ALKOXY-2,4-QUINAZOLINEDIAMINES

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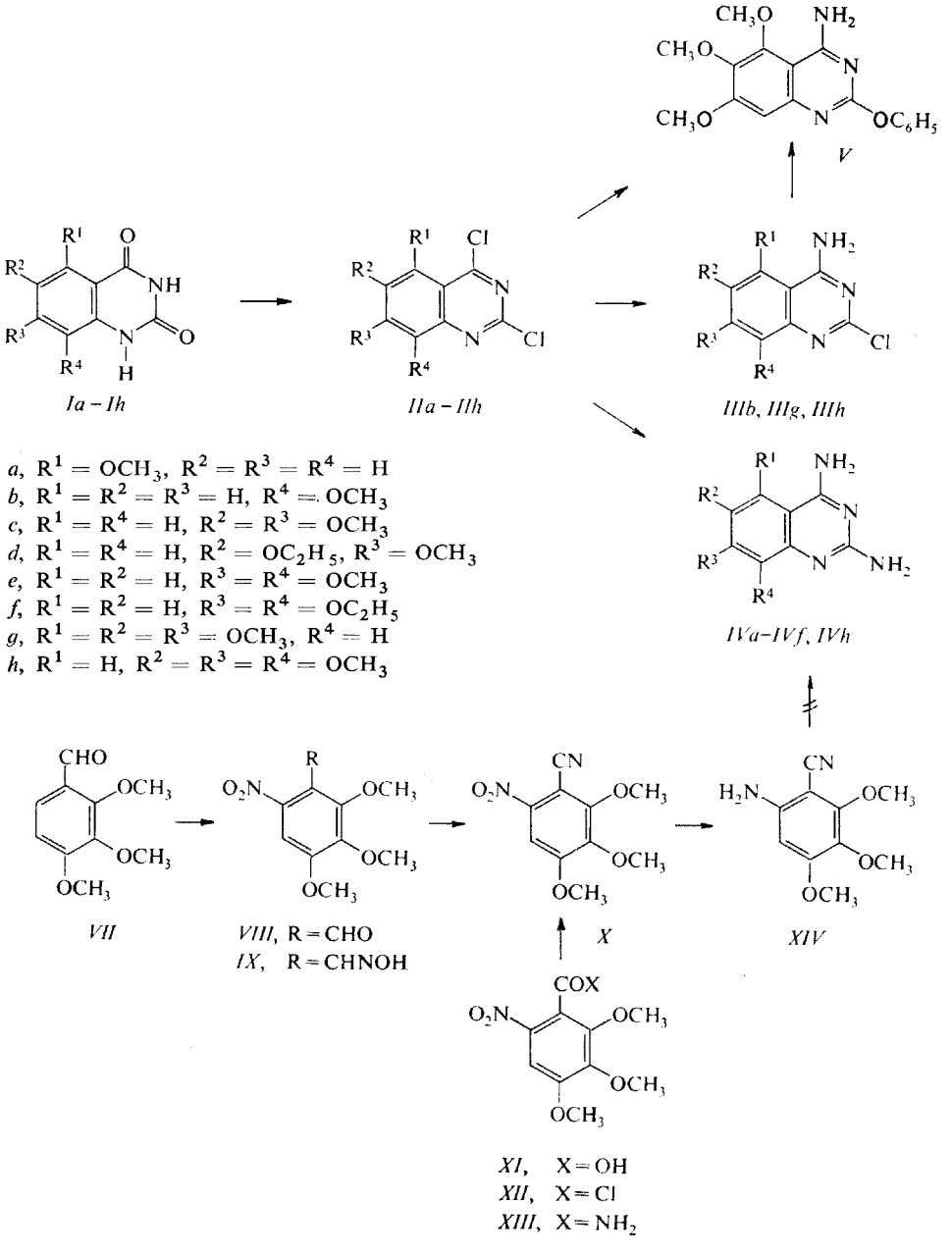
Received February 6th, 1976

Starting from 5-methoxy-, 8-methoxy, 6,7-dimethoxy-, 6-ethoxy-7-methoxy-, 7,8-dimethoxy-, 7,8-diethoxy-, 5,6,7-trimethoxy- and 6,7,8-trimethoxy-2,4-quinazolinediones (*Ia—Ih*) and proceeding *via* the corresponding 2,4-dichloro derivatives *IIa—IIh*, 2,4-quinazolinediamines *IVa—IVf* and *IVh* and further 8-methoxy-, 5,6,7-trimethoxy- and 6,7,8-trimethoxy-2-chloro-4-quinazolinamines (*IIIb*, *IIIg*, *IIIh*) were prepared. The amino derivatives were tested for antibacterial activity toward *Streptococcus β-haemolyticus*, *Staphylococcus pyogenes aureus* and *Escherichia coli*. The highest efficiency was shown by *IVa*.

