Monatshefte für Chemie 114, 1197—1203 (1983)

Monatshefte für Chemie
Chemical Monthly

Reactions with 2-Aminonicotinic Acid, I
Some 8-Aza Analogs of Quinazolinones and Derived Tricyclic Compounds

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(Received 9 February 1983. Accepted 14 March 1983)

The fusion of 2-acetamidonicotinic acid with *o*-toluidine, *p*-bromoaniline or *o*-chloroaniline afforded the corresponding 3-aryl-2-methyl-pyrido-[2,3-d]pyrimidin-4(3*H*)-ones (**4**), the 8-aza analogs of 3-aryl-2-methyl-4-quinazolinones, alongside 2-aminonicotinic acid. 2-Methyl-3-(2-methylphenyl)-pyrido[2,3-d]pyrimidin-4(3*H*)-one (**4a**), the 8-aza analog of methaqualone, was converted to the 2-substituted styryl derivatives **6** by condensation with some aromatic aldehydes and to the tricyclic system, 10-aza-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-2-substituted-1*H*-pyrido[1,2-a]quinazoline-1,6-diones (**8**) by reaction with monosubstituted bis-2,4,6-trichlorophenyl malonates.

(Keywords: 10-Aza-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-2-substituted-1H-pyrido[1,2-a]quinazoline-1,6-diones; Bis-2,4,6-trichlorophenyl malonates; 3H-Pyrido[2,3-d]pyrimidin-4-ones)

Reaktionen mit 2-Aminonikotinsäure, 1. Mitt.:
Einige 8-Aza-Analoge von Chinazolinonen und davon abgeleiteten tricyclischen Systemen

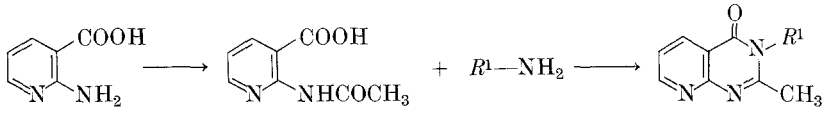
Die Fusion von 2-Acetamidonikotinsäure mit *o*-Toluidin, *p*-Bromanilin oder *o*-Chloranilin ergab die entsprechenden 3-Aryl-2-methyl-pyrido-[2,3-d]pyrimidin-4(3*H*)-one (**4**) und die 8-Aza-Analogen von 3-Aryl-2-methyl-4-chinazolinonen zusammen mit 2-Aminonikotinsäure. 2-Methyl-3-(2-methylphenyl)-pyrido[2,3-d]pyrimidin-4(3*H*)-on (**4a**), das 8-Aza-Analog von Methaqualon, wurde mittels Kondensation mit einigen aromatischen Aldehyden zu den 2-substituierten Styryl-Derivaten **6** umgesetzt. Die Reaktion mit monosubstituierten Bis-2,4,6-trichlorphenylmalonaten ergab tricyclische 10-Aza-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-2-substituierte 1*H*-Pyrido-[1,2-a]quinazolin-1,6-dione (**8**).

0026-9247/83/0114/1197/$ 01.40

Introduction

The 4-quinazolinone nucleus served as the basis of several compounds possessing diverse pharmacological and biological properties. These properties include CNS depressant[1–3], diuretic[4], antiinflammatory[5], antimalarial[6] and antimicrobial activities[7–13]. Looking for other active agents, a good deal of attention has been directed towards the heterocyclic replacement of the benzene ring in the 4-quinazolinone molecule. This resulted in the preparation of some subsituted thieno[2,3-d]pyrimidin-4(3*H*)-ones[14], pyrrolo[2,3-d]pyrimidin-2,4-diones[15,16] and pyrido[2,3-d]pyrimidin-4(3*H*)-ones[17,18] associated with useful pharmacological activities.

