3-(3-AMINO-2-HYDROXYPROPYL)- AND 3-(3-AMINOACETONYL)-4(3*H*)-QUINAZOLINES

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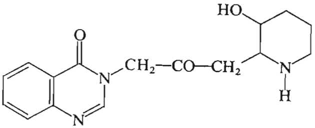
Reactions of 4(3*H*)-quinazolinone and of its 5-chloro, 7-chloro, 5,6-dichloro, 6,7-dichloro, 5-bromo-6-chloro and 6-chloro-7-bromo derivatives with 1-chloro-2,3-epoxypropane yielded 3-(2,3-epoxy-propyl)-4(3*H*)-quinazolinones *III*–*IX* which reacted with aniline, its chloro, methoxy and methyl derivatives, with pyrrolidine, piperidine and morpholine to yield the corresponding 3-(3-amino-2-hydroxypropyl)-4(3*H*)-quinazolinones *X*–*LVIII*. Oxidation of these alcohols with dimethyl sulfoxide in acetic anhydride gave rise to acetylated ketones *LIX*–*LXVII* which were acid-hydrolyzed to 3-(3-anilinoacetonyl)-4(3*H*)-quinazolinones *LXVIII*–*LXHVI*. A clear coccidiostatic activity against *Eimeria tenella* was recorded with *XV*, *XXIII*, *XXIX*, *XLV*, *XLVI*, *XLVII*, *LVII*, *LXII* and *LXV*. Compounds *XXVII* and *XLV* were anthelminthically active against *Nippostrongylus brasiliensis* and compounds *X*, *XI* and *XVIII* against *Fasciola hepatica*.

The alkaloid febrifugin (A) known for its antimalarial and antipyretic activity is simultaneously one of the most effective coccidiostatics[1]. Febrifugin itself, as well as a number of its close analogues, has been prepared synthetically[2-11]. Of special interest for coccidiostatic activity is 6-chloro-7-bromofebrifugin which is prophylactically active against *Eimeria tenella* when added to the fodder in an amount of 0·0003% (ref.[11,12]). The synthesis of febrifugin and of closely related compounds containing 3-piperidinol is laborious and this seems to be the main reason why the compounds have not been employed in veterinary practice.

It was investigated here to what extent the coccidiostatic effect of febrifugin and of related compounds is associated with the presence of the 3-piperidinol component and with the carbonyl of the acetonyl bridge through which 3-piperidinol is linked to 4(3*H*)-quinazolinone, and further in what way substitution of the benzene ring of the quinazolinone moiety will manifest itself. In the present compounds, 3-piperidinol was replaced with readily available bases, such as aniline and its substitution derivatives and further with pyrrolidine, piperidine and morpholine bound across the nitrogen atom directly to the acetonyl group.

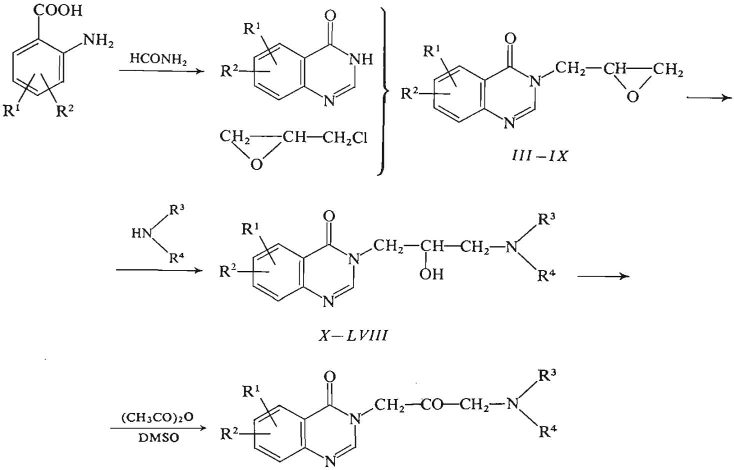
Most of the work was done here with 3-(3-amino-2-hydroxypropyl)-4(3*H*)-quinazolinones ***X*** – *LVIII*, for the synthesis of which we used the scheme developed by Baker and coworkers[2]. The starting 4(3*H*)-quinazolinones are all well known with the exception of 5-bromo-6-chloro-4(3*H*)-quinazolinone (*I*) and they are synthesized from the corresponding anthranilic acids and formamide by melting or boiling in dimethylformamide. In the synthesis of *I* we proceeded from 3-bromoaniline which underwent Sandmeyer's reaction with trichloroacetyldehyde hydrate and hydroxylamine to 3-bromoisonitrosoacetanilide which was cyclized with concentrated sulfuric acid to a mixture of 4-bromo- and 6-bromoisatin[13,14]. The two substances have very close values of pK_a; 10·45 for 4-bromoisatin and 10·35 for 6-bromoisatin (measured in 80% methyl cellosolve) but still they can be easily separated by fractionation of an alkaline solution with hydrochloric acid, such as is described for analogous chloroisatins[14]. The first to precipitate was 4-bromoisatin which was chlorinated to 4-bromo-6-chloroisatin and this was hydrolyzed to 6-bromo-5-chloroanthranilic acid.