An important accomplishment of antibacterial chemotherapy of recent years is no doubt the discovery of 5-(3,4,5-trimethoxybenzyl)-2,4-pyrimidinediamine (generic name trimethoprim). As inhibitor of dihydrofolate reductase it shows a synergistic effect when combined with sulfamides which are inhibitors of dihydrofolate synthesis. In this context it was of interest to examine the antibacterial activity of 2,4-quinazolinediamines alkoxylated at the benzene ring which represent structurally related analogues of trimethoprim. Of substances belonging to this type only the 5-methoxy- and 7-methoxy-2,4-quinazolinediamines are known, the first of which displays a pronounced antimicrobial activity[1].

When synthesizing the alkoxy-2,4-quinazolinediamines we used the procedure where the starting substances are amides of the appropriately substituted anthranilic acids which are condensed with cyanic acid to 2-ureidobenzamides and then are cyclized to 2,4-quinazolinediones. Amides of anthranilic acids can be fused with urea to convert them directly to 2,4-quinazolinediones. From these, 2,4-quinazolinediamines are obtained *via* the corresponding 2,4-dichloro derivatives by amination. In this way it was possible to prepare besides the known 5-methoxy-2,4-quinazolinediamine (*IVa*) also 8-methoxy-, 6,7-dimethoxy-, 6-ethoxy-7-methoxy-, 7,8-dimethoxy-, 7,8-diethoxy- and 6,7,8-trimethoxy-2,4-quinazolinediamines (*IVb*, *IVf*, *IVh*). It was attempted to prepare 5,6,7-trimethoxy-2,4-quinazolinediamine by a procedure according to Rossowsky and coworkers[1] using a reaction of 4,5,6-trimethoxyanthranilonitrile (*XIV*) with cyanoguanidine but without success. The starting nitrile *XIV* was prepared from 2,3,4-trimethoxybenzaldehyde (*VII*) *via* the 6-nitro derivative *VIII*, oxime *IX* and 2,3,4-trimethoxy-6-nitrobenzonitrile (*X*). This last compound



a, $R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$
b, $R^1 = R^2 = R^3 = H$, $R^4 = OCH_3$
c, $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$
d, $R^1 = R^4 = H$, $R^2 = OC_2H_5$, $R^3 = OCH_3$
e, $R^1 = R^2 = H$, $R^3 = R^4 = OCH_3$
f, $R^1 = R^2 = H$, $R^3 = R^4 = OC_2H_5$
g, $R^1 = R^2 = R^3 = OCH_3$, $R^4 = H$
h, $R^1 = H$, $R^2 = R^3 = R^4 = OCH_3$

was also obtained from 2,3,4-trimethoxy-6-nitrobenzoic acid (*XI*) *via* chloride *XII* and amide *XIII*. Therefore, the amination method was finally resorted to, the key intermediate being here the 5,6,7-trimethoxy-2,4-quinazolinedione (*Ig*). In its prepa-

