A NEW SYNTHESIS OF THE QUINAZOLINE NUCLEUS*

Z. BUDĚŠÍNSKÝ and P. LEDERER

Research Institute for Pharmacy and Biochemistry, Prague 3

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7-Methoxy-, 7-acetoxy-, and 7-methyl-4-R^1-2(1*H*)-qiunazolinones *IIa*—*IIj*, *IIr*, and *IIs* were prepared on cyclodehydration of 1-acyl-3-phenylureas substituted in the position 3 of the benzene nucleus by methoxy-, acetoxy-, or methyl group. 6,7-Dimethoxy-4-R^1-2(1*H*)-quinazolinones *IIk*—*IIp* were prepared from 1-acyl-3-(3,4-dimethoxyphenyl)ureas in a similar manner.

The condensation of *o*-aminobenzaldehyde and *o*-aminophenones with urea[1,2] as well as the condensation of *o*-aminobenzonitrile or its derivatives with urea, urethane, phosgene *etc.*[3,4] represent general methods of preparation of 2(1*H*)-quinazolinones. The mentioned methods, however, require in the synthesis of 2(1*H*)-quinazolinones, substituted in the benzene nucleus, a lengthy preparation of correspondingly substituted aromatic amino derivatives, as follows from the synthesis of 4-phenyl-7-methoxy-2(1*H*)-quinazolinone (*IIg*) shown below.

For the preparation of 2-(1*H*)-quinazolinones variously substituted in the position 4 we tried, therefore, to apply the principle of Bischler–Napieralsky cyclodehydration of N-(2-phenylethyl)-amides to 3,4-dihydroisoquinolines. In our first experiments we used 1-acetyl-3-phenylurea as the starting substance on which we acted with various dehydration agents, as for example sodium ethoxide, phosphorus oxychloride, phosphorus pentoxide, polyphosphoric acid, and sulfuric acid, but without results. Therefore we came to the conclusion that the benzene nucleus of the starting 1-acetyl- or 1-benzoyl-3-phenylurea is evidently not sufficiently reactive for this electrophilic reaction. Contrary to this, heating of 1-acetyl-3-(3-methoxyphenyl)urea (*Ia*) with polyphosphoric acid afforded 4-methyl-7-methoxy-2(1*H*)-quinazolinone (*IIa*). Introduction of a methoxy group into the position 3 caused, under the influence of its +M effect, a sufficient increase of the electron density in the position 6, thus enabling the formation of a bond with the carbonyl group carbon atom. An increase in electron density takes place in the position 2; however, evidently for sterical reasons, the closure of the pyrimidine ring takes place at the carbon atom 6 exclusively, as we have demonstrated by an unambiguous synthesis. This new cyclisation reaction

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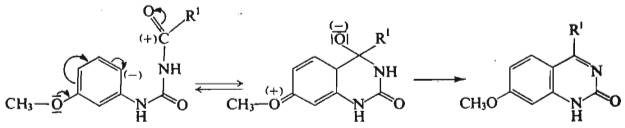
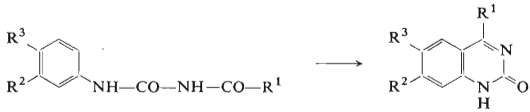
(Scheme 1) was then successfully applied to further 1-acyl-3-(3-methoxyphenyl)ureas *Ia–Ij* (Table I).



SCHEME 1

In order to establish optimum reaction conditions we followed the effect of temperature, reaction time and the amount of polyphosphoric acid on the cyclisation of 1-acetyl and 1-benzoyl-3-(3-methoxyphenyl)urea (*Ia*, *Ig*). The amounts of the quinazoline *IIa* or *IIg* formed were determined spectrophotometrically in the UV region after dilution and neutralisation. These experiments have shown that after 2 hours heating at 125°C the content of *IIa* and *IIg* respectively

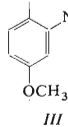


I

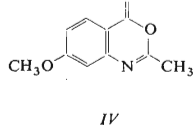
a, $R^1 = CH_3$, $R^2 = OCH_3$, $R^3 = H$
b, $R^1 = C_2H_5$, $R^2 = OCH_3$, $R^3 = H$
c, $R^1 = n\text{-}C_3H_7$, $R^2 = OCH_3$, $R^3 = H$
d, $R^1 = i\text{-}C_3H_7$, $R^2 = OCH_3$, $R^3 = H$
e, $R^1 = (CH_2)_{12}CH_3$, $R^2 = OCH_3$, $R^3 = H$
f, $R^1 = (CH_2)_{16}CH_3$, $R^2 = OCH_3$, $R^3 = H$
g, $R^1 = C_6H_5$, $R^2 = OCH_3$, $R^3 = H$
h, $R^1 = CH_2C_6H_5$, $R^2 = OCH_3$, $R^3 = H$
i, $R^1 = C_6H_4Cl(4)$, $R^2 = OCH_3$, $R^3 = H$