A

Through the action of 1-chloro-2,3-epoxypropane one can convert 4(3*H*)-quinazolines to 3-(3-chloro-2-hydroxypropyl)-4(3*H*)-quinazolinones or, in the presence of KOH, to 3-(2,3-epoxypropyl)-4(4*H*)-quinazolinones *III*–*IX*. The second procedure is more suitable as epoxides are easy to isolate and, in another step, react with a primary or a secondary amine, to 3-(3-amino-2-hydroxypropyl)-4(3-)-quinazolines *X*–*LVIII*. It was attempted to oxidize the secondary alcoholic group of these compounds with various agents (such as potassium permanganate, chromic oxide, sodium dichromate, manganese dioxide, Fehling's solution, and air) to the corresponding ketones but with no success. Only when dimethyl sulfoxide was used[15] was the goal reached. Since these oxidations are carried out in acetic anhydride, they are accompanied by acetylation of the secondary amino group, resulting in the corresponding 3-(N-acetyl-3-anilinoacetonyl)-4(3*H*)-quinazolinone *LIX*–*LXVII*.Pyrrolidino, piperidino and morpholino derivatives could not be prepared even by this method. Deacetylation of N-acetyl derivatives *LIX*–*LXVIII* was done by heating with ethanolic hydrogen chloride and the hydrochlorides were treated with sodium carbonate to release bases *LXVIII*–*LXXVI*.

The coccidiostatic efficiency of *X*–*LXXVI* was evaluated in chicks invaded with *Eimeria tenella* using the so-called battery test[16]. The results permit one to derive some relationships between structure and effect. Replacement of the 3-piperidinol component of febrifugin with aromatic amines and nitrogenous heterocycles bound through nitrogen to the side acetonyl chain of 4(3*H*)-quinazolinone resulted in a decrease of coccidiostatic activity by two orders of magnitude. The difference between an acetonyl and a 2-hydroxypropyl bridge was not significant. As to the basic radical bound to the three-carbon chain, most effective were compounds containing *p*-chloroanilino, *p*-anisidino or *p*-toluidino groups attached through the above bridge to 7-chloro-, 6,7-dichloro- and 7-bromo-6-chloro-4(3*H*)-quinazolinone (*XXIX*, *XLV*, *LXV*, *XV*, *XXIII*, *XLVI*, *LVII*, *XLVII*, *LXII*). Anthelminthic screening on rats invaded with *Nippostrongylus brasiliensis*[16] established a statistically significant efficiency of compounds *XXVII* and *XLV* while *X*, *XI* and *XVIII* were active against animals invaded by the liver fluke *Fasciola hepatica*.



LIX–LXVII, R^4 = $COCH_3$
LXVIII–LXXVI, R^4 = H

EXPERIMENTAL

The melting points were determined in Kofler's block.

4- and 6-Bromoisatin

A mixture of 3-bromoaniline (93·1 g, 0·54 mol), hydroxylamine sulfate (79·5 g, 0·97 mol) and sodium sulfate (460 g) in 2·5 l water was acidified with 100 ml 2·5M-H_2SO_4, heated under stirring to 70—75°C and then trichloroacetaldehyde hydrate was added (98·0 g, 0·59 mol). The mixture was boiled for 15 min, on the next day the precipitate was filtered and washed with water (3 . 200 ml). The yield was 156 g crude 3-bromoisonitrosoacetanilide. The triturated product

(140 g) was introduced in parts and under stirring into 650 ml concentrated sulfuric acid at 80—90°C. The mixture was cooled, poured onto ice, the precipitate was filtered, washed with water and dissolved while wet in 1 litre 0·5M-NaOH, the solution was stirred with kieselguhr (10 g) and filtered. The filtrate was combined under stirring with 50 ml 5M-HCl, the precipitated orange product was filtered (compound A, yield 36·9 g). The filtrate was acidified with further 50 ml 5M-HCl and the precipitated product B was filtered (yield 34·8 g). Acidification of the mother liquor with 100 ml 5M-HCl precipitated a yellow compound (product C, yield 22·0 g). Compound A was chromatographed in a thin layer (Silufol, ethyl acetate and tetrachloromethane 2 : 3) and found to be practivally pure 4-bromoisatin. Product B was a mixture of approximately equal amounts of 4- and 6-bromoisatin while compound C was pure 6-bromoisatin. Reprecipitation of A from the alkaline solution with hydrochloric acid yielded chromatographically pure 4-bromoisatin, melting at 270·3—271·6°C (Mettler FP 2). For C_8H_4 $BrNO_2$ (226·0) calculated: 42·51% C, 1·78% H, 6·20% N, 35·35% Br; found: 42·67% C, 1·86% H, 6·21% N, 35·24% Br. 6-Bromoisatin melted at 273·3—274·1°C (Mettler FP 2).