ration we proceeded from pyrogallol from which, using Kolbe's reaction, 2,3,4-trihydroxybenzoic acid was obtained[2]. This was methylated with dimethyl sulfate to 2-hydroxy-3,4-dimethoxybenzoic acid[3]. This was esterified and methylated with diazomethane to the methyl ester of 2,3,4-trimethoxybenzoic acid. Nitration of this ester to the 6-nitro derivative is mentioned in the literature[4] but without experimental details. A series of experiments was conducted along these lines and even if the final procedure is not optimal it is reproducible. It is not recommended to carry out the nitration at a low temperature (between -10 and $+10$°C) when, after a certain amount of nitric acid has been added a spontaneous exothermic reaction takes place. If, however, nitration is carried out at 50–60°C from the beginning, its progress can be controlled by the rate of adding the nitric acid and by slight cooling. The methyl ester of 1,3,4-trimethoxy-6-nitrobenzoic acid obtained was reduced to the amino derivative which reacted with urea to the known 5,6,7-trimethoxy-2,4-quinazolinedione[4] (*Ig*). It was assumed that after conversion to the 2,4-dichloro derivative *IIg* amination will yield the expected 2,4-diamino derivative. When heating with liquid ammonia in an autoclave for 5 h at 120°C, as well as by treatment with ammonia in methanol or 2-methylpropanol at 170°C, only one chlorine atom is substituted which gives rise to 2-chloro-5,6,7-trimethoxy-4-quinazolinamine (*IIIg*). The fact that chlorine in position 4 is the first to react is known from several similar cases[5]. Attempts at further amination of *IIIg* had no effect. Finally the method of Keneford and coworkers[6] was used, based on amination in molten phenol with introduction of gaseous ammonia. It was found at 120°C that both chlorine atoms are split but, instead of the expected diamine, 2-phenoxy-5,6,7-trimethoxy-4-quinazolinamine (*V*) was obtained. The same compound was prepared when aminating derivative *IIIg* in phenol, whereby the structure of *V* was confirmed.

Certain difficulties were encountered when preparing 6,7,8-trimethoxy-2,4-quinazolinediamine (*IVh*). On heating with liquid ammonia to 80°C or with methanolic ammonia to 130°C, 2-chloro-6,7,8-trimethoxy-4-quinazolinamine (*IIIh*) was obtained in analogy to the preceding case and it was only on using ammonia in 2-methylpropanol at 150°C that both chlorine atoms could be substituted with the formation of 6,7,8-trimethoxy-2,4-quinazolinediamine (*IVh*). The last compound of this series to be prepared was 4-ethyl-6,7-dimethoxy-2-quinazolinamine (*XVII*) using amination of the corresponding 2-chloroquinazoline.

All the alkoxyquinazolinamines prepared were tested *in vitro* for antibacterial activity. It follows from the results shown in Table I that the most effective one was 5-methoxy-2,4-quinazolinediamine (*IVa*) which approaches trimethoprim in antibacterial activity while the 8-methoxy derivative *IVb* is one or two orders of magnitude less effective. By introducing further methoxy or ethoxy groups into the benzene ring of quinazoline the efficiency also decreases in comparison with *IVa*. It was also found that there is no difference between methoxy and ethoxy derivatives (*IVc–f*). Quinazolines with a single amino group (*IIIb*, *IIIg*, *V* and *XVII*) are practically inactive.

TABLE I

Minimum Inhibitory Concentrations (μg/ml) of Alkoxyquinazolinamines *in vitro*

Amine	*Streptococcus β-haemolyticus* C 4/49	*Staphylococcus pyogenes aureus* Mau 1/45	*Escherichia coli* O 4
IIIb	[a]	[a]	[a]
IIIg	[a]	[a]	[a]
IIIh	[a]	[a]	[a]
IVa	0·64	20	0·64
IVb	10	50	40
IVc	10	10	80
IVd	10	6·25	40
IVe	20	50	[a]
IVf	40	40	[a]
IVh	2·5	12·5	80
V	50	[a]	[a]
XVII	25	[a]	[a]
Trimethoprim	0·78	0·64	0·64

[a] No inhibition could be observed even on using 100 μg/ml.

EXPERIMENTAL

The melting points were determined in a Mettler FP 2 apparatus.

2,4-Dichloroquinazolines *IIa—h*

The compounds were prepared in the usual way from the appropriate 2,4-quinazolinediones *Ia—Ih* by boiling for 3—5 h with phosphoryl chloride with an addition of dimethylaniline, with the exception of *Ih*. The yields, m.p. and elementary analyses are shown in Table II.

5-Methoxy-2,4-quinazolinediamine (*IVa*)

The compound was prepared from *IIa* in the same way as *IVb* from *IIb*. The m.p. of 208—209°C was identical with that in ref.[1].

2-Chloro-8-methoxy-4-quinazolinamine (*IIIb*)

0·5 g *IIb* was heated in an autoclave with 12 ml 15% methanolic ammonia for 3 h to 100—110°C. After cooling, the precipitated product was filtered, washed with water and dried. The yield was 0·3 g (65·5%), m.p. 228°C (methanol). For $C_9H_8ClN_3O$ (209·6) calculated: 51·56% C, 3·84% H, 20·04% N; found: 51·66% C, 3·60% H, 20·66% N.

