The extract was taken to dryness and crystallized from benzene; yield of *XII* 6·2 g (46%), m.p. 112–116°C. For $C_{15}H_{11}ClN_2O$ (270·7) calculated: 66·53% C, 4·10% H, 13·09% Cl, 10·38% N; found: 66·28% C, 4·18% H, 13·42% Cl, 10·58% N. Yield of *XIII* 6·9 g (51%), m.p. 132–134°C (benzene). For $C_{15}H_{11}ClN_2O$ (270·7) found: 66·82% C, 4·03% H, 13·24% Cl, 10·48% N.

3-(3,4,5-Trimethoxybenzoyl)-4(3*H*)-quinazolinone (*XIV*)

A mixture of 4(3*H*)-quinazolinone (4·4 g, 30 mmol) and 3,4,5-trimethoxybenzoyl chloride (6·9 g, 30 mmol) in pyridine (15 ml) was heated to 140°C for 2 h. The solid substance that had separated in the course of standing was stirred up in a 5% solution of $NaHCO_3$, collected on a filter and washed with water; yield 7·0 g (68%), m.p. 196–198°C. The sample for analysis melted at 201–203°C (benzene). For $C_{18}H_{16}N_2O_5$ (340·3) calculated: 63·52% C, 4·74% H, 8·23% N; found: 63·56% C, 4·88% H, 8·28% N.

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