4-Bromo-5-chloroisatin

A mixture of 4-bromoisatin (39·0 g, 0·172 mol) and sulfuryl chloride (40 ml, 0·5 mol) was heated in 700 ml acetic acid with a trace of iodine under stirring for 6 h at 50°C. After cooling, the precipitated product was filtered and washed with acetic acid. The yield was 28·6 g (63·4%), m.p. 276 to 278°C (ethanol). For $C_8H_3BrClNO_2$ (260·5) calculated: 36·89% C, 1·16% H, 5·39% N, 30·67% Br, 13·61% Cl; found: 36·88% C, 1·25% H, 5·75% N, 30·46% Br, 13·47% Cl.

2-Amino-6-bromo-5-chlorobenzoic Acid

30% hydrogen peroxide (45 ml) was added dropwise to a solution of 4-bromo-5-chloroisatin in 450 ml 5% NaOH over a period of 45 min. During the following 30 min, the mixture was filtered, the filtrate was acidified with concentrate hydrochloric acid. The precipitate was filtered and washed with ice-cold water. The yield was 31·5 (88·9%), m.p. 183·9—184·4°C (water). For $C_7H_5BrClNO_2$ (250·5) calculated: 33·57% C, 2·01% H, 5·59% N; found: 33·41% C, 1·98% H, 5·51% N.

5-Bromo-6-chloro-4(3*H*)-quinazolinone (*I*)

A mixture of 2-amino-6-bromo-5-chlorobenzoic acid (31·0 g, 0·12 mol) and formamide (50 g, 1·1 mol) was heated for 1 h to 130°C and for 1·5 g to 170—180°C. The hot melt was stirred with methyl cellosolve and the solution was poured into water. The precipitate was filtered, washed with water and crystallized from methyl cellosolve. The yield was 18·2 g (56·9%) of a compound melting at 277—281°C. For $C_8H_4BrClN_2O$ (259·4) calculated: 37·03% C, 1·55% H, 10·79% N, 30·79% Br, 13·66% Cl; found: 37·07% C, 1·46% H, 10·95% N, 31·12% Br, 13·88% Cl.

3-(3-Chloro-2-hydroxypropyl)-5-chloro-4(3*H*)-quinazolinone (*II*)

A mixture of 5-chloro-4(3*H*)-quinazolinone (2·0 g, 0·011 mol) and 1-chloro-2,3-epoxypropane (40) was heated for 4 h to 100—120°C, whereupon the nonreacted 1-chloro-2,3-epoxypropane was distilled at reduced pressure and the residue was dissolved in a mixture of chloroform and ethyl acetate (1 : 1). The solution was chromatographed on a column of silica gel by the above solvent mixture. Product *II* was eluted first. The residue of combined fractions crystallized from methanol. The yield was 0·9 g (29·8%), m.p. 162—163°C. For $C_{11}H_{10}Cl_2N_2O_2$ (273·1) calculated: 48·37% C, 3·69% H, 10·26% N, 25·96% Cl; found: 48·68% C, 3·49% H, 10·20% N, 26·06% Cl.

3-(2,3-Epoxypropyl)-5-chloro-4(3*H*)-quinazolinone (*IV*)

Two drops of a phenolphthalein solution were added to a solution of *II* (0·5 g, 1·8 mmol) in 10 ml ethanol and this was followed by a slow addition of 10% sodium hydroxide in ethanol to alkaline reaction. After a brief boiling, the mixture was evaporated, the residue was dissolved in chloroform, the inorganic salts were filtered and the filtrate was evaporated. The residue crystallized from a mixture of light petroleum and chloroform. The yield was 0·35 g (81·4%), m.p. 134—136°C. The compound showed no depression of the m.p. in mixture with a preparation obtained directly from *I* and epichlorhydrin by the method described below.