8-Methoxy-2,4-quinazolinediamine (*IVb*)

IIb (0·5 g) was heated in a stainless-stell autoclave with 12 ml 15% methanolic ammonia for 3 h to 150°C. The mixture was evaporated and the residue crystallized from water. The yield was 0·3 g (71%), m.p. 267—267·9°C. For $C_9H_{10}N_4O.1/4\ H_2O$ (194·7) calculated: 55·72% C, 5·42% H, 28·40% N; found: 55·84% C, 5·29% H, 28·16% N.

6,7-Dimethoxy-2,4-quinazolinediamine (*IVc*)

IIc (2·0 g) (see ref.[7]) and 150 ml saturated ethanolic ammonia were heated in an autoclave for 7 h to 180°C. The mixture was evaporated and the residue was extracted with ethanol containing some sodium ethanolate. The combined extracts were evaporated and the residue crystallized

TABLE II

2,4-Dichloroquinazolines *II*

Compound (yield, %)	Formula (m.w.)	M.p., °C (solvent)	Calculated/Found			
			% C	% H	% Cl	% N
IIa[a]	—	165—166	—	—	—	—
(83·9)		methanol	—	—	—	—
IIb[b]	$C_9H_6Cl_2N_2O$	157—159	—	—	30·95	—
(69·9)	(229·1)	methanol	—	—	30·27	—
IIc[c]	—	159	—	—	—	—
(69)		chloroform–light petroleum	—	—	—	—
IId	$C_{11}H_{10}Cl_2N_2O_2$	162—163	48·37	3·69	25·96	10·26
(49·2)	(273·1)	chloroform–light petroleum	48·09	3·79	26·17	10·42
IIe	$C_{10}H_8Cl_2N_2O_2$	155—156	46·36	3·11	27·37	10·81
(73·5)	(259·1)	benzene	46·27	3·16	27·58	10·99
IIf	$C_{12}H_{12}Cl_2N_2O_2$	101—102	50·19	4·21	24·70	9·76
(83)	(287·2)	benzene	50·21	4·16	24·76	9·70
IIg[d]	$C_{11}H_{10}Cl_2N_2O_3$	139—140	45·69	3·49	24·52	9·69
(67)	(289·1)	methanol	45·96	3·63	23·76	9·54
IIh	$C_{11}H_{10}Cl_2N_2O_3$	149—150				
(62·3)	(289·1)	ethyl acetate	45·45	3·63	24·34	9·72

[a] Prepared according to ref.[7] where a m.p. of 160—162°C is reported. [b] The starting 8-methoxy-2,4-quinazolinedione prepared according to ref.[8]. [c] Prepared according to ref.[7] where a m.p. of 158°C is reported. [d] The starting 5,6,7-trimethoxy-2,4-quinazolinedione was prepared according to ref.[4].

from ethanol. The yield was 1·2 g (70·6%), m.p. 245–248°C. For $C_{10}H_{12}N_4O_2$ (220·2) calculated: 54·54% C, 5·49% H, 25·44% N; found: 54·55% C, 5·55% H, 25·34% N. The hydrochloride melts at 323–325°C. For $C_{10}H_{12}N_4O_2.HCl.H_2O$ (274·7) calculated: 12·90% Cl; found: 12·88% Cl.

2-Amino-5-ethoxy-4-methoxybenzoic Acid (*VId*)

5-Ethoxy-4-methoxy-2-nitrobenzoic acid[9] (18·7) was hydrogenated in 350 ml ethanol under catalysis of 5 g 5% Pd–C. After evaporation of the solvent, the crude product was crystallized from aqueous ethanol. The yield was 8·1 g (49·3%), m.p. 173–176°C. For $C_{10}H_{13}NO_4$ (211·2) calculated: 56·86% C, 6·20% H, 6·68% N; found: 56·23% C, 6·16% H, 6·44% N.

6-Ethoxy-7-methoxy-2,4-quinazolinedione (*Id*)

A suspension of 3·5 g *VId* in 70 ml water was combined first with 2·5 ml acetic acid and then slowly under stirring with 3·5 g potassium cyanate in 10 ml water. After 20 min, 25 g NaOH was added to the mixture in parts and under cooling below 40°C. The precipitated salt was filtered, dissolved in hot water and the crude product was precipitated with dilute sulfuric acid. This was then filtered and washed with water. Crystallization from a mixture of dimethylformamide and water (2 : 1) yielded 1·15 g (26·4%) compound melting at 265–273°C. For $C_{11}H_{12}N_2O_4 .1/2\ H_2O$ (245·2) calculated: 53·87% C, 4·93% H, 11·42% N; found: 53·93% C, 5·39% H, 11·41% N.