II

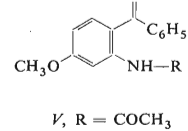
j, R^1 = 3-pyridyl, $R^2 = OCH_3$, $R^3 = H$
k, $R^1 = CH_3$, $R^2 = R^3 = OCH_3$
l, $R^1 = C_2H_5$, $R^2 = R^3 = OCH_3$
m, $R^1 = n\text{-}C_3H_7$, $R^2 = R^3 = OCH_3$
n, $R^1 = (CH_2)_{16}CH_3$, $R^2 = R^3 = OCH_3$
o, $R^1 = C_6H_5$, $R^2 = R^3 = OCH_3$
p, $R^1 = CH_2C_6H_5$, $R^2 = R^3 = OCH_3$
r, $R^1 = CH_3$, $R^2 = OCOCH_3$, $R^3 = H$
s, $R^1 = R^2 = CH_3$, $R^3 = H$



III



IV



V, R = $COCH_3$
VI, R = H

in the reaction mixture did not further increase, and the yield was about 90%. Above 130°C decomposition of the starting ureas *Ia* or *Ig* began to take place distinctly in both cases as a competitive reaction. We proved that the reaction indeed was decomposition of the starting urea both by a stability test of quinazolinone *IIg* in polyphosphoric acid (320 min at 125°C) and by ki-

TABLE I

1-Acyl-3-phenylureas *I* (R^2 = OCH_3)

Compound	R^1 / R^3	M.p., °C (yield, %)	Formula (mol. weight)	Calculated/Found % C	% H	% N
Ia	CH_3	207—208[a]	$C_{10}H_{12}N_2O_3$	57·68	5·81	13·45
	H	(90)	(208·2)	57·62	5·96	13·64
Ib	C_2H_5	123—125	$C_{11}H_{14}N_2O_3$	59·44	6·35	12·61
	H	(60)	(222·2)	59·56	6·23	12·92
Ic	n-C_3H_7	120—121	$C_{12}H_{16}N_2O_3$	61·00	6·83	11·86
	H	(92)	(236·3)	60·92	6·71	11·86
Id	i-C_3H_7	83—90	$C_{12}H_{16}N_2O_3$	61·00	6·83	11·86
	H	(47)	(236·3)	60·42	6·71	11·89
Ie	$(CH_2)_{10}CH_3$	88—91	$C_{20}H_{32}N_2O_3$	68·93	9·26	8·04
	H	(60)	(348·5)	69·05	9·25	8·14
If	$(CH_2)_{16}CH_3$	86—90	$C_{26}H_{44}N_2O_3$	72·16	10·27	6·48
	H	(53)	(432·7)	72·17	10·17	6·35
Ig	C_6H_5	184—186	$C_{15}H_{14}N_2O_3$	66·65	5·22	10·37
	H	(96)	(270·3)	66·65	5·20	10·50
Ih	$CH_2C_6H_5$	140—144	$C_{16}H_{16}N_2O_3$	67·59	5·67	9·86
	H	(71)	(284·3)	67·46	5·33	9·96
Ii[b]	C_6H_4Cl-(*p*)	236—238	$C_{15}H_{13}ClN_2O_3$	58·92	4·62	9·16
	H	(83)	(305·7)	58·83	4·62	9·28
Ij	3-pyridyl	170—173	$C_{14}H_{13}N_3O_3$	61·98	4·83	15·49
	H	(62)	(271·3)	62·14	4·96	15·78
Ik[c]	CH_3	208—210	$C_{11}H_{14}N_2O_4$	55·45	5·92	11·76
	OCH_3	(66)	(238·2)	55·43	5·97	11·57
Il	C_2H_5	214—215	$C_{12}H_{16}N_2O_4$	57·13	6·39	11·11
	OCH_3	(63)	(252·3)	57·33	6·53	10·82
Im	n-C_3H_7	176—180	$C_{13}H_{18}N_2O_4$	58·63	6·81	10·52
	OCH_3	(68)	(266·3)	58·69	6·92	10·53
In	$(CH_2)_{16}CH_3$	108—109	$C_{27}H_{46}N_2O_4$	70·09	10·02	6·06
	OCH_3	(87)	(462·7)	69·97	9·99	5·89
Io	C_6H_5	193—195	$C_{16}H_{16}N_2O_4$	63·99	5·37	9·33
	OCH_3	(43)	(300·3)	63·85	5·43	9·36
Ip[d]	$CH_2C_6H_5$	187—188	$C_{17}H_{18}N_2O_4$	64·95	5·77	8·91
	OCH_3	(46)	(314·3)	64·67	5·91	8·86