3-(2,3-Epoxypropyl)-4(3*H*)-quinazolinones *III*—*IX*

A mixture of the corresponding quinazolinone (47 mmol), powdery potassium hydroxide (6 g) and 1-chloro-2,3-epoxypropane (200 g) was heated for 1 h to 100°C. After cooling, the inorganic

TABLE I
3-(2,3-Epoxypropyl)-4(3*H*)-quinazolines

Compound (yield, %)	R^1 R^2	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% Cl	% N
III[a] (15·0)	H H	80—82 dioxane	— —	— —	— —	— —	— —
IV (81·4)	5-Cl H	134—136 light petroleum-chloroform	$C_{11}H_9ClN_2O_2$ (236·7)	55·83 55·81	3·83 3·91	14·98 15·40	11·84 11·69
V (30·3)	H 7-Cl	102—105 light petroleum-chloroform	$C_{11}H_9ClN_2O_2$ (236·7)	55·83 55·47	3·83 3·89	14·98 14·51	11·84 12·29
VI (30·4)	5-Cl 6-Cl	152—155 dioxane-ether	$C_{11}H_8Cl_2N_2O_2$ (271·1)	48·74 48·86	2·97 3·02	26·16 26·34	10·23 10·23
VII (58·4)	6-Cl 7-Cl	148—152 dioxane	$C_{11}H_8Cl_2N_2O_2$ (271·1)	48·74 48·47	2·97 2·90	26·16 26·40	10·33 10·37
VIII (24·7)	5-Br 6-Cl	149—151 dioxane	$C_{11}H_8BrClN_2O_2$[b] (315·5)	41·87 42·15	2·55 2·62	11·23 11·43	8·88 9·13
IX (29·1)	6-Cl 7-Br	150—153 dioxane	$C_{11}H_8BrClN_2O_2$[c] (315·5)	41·87 42·36	2·55 2·57	11·23 11·03	8·88 8·52

[a] Prepared according to[2]. [b] Calculated: 25·32% Br; found: 25·76% Br. [c] Calculated: 25·32% Br; found: 24·84% Br.

TABLE II

3-(3-Amino-2-hydroxypropyl)-4(3*H*)-quinazolinones

Compound (yield, %)	R^1 R^2	R^3 R^4	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% N
X[a]	H	C_6H_5	153—156	$C_{17}H_{17}N_3O_2$	69·14	5·80	—	14·23
(27·8)	H	H	chloroform–benzene	(295·4)	68·18	5·91	—	13·96
XI[b]	H	C_6H_{11}	146—147·5	$C_{17}H_{23}N_3O_2$	67·75	7·69	—	13·94
(48·6)	H	H	benzene	(301·4)	67·64	7·71	—	13·61
XII	H	3-ClC_6H_4	133—136	$C_{17}H_{16}ClN_3O_2$	61·92	4·89	10·75	12·74
(16·6)	H	H	benzene	(329·8)	62·37	5·19	10·44	12·56
XIII	H	4-ClC_6H_4	152—157	$C_{17}H_{16}ClN_2O_2$	61·92	4·89	10·75	12·74
(14·8)	H	H	benzene	(329·8)	62·40	4·76	10·67	12·34
XIV	H	3-$CH_3OC_6H_4$	144—145·5	$C_{18}H_{19}N_3O_3$	66·45	5·89	—	12·91
(18·4)	H	H	benzene	(325·4)	66·00	6·01	—	12·78
XV	H	4-$CH_3OC_6H_4$	144—147	$C_{18}H_{19}N_3O_3$	66·45	5·89	—	12·91
(12·2)	H	H	benzene–ethanol	(325·4)	66·68	6·16	—	12·90
XVI	H	2-$CH_3C_6H_4$	137—139	$C_{18}H_{19}N_3O_2$	69·88	6·19	—	13·58
(19·4)	H	H	benzene	(309·4)	69·88	6·43	—	13·40
XVII	H	3-$CH_3C_6H_4$	114—117	$C_{18}H_{19}N_3O_2$	69·88	6·19	—	13·58
(11·4)	H	H	benzene	(309·4)	70·00	6·26	—	13·95
XVIII	H	4-$CH_3C_6H_4$	156—160	$C_{18}H_{19}N_3O_2$	69·88	6·19	—	13·58
(17·9)	H	H	benzene–acetone	(309·4)	69·47	6·24	—	13·60
XIX[c]	H	$(CH_2)_2O(CH_2)_2$	110·5—111·5	$C_{15}H_{19}N_3O_3$	62·27	6·62	—	14·52
(25·7)	H		n-hexane	(289·3)	62·23	6·76	—	14·48
XX	5-Cl	C_6H_{11}	108—110	$C_{17}H_{21}ClN_3O_2$	60·98	6·32	10·54	12·55
(43·7)	H	H	ethanol–water	(334·8)	60·05	6·88	10·39	12·46