6-Ethoxy-7-methoxy-2,4-quinazolinediamine (*IVd*)

IId (0·5 g) and 70 ml ethanolic ammonia was heated in a stainless-steel autoclave for 8 h to 180°C. The mixture was evaporated and the residue was extracted with hot ethanol with a small amount of sodium ethanolate. The extract was evaporated and the residue crystallized from ethanol. The yield was 0·3 g (70%), m.p. 214–216°C. For $C_{11}H_{14}N_4O_2$ (234·3) calculated: 56·40% C, 6·02% H, 23·92% N; found: 53·69% C, 6·28% H, 22·30% N.

7,8-Dimethoxy-2,4-quinazolinedione (*Ie*)

Acetic acid (16·8 g) was added to a solution of 39·4 g 2-amino-3,4-dimethoxybenzoic acid[10] in 800 ml water followed by a dropwise addition of a solution of 22·7 g potassium cyanate in 80 ml water. After 1 h of stirring, 284 g NaOH was added in parts, the precipitated sodium salt was filtered, washed with methanol and reprecipitated from hot water by acidification with acetic acid. A total of 17 g (38·3%) compound was prepared, melting at 308–311°C. A sample for analysis was crystallized from dimethylformamide and melted at 313–315°C. For $C_{10}H_{10}N_2O_4$ (222·2) calculated: 54·06% C, 4·54% H, 12·61% N; found: 53·76% C, 4·56% H, 12·91% N.

7,8-Dimethoxy-2,4-quinazolinediamine (*IVe*)

A mixture of 6·5 g *IIe* and 125 ml methanolic ammonia was heated in an autoclave for 10 h to 170–180°C, evaporated to dryness and the residue was stirred with 30 ml aqueous ammonia. The insoluble fraction was filtered and crystallized from 50% ethanol. The yield was 2·0 g (36·4%), m.p. 261–262·5°C. For $C_{10}H_{12}N_4O_2$ (220·2) calculated: 54·54% C, 5·49% H, 25·44% N; found: 54·40% C, 5·57% H, 25·84% N.

3,4-Diethoxyanthranilic Acid (*VIf*)

A solution of 39 g crystalline ferrous sulfate in 170 ml water was combined dropwise with 32 ml ammonia and with an ammonia solution of 2-nitro-3,4-diethoxybenzoic acid[11], the mixture was boiled for 15 min and filtered while hot. Acidification of the filtrate yielded 4·0 g (89%) compound melting at 168—171°C. An analytical solution melted at 170—172°C (ethanol). For $C_{11}H_{15}NO_4$ (225·3) calculated: 58·64% C, 6·71% H, 6·22% N; found: 58·69% C, 6·62% H, 6·28% N.

7,8-Diethoxy-2,4-quinazolinedione (*If*)

A mixture of 16·6 g *VIf* and 23 g urea was slowly heated to 200°C and kept at that temperature for 2 h. After cooling the solidified melt was boiled with 100 ml diluted ethanol and the insoluble residue was filtered. A total of 11·3 g (60·4%) compound melting at 290—292°C was obtained. A sample for analysis melted at 294—295°C (dimethylformamide). For $C_{12}H_{14}N_2O_4$ (250·3) calculated: 57·60% C, 5·64% H, 11·20% N; found: 57·20% C, 5·42% H, 11·34% N.

7,8-Diethoxy-2,4-quinazolinediamine (*IVf*)

IIf (7·0 g) and 110 ml methanolic ammonia was heated in an autoclave for 8 h 160—170°C. After evaporation of the solvent, the residue was digested with 10 ml ammonia and the insoluble residue was filtered. The yield was 5·0 g (84%), m.p. 222—224°C. An analytical sample melted at 229—230°C (dimethylformamide). For $C_{12}H_{16}N_4O_2$ (248·3) calculated: 58·05% C, 6·49% H, 22·57% N; found: 58·04% C, 6·45% H, 22·50% N.