[a] Crystallised from acetone, lit.[8] gives m.p. 200°C; [b] calculated: 11·60% Cl; found: 11·61% Cl; [c] lit.[9] gives m.p. 227°C; [d] lit.[9] gives m.p. 249°C.

TABLE II
2(1*H*)-Quanazolinones

Compound	R^1 / R^2	R^3	M.p., °C (yield, %)	Formula (mol. weight)	Calculated/Found % C	% H	% N
IIa	CH_3 / OCH_3	H	258—263 (55)	$C_{10}H_{10}N_2O_2$ (190·2)	63·14 / 63·18	5·30 / 5·36	14·73 / 14·56
IIb	C_2H_5 / OCH_3	H	210—215 (37)	$C_{11}H_{12}N_2O_2$ (204·3)	64·69 / 64·27	5·92 / 5·93	13·72 / 13·67
IIc	n-C_3H_7 / OCH_3	H	229—233 (70)	$C_{12}H_{14}N_2O_2$ (218·3)	66·03 / 66·22	6·46 / 6·49	12·84 / 13·02
IId	i-C_3H_7 / OCH_3	H	188—193 (5)	$C_{12}H_{14}N_2O_2$ (218·3)	66·03 / 65·80	6·46 / 6·54	12·84 / 12·94
IIe	$(CH_2)_{10}CH_3$ / OCH_3	H	173—175 (38)	$C_{20}H_{30}N_2O_2$ (330·5)	72·69 / 72·40	9·15 / 9·18	8·48 / 8·19
IIf	$(CH_2)_{16}CH_3$ / OCH_3	H	160—170 (41)	$H_{26}H_{42}N_2O_2$ (414·7)	75·30 / 75·61	10·25 / 10·22	5·76 / 6·24
IIg	C_6H_5 / OCH_3	H	272—278 (53)	$C_{15}H_{12}N_2O_2$ (252·3)	71·41 / 71·34	4·80 / 4·86	11·11 / 11·00
IIh	$CH_2C_6H_5$ / OCH_3	H	204—207 (21)	$C_{16}H_{14}N_2O_2$ (266·3)	72·16 / 72·30	5·30 / 5·45	10·52 / 10·25
Ii[a]	C_6H_4Cl-(*p*) / OCH_3	H	295—305 (16)	$C_{15}H_{11}ClN_2O_2$ (286·7)	62·83 / 61·95	3·87 / 3·79	9·77 / 9·38
IIj	3-pyridyl / OCH_3	H	290—292 (4)	$C_{14}H_{11}N_3O_2$ (253·6)	66·39 / 63·33	4·38 / 4·39	16·59 / 15·86
IIk	CH_3 / OCH_3	OCH_3	260—270 (43)	$C_{11}H_{12}N_2O_3$ (220·2)	59·99 / 60·19	5·49 / 5·77	12·72 / 11·23
III	C_2H_5 / OCH_3	OCH_3	252—255 (86)	$C_{12}H_{14}N_2O_3$ (234·3)	61·52 / 61·14	6·02 / 6·32	11·96 / 11·74
IIm	n-C_3H_7 / OCH_3	OCH_3	235—242 (80)	$C_{13}H_{16}N_2O_3$ (248·3)	62·88 / 62·60	6·50 / 6·59	11·29 / 11·46
IIn	$(CH_2)_{16}CH_3$ / OCH_3	OCH_3	125—135 (72)	$C_{27}H_{44}N_2O_3$ (444·6)	72·93 / 69·59	9·97 / 9·97	6·30 / 6·31
IIo[b]	C_6H_5 / OCH_3	OCH_3	187—190 (40)	$C_{16}H_{14}N_2O_3$ (282·3)	68·07 / 66·66	5·00 / 5·14	9·92 / 9·86
IIp	$CH_2C_6H_5$ / OCH_3	OCH_3	212—215 (70)	$C_{17}H_{16}N_2O_3$ (296·3)	68·80 / 67·53	5·44 / 5·37	9·46 / 9·37
IIr	CH_3 / $OCOCH_3$	H	245—250 (80)	$C_{11}H_{10}N_2O_3.H_2O$ (236·2)	55·93 / 54·30	5·12 / 5·09	11·86 / 11·80
IIs	CH_3 / CH_3	H	248—253 (2·7)	$C_{10}H_{10}N_2O$ (174·2)	68·95 / 68·52	5·79 / 6·11	16·08 / 15·88