XXI (35·7)	5-Cl H	2-ClC_6H_4 H	99—102 ethanol–water	$C_{17}H_{15}Cl_2N_3O_2$ (364·2)	56·06 55·80	4·15 4·41	19·47 18·37	11·54 11·43
XXII (61·9)	5-Cl H	4-ClC_6H_4 H	160—162 methanol–water	$C_{17}H_{15}Cl_2N_3O_2$ (364·2)	56·06 55·99	4·15 4·22	19·47 19·47	11·54 11·82
XXIII (50·0)	5-Cl H	4-$CH_3OC_6H_4$ H	139—142 ethanol–water	$C_{18}H_{18}ClN_3O_3$ (359·8)	60·09 59·79	5·04 5·05	9·85 9·92	11·68 11·67
XXIV (76·0)	5-Cl H	4-$CH_3C_6H_4$ H	129—132 ethanol	$C_{18}H_{18}ClN_3O_2$ (343·8)	62·88 62·69	5·28 5·36	10·31 10·30	12·22 12·19
XXV (27·4)	7-Cl H	C_6H_5 H	165—166 benzene–acetone	$C_{17}H_{16}ClN_3O_2$ (329·8)	61·92 62·17	4·89 5·06	10·75 10·62	12·74 12·76
XXVI (45·0)	7-Cl H	C_6H_{11} H	164—167 benzene–ethanol	$C_{17}H_{21}ClN_3O_2$ (334·8)	60·98 60·58	6·32 6·61	10·59 10·71	12·55 12·86
XXVII (22·7)	7-Cl H	2-ClC_6H_4 H	129—131 benzene	$C_{17}H_{15}Cl_2N_3O_2$ (364·2)	56·04 55·90	4·15 4·08	19·47 19·30	11·54 11·65
XXVIII (6·2)	7-Cl H	3-ClC_6H_4 H	124—127 benzene–light –petroleum	$C_{17}H_{15}Cl_2N_3O_2$ (364·2)	56·04 55·83	4·16 4·41	19·47 18·75	11·54 11·54
XXIX (37·2)	7-Cl H	4-ClC_6H_4 H	155—157 benzene–light petroleum	$C_{17}H_{15}Cl_2N_3O_2$ (364·2)	56·04 55·40	4·15 4·15	19·47 18·62	11·54 11·40
XXX (8·4)	7-Cl H	2-$CH_3OC_6H_4$ H	135—137 benzene	$C_{18}H_{18}ClN_3O_3$ (359·8)	60·09 59·84	5·04 5·02	9·85 10·22	11·68 11·73
XXXI (37·7)	7-Cl H	3-$CH_3OC_6H_4$ H	179—181 benzene–acetone	$C_{18}H_{18}ClN_3O_3$ (359·8)	60·09 60·34	5·04 5·28	9·85 9·74	11·68 11·62
XXXII (23·4)	7-Cl H	4-$CH_3OC_6H_4$ H	164—165 benzene–ethanol	$C_{18}H_{18}ClN_3O_3$ (359·8)	60·09 60·44	5·04 5·08	9·85 9·94	11·68 11·66
XXXIII (8·2)	7-Cl H	2-$CH_3C_6H_4$ H	141—143 benzene	$C_{18}H_{18}ClN_3O_2$ (343·8)	62·88 62·11	5·28 5·03	10·31 10·71	12·22 12·47

TABLE II
(*Continued*)