2,3,4-Trimethoxy-6-nitrobenzaldehyde (*VIII*)

2,3,4-Trimethoxybenzaldehyde[12] (19·6 g) was added dropwise under stirring over a period of 2 h to 120 ml concentrated nitric acid at 18—20°C. After 30 min, the mixture was poured into 1 liter ice-cold water. The precipitated product was filtered and washed with water. The yield was 16·2 g (67·2%) of a compound melting at 80—81°C. The position of the nitro group which could also be at carbon 5 was determined by ^{1}H-NMR spectra on a EKR 60 spectrometer, in deuteriochloroform with tetramethylsilane as standard. The position of the free aromatic H (7·23 p.p.m.) indicates it to be a 6-nitro derivative.

Oxime IX: A solution of 5·0 g *VIII* in 60 ml methanol heated to 45°C was mixed with a solution of 12·5 g hydroxylamine hydrochloride and 21 g crystalline sodium acetate in 40 ml. Within several min the oxime began to precipitate. The mixture was diluted with 60 ml water and, after 30 min, the precipitated product was filtered and crystallized from 80% ethanol. The yield was 4·3 g (81%) of a substance melting at 120°C. For $C_{10}H_{12}N_2O_6$ (256·2) calculated: 46·88% C, 4·72% H, 10·93% N; found: 46·55% C, 4·82% H, 10·73% N.

2,3,4-Trimethoxy-6-nitrobenzamide (*XIII*)

A mixture of 24 g 2,3,4-trimethoxy-6-nitrobenzoic acid[4] (*XI*), 50 ml thionyl chloride and 1 ml dimethylformamide was refluxed for 2 h, evaporated at reduced pressure and the viscous residue was poured under stirring into 60 ml ammonia. The precipitated amide was crystallized from 80% ethanol. The yield was 15 g (62·7%), m.p. 170—171°C. For $C_{10}H_{12}N_2O_6$ (256·2) calculated: 46·88% C, 4·72% H, 10·93% N; found: 46·59% C, 4·66% H, 11·23% N.

2,3,4-Trimethoxy-6-nitrobenzonitrile (*X*)

a) *By dehydration of oxime* IX: A mixture of 2·6 and *IX* and 28 ml acetic anhydride was refluxed for 2 g then diluted with 140 ml water. A total of 1·8 g (74·5%) product precipitated; m.p. 118 to 119°C. For $C_{10}H_{10}N_2O_5$ (238·2) calculated: 50·40% C, 4·24% H, 11·75% N; found: 50·50% C, 4·37% H, 11·59% N.

b) *By dehydration of amide XIII*: 10 g *XIII* and 11 ml phosphoryl chloride was heated for 45 min to 100°C. After cooling, the mixture was poured into 100 ml ice-cold water, the precipitated product was filtered, washed with water and crystallized from ethanol. The yield was 7·5 g (80·7%), m.p. 115—117°C. It gave no melting point depression with the preparation obtained as under (*a*).

4,5,6-Trimethoxyanthranilonitrile (*XIV*)

A boiling solution of 2·0 g *X* in 16 ml ethanol was combined under stirring with 8 ml concentrated HCl and 4·0 g powdered Fe. After 30 min the mixture was cooled and made alkaline with ammonia. The precipitated compound was filtered, washed with 20 ml ethanol and the combined filtrates were concentrated at reduced pressure to about one-half and the residue was shaken with chloroform (3 × 6 ml). Evaporation of the chloroform extract yielded a product which crystallized from 50% ethanol to melt at 101—102°C. The yield was 1·5 g (85·8%). For $C_{10}H_{12}N_2O_3$ (208·2) calculated: 57·68% C, 5·81% H, 13·45% N; found: 57·71% C, 5·55% H, 13·33% N.

2-Chloro-5,6,7-trimethoxy-4-quinazolinamine (*IIIg*)

The compound was prepared in the same way as *IIIb* by heating with methanolic ammonia to 150°C. The yield was 53·7%, m.p. 232—233°C (methanol). For $C_{11}H_{12}ClN_3O_3$ (269·6) calculated: 48·99% C, 4·52% H, 13·14% Cl, 15·58% N; found: 48·93% C, 4·42% H, 13·23% Cl, 15·60% N.