[a] Calculated: 12·37% Cl; found: 12·23% Cl; [b] lit.[11] does not give the preparative procedure and the m.p.

netic calculations. Optimum weight ratio of urea to polyphosphoric acid was 1 : 10 to 1 : 30. A larger amount of polyphosphoric acid already had a negative effect on yields. According to spectrophotometric determination, this cyclisation took place in 70—90% yield; however, the isolated amount is lower (Table II).

Under approximately similar conditions (as above), we cyclised some 1-acyl-3-(3,4-dimethoxyphenyl)urea (*Ik—Ip*) under the formation of corresponding 6,7-dimethoxy-4-R^1-2(1*H*)-quinazolinones *IIk—IIp*. Finally, we also succeeded in cyclising 3-(3-acetoxyphenyl)-and 3-(3-tolyl)-1-acetylurea (*Ir*, *Is*) to quinazolinones *IIr* and *IIs*. The starting 1-acyl-3-phenylureas were prepared generally by addition of phenylisocyanates to the amides of corresponding carboxylic acids. Only compound Ir was obtained by acetylation of 3-methoxyphenylurea with acetic anhydride, and *Is* by reaction of acetylurea with *m*-toluidine.

In order to show that the cyclisation of 1-acyl-3-(3-methoxyphenyl)ureas takes place at the position 6 and not at the position 2 of the benzene nucleus, and, hence, that 4-R^1-7-methoxy-2(1*H*)-quinazolinones and not the isomeric 5-methoxy derivatives are formed, we prepared 4-phenyl-7-methoxy-2(1*H*)-quinazoline (*IIg*) by an unambiguous synthesis according to Schofield[5]. From *o*-toluidine we prepared in 6 reaction steps 2-amino-4-methoxybenzoic acid[6] (*III*) from which we obtained acetanthranil (*IV*) by treatment with acetic anhydride. On reaction of the latter with phenylmagnesium bromide and subsequent deacetylation we prepared 2-amino-4-methoxybenzophenone (*VI*) which on fusing with urea gave quinazolinone *IIg* in a 28·2% yield. It was identical with the substance obtained by cyclisation of *Ig*.

The UV spectra of ureas exhibit maxima between 212—231, 246—261, and 280—289 nm. In ureas containing two aromatic nuclei (*Ig—Ij*) these maxima are shifted to higher wave-lengths. In the IR spectra of these substances an important band at 1690—1720 cm^{-1} is present, due to the amidic C=O group. Further bands in the 1040—1050, 1145—1165, and 1225—1245 cm^{-1} regions, typical of ethers (methoxyl groups), and a band at 1590—1610 cm^{-1} due to aryl, and possibly a band at 760—790 cm^{-1} characteristic of a *meta*-substituted benzene ring, are observed. In the obtained 2(1*H*)-quinazolinones maxima in the UV spectrum are obtained at 225—240, 285—300, and 300—360 nm. Thus, in comparison with unsubstituted quinazoline, the maxima of which occur at 222, 271, and 305, a bathochromic shift is observed in former compounds. In their IR spectra these substances also contain a band typical of an amide C=O group (1670—1675 cm^{-1}), further three bands at 1000—1030, 1141—1150, and 1220 cm^{-1}, due to ether bonds (methoxyls), a band at 1600—1620 cm^{-1} corresponding to an aryl, and finally a band at 790 cm^{-1}, characteristic of 1,2,4-trisubstituted benzene nucleus.

The prepared substances were submitted to a bacteriological screening and some of them also to pharmacological testing. In the case of substance *IIc*, an important hypotensive effect was observed in a 300 mg/kg dose *per os* in mice.