Compound (yield, %)	R^1 R^2	R^3 R^4	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% N
XXXIV	7-Cl	3-$CH_3C_6H_4$	155–157	$C_{18}H_{18}ClN_3O_2$	62·88	5·28	10·31	12·22
(16·9)	H	H	benzene–acetone	(343·8)	62·46	5·39	10·52	12·48
XXXV	7-Cl	4-$CH_3C_6H_4$	168–170	$C_{18}H_{18}ClN_3O_2$	62·88	5·28	10·31	12·22
(24·1)	H	H	ethyl acetate	(343·8)	62·65	5·41	10·46	12·34
XXXVI	7-Cl	$(CH_2)_5$	87–90	$C_{16}H_{20}ClN_3O_2$	59·72	6·26	11·02	13·06
(44·1)	H		benzene	(321·8)	56·62	6·54	10·85	12·66
XXXVII	7-Cl	$(CH_2)_2O(CH_2)_2$	107–108	$C_{15}H_{18}ClN_3O_3$	55·65	5·60	10·95	12·98
(58·8)	H		benzene	(323·8)	55·72	5·62	10·90	13·26
XXXVIII	5-Cl	C_6H_{11}	140–142	$C_{17}H_{21}Cl_2N_3O_2$	55·14	5·72	19·15	11·35
(75·2)	6-Cl	H	ethanol–water	(370·3)	55·44	5·84	19·63	11·42
XXXIX	5-Cl	2-ClC_6H_4	162–164	$C_{17}H_{14}Cl_3N_3O_2$	51·22	3·54	26·68	10·54
(34·1)	6-Cl	H	ethanol–water	(398·7)	51·10	3·76	26·45	10·53
XL	5-Cl	4-ClC_6H_4	175–182	$C_{17}H_{14}Cl_3N_3O_2$	51·22	3·54	26·68	10·54
(42·4)	6-Cl	H	ethyl acetate	(398·7)	50·75	3·55	26·23	10·39
XLI	5-Cl	4-$CH_3OC_6H_4$	189–192	$C_{18}H_{17}Cl_2N_3O_3$	54·84	4·35	17·98	10·66
(50·8)	6-Cl	H	ethyl acetate	(394·3)	54·86	4·45	17·86	10·23
XLII	5-Cl	4-$CH_3C_6H_4$	135–140	$C_{18}H_{17}Cl_2N_3O_2$	57·16	4·53	18·75	11·11
(73·2)	6-Cl	H	ethanol–water	(378·3)	56·54	4·44	19·49	11·07
XLIII	6-Cl	C_6H_4	170–171	$C_{17}H_{15}Cl_2N_3O_2$	56·06	4·15	19·47	11·54
(71·4)	7-Cl	H	benzene–chloroform	(364·2)	56·56	4·19	19·70	11·39

XLIV	6-Cl	C_6H_{11}	180—182	$C_{17}H_{21}Cl_2N_3O_2$	55·14	5·72	19·15	11·35
(64·9)	7-Cl	H	chloroform–	(370·3)	54·89	5·53	19·33	11·27
			–light petroleum					
XLV	6-Cl	$4-ClC_6H_4$	205—206	$C_{17}H_{14}Cl_3N_3O_2$	51·22	3·54	26·68	10·54
(63·3)	7-Cl	H	chloroform–	(398·7)	50·98	3·40	26·85	10·59
			–light petroleum					
XLVI	6-Cl	$4-CH_3OC_6H_4$	176—179	$H_{18}H_{17}Cl_2N_3O_3$	54·84	4·35	17·99	10·66
(76·4)	7-Cl	H	benzene–chloroform	(394·3)	55·09	4·38	18·09	10·58
XLVII	6-Cl	$4-CH_3C_6H_4$	204—205	$C_{17}H_{17}Cl_2N_3O_2$	57·16	4·53	18·75	11·11
(98·2)	7-Cl	H	benzene–ethanol	(378·3)	56·80	4·55	19·51	11·14
XLVIII	6-Cl	$(CH_2)_4$	129—131	$C_{15}H_{17}Cl_2N_3O_2$	52·64	5·01	20·72	12·28
(44·1)	7-Cl		chloroform–	(342·2)	52·81	5·12	20·57	12·20
			–light petroleum					
IL	6-Cl	$(CH_2)_5$	143—145	$C_{16}H_{19}Cl_2N_3O_2$	53·94	5·38	19·90	11·79
(82·8)	7-Cl		chloroform–	(356·3)	53·79	5·39	20·10	11·83
			–light petroleum					
L	6-Cl	$(CH_2)_2O(CH_2)_2$	101·5—102·5	$C_{15}H_{17}Cl_2N_3O_3$	50·29	4·78	19·79	11·73
(78·5)	7-Cl		chloroform–	(358·2)	48·74	4·92	19·81	11·10
			–light petroleum					
LI	5-Br	$2-ClC_6H_4$	163—165	$C_{17}H_{14}BrCl_2N_3O_2$[d]	46·08	3·18	16·00	9·48
(59·5)	6-Cl	H	ethanol	(443·1)	46·20	3·35	16·07	9·23
LII	5-Br	$4-ClC_6H_4$	179—182	$C_{17}H_{14}BrClN_3O_3$[e]	46·08	3·18	16·00	9·48
(36·1)	6-Cl	H	ethanol	(443·1)	46·64	3·25	15·70	9·24
LIII	5-Br	$4-CH_3OC_6H_4$	141—149	$C_{18}H_{17}BrClN_3O_3$[f]	49·23	3·91	8·09	9·59
(53·0)	6-Cl	H	ethanol	(438·1)	49·18	3·99	8·17	9·33
LIV	5-Br	$4-CH_3C_6H_4$	134—138	$C_{18}H_{17}BrClN_3O_2$[g]	51·15	4·05	8·39	9·94
(43·3)	6-Cl	H	ethanol	(422·7)	50·89	3·98	8·54	9·97