2-Phenoxy-5,6,7-trimethoxy-4-quinazolinamine (*V*)

Phenol (4·0 g) was saturated with gaseous ammonia whereupon 0·58 g *IIg* was added and the mixture was heated while introducing gaseous ammonia, for 2 h at 125°C. The phenol was then steamdistilled. The product precipitated from the residue was filtered and washed with water, the yield was 0·34 g (51·9%). The crude product was dissolved in a small amount of hot 2M-HCl. The precipitated hydrochloride was filtered, dissolved in hot water and precipitated with ammonia. The base obtained was crystallized from 40% ethanol and melted at 154·5—155·6°C. For $C_{17}H_{17}N_3O_4$ (327·4) calculated: 62·38% C, 5·24% H, 12·84% N; found 61·94% C, 5·31% H, 13·04% N.

2-Amino-3,4,5-trimethoxybenzamide (*XV*)

Methyl ester of 2-amino-3,4,5-trimethoxybenzoic acid (30 g) and 150 ml aqueous ammonia saturated at 0°C was heated in an autoclave for 16 h at 140°C. After evaporation, the residue crystallized from dilute hydrochloric acid (1 : 1). The yield of the hydrochloride was 26 g (79·6%), melting at 205—210°C. The base liberated with ammonia from the hydrochloride melted at 134°C (ref.[13] reports 134°C).

3,4,5-Trimethoxy-2-ureidobenzamide (*XVI*)

Suspension of hydrochloride *XV* (35·0 g) in 250 ml acetic acid was combined under cooling below 20°C with 25 g powdery KCNO. The solution formed was stirred for 1 h and left to stand overnight, whereupon it was diluted with water, the precipitated product was filtered and recrystallized from water. The yield was 22·7 g (63·3%), m.p. 224—226°C. For $C_{11}H_{15}N_3O_5$ (269·3) calculated: 49·06% C, 5·62% H, 15·61% N; found: 49·31% C, 5·70% H, 15·24% N.

6,7,8-Trimethoxy-2,4-quinazolinedione (*IIh*)

A solution of 18 g *XVI* in 100 ml 35% NaOH was refluxed for 30 min, cooled, the precipitated product was filtered, washed with water, dissolved in 500 ml and acidified acetic acid. The precipitated substance melted at 271°C. Yield 14·5 g (86%). For $C_{11}H_{12}N_2O_5$ (252·2) calculated: 52·38% C, 4·80% H, 11·11% N; found: 52·22% C, 4·87% H, 11·32% N.

2-Chloro-6,7,8-trimethoxy-4-quinazolinamine (*IIIh*)

IIh (2·6 g) was heated in an autoclave with 60 ml methanolic ammonia for 4 h to 14°C. The mixture was evaporated at reduced pressure and the residue crystallized from ethanol. The yield was 1·4 g (57·7%), m.p. 241—242°C. For $C_{11}H_{12}ClN_3O_3$ (269·7) calculated: 48·99% C, 4·49% H, 13·15% Cl, 15·58% N; found: 49·01% C, 4·51% H, 13·17% Cl, 15·68% N.

6,7,8-Trimethoxy-2,4-quinazolinediamine (*IVh*)

IIh (2·6 g) was heated with 60 ml 2-methylpropanol saturated with ammonia in an autoclave for 6 h at 150°C. The residue obtained by evaporation of the solvent at reduced pressure was first digested with ammonia and crystallized from water (yield 0·50 g, 22%). Sample for analysis melted at 240—241°C. For $C_{11}H_{14}N_4O_3$ (250·3) calculated: 52·79% C, 5·64% H, 22·39% N; found 52·18% C, 5·22% H, 22·11% N.

4-Ethyl-6,7-dimethoxy-2-quinazolinamine (*XVII*)

2-Chloro-4-ethyl-6,7-dimethoxyquinazoline[14] (1·0 g) and 75 ml ethanolic ammonia was heated in an autoclave for 7 h to 180°C, mixed with a calculated amount of ethanolic solution of sodium ethanolate, the precipitated sodium chloride was filtered and the filtrate was evaporated. The residue crystallized from ethanol. Yield 0·45 g (49·1%), m.p. 190—193°C. For $C_{12}H_{15}N_3O_2$ (233·3) calculated: 61·79% C, 6·48% H, 18·01% N; found: 61·61% C, 6·40% H, 17·88% N.

The elementary analyses were done by Mrs J. Komancová, Mrs A. Slavíková and Mr M. Čech of the analytical department of this institute. We are indebted to Dr J. Turinová of the bacteriological department for carrying out the bacteriological tests and to Drs B. Kakáč and J. Holubek of the physico-chemical department of this institute for recording and interpreting the NMR spectra of VIII.

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Translated by A. Kotyk.