EXPERIMENTAL

Melting points of the analytical samples were determined on the Kofler block. Analytical samples were dried *in vacuo* at approximately 0·2 Torr and temperature corresponding to the melting point; over P_2O_5 for 2 h.

3,4-Dimethoxyphenylisocyanate

A 20% solution of phosgene in benzene was added dropwise under cooling and stirring to a solution of 46 g (0·3 mol) of 4-aminoveratrol in 600 ml of benzene, followed by a 50% phosgene solution in the same solvent, and the reaction mixture was heated slowly to boiling point and then refluxed for 6 h. Benzene was evaporated and the residue distilled under reduced pressure. Yield 38 g (70·5%) of a product, b.p. 90°C/2 Torr. For $C_9H_9NO_3$ (179·2) calculated: 60·33% C, 5·06% H, 7·82% N; found: 60·25% C, 5·15% H, 8·03% N.

1-Acetyl-3-(3-acetoxyphenyl)urea (*Ir*)

3-Hydroxyphenylurea[7] (32·5 g; 0·21 mol) and acetic anhydride (350 ml) were refluxed for 10 h. After evaporation of the solvent under reduced pressure to dryness, the residue was crystallised thrice from ethanol. Yield 8·0 g (15·8%), m.p. 169—172°C. For $C_{11}H_{12}N_2O_4$ (236·2) calculated: 55·92% C, 5·12% H, 11·86% N; found: 55·92% C, 5·32% H, 12·35% N.

1-Acetyl-3-(3-tolyl)urea (*Is*)

A mixture of 8·8 g (0·086 mol) of acetylurea and 11·6 g (0·12 mol) of m-toluidine was refluxed for 100 min at 170°C. After cooling the melt was triturated with water under addition of hydrochloric acid and the suspension was decanted several times with water, filtered off under suction, and crystallised from ethanol. Yield, 8·8 g (53%) of product, m.p. 126—127°C. The same substance was obtained by Bhattacharyya and coworkers[8] on reaction with acetylurethane with *m*-toluidine, giving m.p. 123°C for it.

1-Acyl-3-phenylureas *Ia—Ip*

A mixture of 0·1 mol of amide of the corresponding carboxylic acid and 0·15 mol of 3-methoxy- or 3,4-dimethoxyphenylisocyanate was heated at 140—150°C for 30 minutes. After cooling the melt was crystallised from ethanol. The yields, melting points, and elemental analyses are given in Table I.

2(1*H*)-Quinazolinones *IIa—IIs*

A mixture of 0·005 mol of the corresponding 1-acyl-3-phenylurea and 25 g of polyphosphoric acid prepared according to Marthe and Munavalli[10], was heated at 120—130°C for 2 hours. After cooling to 50°C the melt was poured on ice and the solution was alkalised weakly with ammonia. The separated precipitate was filtered off, washed with cold water, and crystallised from ethanol. The yields, melting points, and elemental analyses are given in Table II.

2-Amino-4-methoxybenzoic Acid (*III*)

This substance was prepared by reduction of 2-nitro-4-methoxybenzoic acid[6] with stannous chloride in hydrochloric acid. Yield 50%, m.p. 182—189°C (ethanol). For $C_8H_9NO_3$ (166·1) calculated: 57·48% C, 5·43% H, 8·38% N; found: 57·60% C, 5·57% H, 8·32% N. Literature[6] gives m.p. 166—172°C and a 80% yield.

4-Phenyl-7-methoxy-2(1*H*)quinazolinone (*IIg*)

4-Methoxyacetanthranil (*IV*) was prepared according to Bogert[12,13] in a 85% yield. This compound is also mentioned by Lamchen and Wicken[14] but without indicating the procedure of preparation used. 2-Amino-4-methoxybenzophenone (*VI*) was prepared from *IV via* the non-isolated *V*, according to Lamchen and Wicken[14], in a 21·7% yield, m.p. 106–108°C. A mixture of 1·0 g of *VI* and 0·5 g urea was heated at 195°C for 35 minutes. The cooled melt was digested with hot ethanol and the filtrate was decolorized with charcoal and cooled. Yield 0·4 g (28·7%), m.p. 276–278·5°C. This preparation melted undepressed on admixture of *IIg* obtained by cyclodehydration of *Ig*. Their UV and IR spectra were also identical.

The analyses were carried out in the analytical department of our Institute (head Dr J. Körbl). The UV and IR spectra were evaluated in the physico-chemical department of our Institute (head Dr E. Knobloch).

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