TABLE II
(*Continued*)

Compound (yield, %)	R^1 R^2	R^3 R^4	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% N
LV (66·1)	5-Br 6-Cl	$(CH_2)_2O(CH_2)_2$	147–150 chloroform–light petroleum	$C_{15}H_{17}BrClN_3O_3$[h] (402·7)	44·76 44·48	4·26 4·26	8·80 8·90	10·43 10·54
LVI (48·9)	6-Cl 7-Br	$4-ClC_6H_4$ H	216–219 ethanol	$C_{17}H_{14}BrCl_2N_3O_2$[i] (443·1)	46·08 45·98	3·18 3·26	16·00 15·94	9·48 9·38
LVII (61·1)	6-Cl 7-Br	$4-CH_3OC_6H_4$ H	181–183 ethanol	$C_{18}H_{17}BrClN_3O_3$[j] (438·1)	49·28 49·06	3·91 3·95	8·09 8·30	9·59 9·94
LVIII (43·7)	6-Cl 7-Br	$4-CH_3C_6H_4$ H	205–206 ethanol	$C_{18}H_{17}BrClN_3O_2$[k] (422·7)	51·15 50·94	4·05 4·01	8·39 8·30	9·94 9·97

[a] Ref.[2] reports a m.p. of 196–198°C for the hydrochloride. [b] Ref.[2] reports a yield of 54% and a m.p. of 144–146°C. [c] Ref.[2] reports a yields of 50% and a m.p. of 106–106°C. [d] Calculated: 18·03% Br; found: 18·12% Br. [e] Calculated: 18·03% Br; found: 17·69% Br. [f] Calculated: 18·23% Br; found: 18·40% Br. [g] Calculated: 18·90% Br; found: 19·20% Br. [h] Calculated: 19·84% Br; found: 20·06 % Br. [i] Calculated: 18·03% Br; found: 17·96% Br. [j] Calculated: 18·21% Br; found: 18·60% Br. [k] Calculated: 18·90% Br; found 18·72% Br.

salts were filtered and the filtrate was evaporated at reduced pressure. The sirupy residue was triturated with 25 ml dioxane, on the next day the precipitate was filtered and washed with ether. The yields, the m.p. and the elementary analyses are shown in Table I.

3-(3-Amino-2-hydroxypropyl)-4(3*H*)-quinazolinones *X—LVIII*

A mixture of the corresponding aniline or heterocyclic base (30 mmol) and 3-(2,3-epoxypropyl)-4(3*H*)-quinazolinone (10 mmol) was heated for 45 min at 100°C under an air condenser. After cooling, the melt was dissolved in chloroform, the solution was bleached with charcoal and mixed with light petroleum. The precipitate was filtered and washed with light petroleum. The yields, m.p. and elementary analyses are shown in Table II.

3-(N-Acetyl-3-anilinoacetonyl)-4(3*H*)quinazolinones *LIX—LXVII*

A solution of the corresponding 3-(3-anilino-2-hydroxypropyl)-4(3*H*)-quinazolinone (*X*, *XIII*, *XV*, *XVIII*, *XXIII*, *XXIX*, *XLV*, *XLVI*, *XLVII*) (1·1 mmol) in 5 mol dimethyl sulfoxide and 2·5 ml acetic anhydride was left to stand for 48 h at room temperature, evaporated at reduced pressure and the residue was crystallized from methanol or benzene. The yields, m.p. and elementary analyses are shown in Table III.

3-(3-Anilinoacetonyl)-4(3*H*)-quinazolinones *LXVIII—LXXVI*

A suspension of the corresponding acetyl derivative *LIX—LXVII* (4 mmol) in 100 ml ethanolic hydrogen chloride containing about 0·08 g HCl/ml was refluxed for 2·5 h. After cooling, the precipitated hydrochloride was filtered and, without purification, decomposed with an aqueous solution of sodium carbonate (3·4 g Na_2CO_3 in 150 ml water) stirred for 8 h at room temperature. The base formed was filtered, washed with water and dried. The yields, m.p. and elementary analyses are shown in Table IV.

The efficiency of the compounds against Fasciola hepatica *was tested by Dr R. Špaldonová, Helminthological Institute, Slovak Academy of Sciences. The elementary analyses were done at the analytical department of this institute (under the direction of Dr J. Körbl).*

TABLE III

3-(3-Aminoacetonyl)-4(3*H*)-quinazolinones

Compound (yield, %)	R^1 R^2	R^3 R^4	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found			
					% C	% H	% Cl	% N
LIX	H	C_6H_4	186–187	$C_{19}H_{17}N_3O_3$	68·05	5·11	—	12·53
(58·8)	H	CH_3CO	methanol	(335·4)	68·36	5·21	—	12·83
LX	H	4-ClC_6H_4	175–177	$C_{19}H_{16}ClN_3O_3$	64·50	4·56	10·02	11·88
(33·0)	H	CH_3CO	methanol	(353·0)	62·20	4·32	9·61	11·66
LXI	H	4-$CH_3OC_6H_4$	141–142	$C_{20}H_{19}N_3O_4$	65·74	5·24	—	11·50
(31·1)	H	CH_3CO	benzene	(365·4)	65·68	5·37	—	11·51
LXII	H	4-$CH_3C_6H_4$	158–159	$C_{20}H_{19}N_3O_3$	68·75	5·48	—	12·02
(19·4	H	CH_3CO	methanol	(349·4)	69·17	5·76	—	12·08
LXIII	5-Cl	4-$CH_3OC_6H_4$	178–180	$C_{20}H_{18}ClN_3O_4$	60·08	4·54	8·87	10·51
(42·0)	H	CH_3CO	methanol	(399·8)	60·26	4·56	9·07	10·61
LXIV	H	4-ClC_6H_4	208–212	$C_{19}H_{15}Cl_2N_3O_3$	56·45	3·74	17·54	10·39
(39·0)	7-Cl	CH_3CO	methanol	(404·3)	56·85	4·00	17·37	9·97
LXV	6-Cl	4-ClC_6H_4	223–227	$C_{19}H_{14}Cl_3N_3O_3$	52·02	3·22	24·24	9·58
(57·1)	7-Cl	CH_3CO	methanol	(438·7)	52·01	3·51	24·05	9·33
LXVI	6-Cl	4-$CH_3OC_6H_4$	215–218	$C_{20}H_{17}Cl_2N_3O_4$	55·31	3·95	16·33	9·67
(50·7)	7-Cl	CH_3CO	methanol	(434·3)	55·23	4·02	16·50	9·79
LXVII	6-Cl	4-$CH_3C_6H_4$	220–223	$C_{20}H_{17}Cl_2N_3O_3$	57·43	4·10	16·95	10·04
(50·7)	7-Cl	CH_3CO	methanol	(418·3)	57·05	4·19	17·03	10·66
LXVIII	H	C_6H_5	209–210	$C_{17}H_{15}N_3O_2$	69·61	5·15	—	14·32
(58·1)	H	H	methanol	(293·3)	69·03	5·24	—	13·86
LXIX	H	4-ClC_6H_4	198–201	$C_{17}H_{14}ClN_3O_2$	62·30	4·30	10·82	12·82
(44·6)	H	H	chloroform–ethanol	(327·8)	62·11	4·31	10·86	13·06

LXX	H	4-$CH_3OC_6H_4$	168—171	$C_{18}H_{17}N_3O_3$	66·86	5·30	—	12·99
(18·5)	H	H	chloroform–ethanol	(323·4)	66·61	5·42	—	13·20
LXXI	H	4-$CH_3C_6H_4$	179—182	$C_{18}H_{17}N_3O_2$	70·34	5·58	—	13·67
(73·2)	H	H	chloroform–ethanol	(307·4)	70·18	5·70	—	13·82
LXXII	5-Cl	4-$CH_3OC_6H_4$	178—180	$C_{18}H_{16}ClN_3O_3$	60·42	4·51	9·91	11·74
(28·9)	H	H	ethanol–water	(357·8)	59·71	4·37	10·09	11·47
LXXIII	H	4-ClC_6H_4	200—205	$C_{17}H_{13}Cl_2N_3O_2$	56·37	3·62	19·58	11·60
(76·2)	7-Cl	H	dimethyl sulfoxide–-water	(362·2)	56·33	3·49	19·90	11·75
LXXIIV	6-Cl	4-ClC_6H_4	207—208	$C_{17}H_{12}Cl_3N_3O_2$	51·48	3·08	26·81	10·59
(82·5)	7-Cl	H	2-butanone	(396·7)	51·64	3·00	26·63	10·80
LXXV	6-Cl	4-$CH_3OC_6H_4$	182·5—183·5	$C_{18}H_{15}Cl_2N_3O_3$	55·12	3·85	18·08	10·71
(15·6)	7-Cl	H	2-butanone	(392·3)	55·11	3·95	18·21	10·99
LXXVI	6-Cl	4-$CH_3C_6H_4$	202—205	$C_{18}H_{15}Cl_2N_3O_2$	57·46	4·02	18·85	11·17
(59·8)	7-Cl	H	dioxane	(376·3)	57·54	4·11	18·60	11·17

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