Scheme 1



1 **2** **3 a–c** **4 a–c**

	R^1		R^1
a	o-$CH_3C_6H_4$	**a**	o-$CH_3C_6H_4$
b	p-BrC_6H_4	**b**	p-BrC_6H_4
c	c-ClC_6H_4	**c**	o-ClC_6H_4

Results and Discussion

Continued interest in 2-methyl-3-(2-methylphenyl)quinazolin4(3*H*)-one (methaqualone)[19], a product which has achieved significant clinical use as sedative-hypnotic and as anticonvulsant, led us to synthesize some of its related 8-aza analogs and their derived tricyclic compounds, namely; 3-(2-methylphenyl)-3-substituted styryl-pyrido[2,3-d]pyrimidin-4(3*H*)-ones (**6**) and 10-aza-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-2-substituted-1*H*-pyrido[1,2-a]quinazoline-1,6-diones (**8**), respectively.

The reported synthetic approaches to 2-methyl-3-substituted-pyrido[2,3-d]pyrimidin-4(3*H*)-ones are analogous to those used for the preparation of 2-methyl-3-substituted-4(3*H*)-quinazolinones. In the present work, our previously described facile one-step synthesis of some 2,3-disubstituted-4-quinazolinones[20] was adopted to prepare the intermediate 2-methyl-3-(2-methylphenyl)pyrido[2,3-d]pyrimidin-4(3*H*)-one (**4 a**) as well as its 3-(4-bromophenyl) and 3-(2-chlorophenyl) analogs **4 b** and **4 c**, respectively. Thus, when 2-acetamidonicotinic acid (**2**) was heated with *o*-toluidine (**3 a**), *p*-bromo-aniline (**3 b**) or *o*-chloroaniline (**3 c**) at 180 °C in absence of a catalyst, the desired compounds **4 a, 4 b** or **4 c**

were obtained in low yields alongside 2-aminonicotinic acid (**1**) (Scheme 1). The structures of **4** were confirmed by elemental analysis, spectral data and mixed melting points with authentic samples prepared by known methods[17, 18].

Scheme 2

5a–c

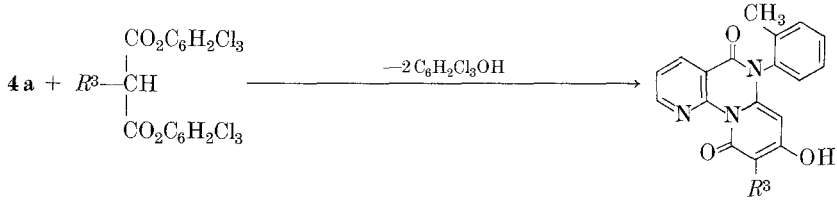
	R^2
a	C_6H_5
b	3,4-$CH_2O_2C_6H_3$
c	4-OH-3-$CH_3OC_6H_3$

6a–c

	R^2
a	C_6H_5
b	3,4-$CH_2O_2C_6H_3$
c	4-OH-3-$CH_3OC_6H_3$

Condensation of **4a** with the proper aldehyde **5** in refluxing glacial acetic acid in the presence of concentrated sulfuric acid afforded good yields of the corresponding 3-(2-methylphenyl)-2-substituted styryl-pyrido[2,3-d]pyrimidin-4(3*H*)-one (**6**). Compound **6a** was also obtained by reacting **4a** with benzaldehyde in boiling methanolic potassium hydroxide according to the published conditions[18] but its yield was lower. Attempts to extend this base-catalyzed condensation to the preparation of **6c** from **4a** and vanillin (**5c**) proved unsuccessful. The ^{1}H NMR spectra of **6b** and **6c** indicated that the two hydrogen atoms of the styryl side chain exist in the *trans* configuration (Scheme 2).

Scheme 3



7a–c

	R^3
a	C_2H_5
b	$(CH_3)_2CH$
c	C_6H_5

8a–c

	R^3
a	C_2H_5
b	$(CH_3)_2CH$
c	C_6H_5

Reacting **4a** with the appropriate monosubstituted bis-2,4,6-trichlorophenyl malonates **7** at the fusion point of the mixture yielded the corresponding tricyclic compound **8** (Scheme 3). The cyclization is identical to one which occured previously in an analogous reaction of 3-aryl-2-methyl-4-quinazolinones with reactive malonates[21] involving the interaction between the 1,3-dinucleophilic centers of **4a** and a ketene-carboxylate intermediate[22] generated from **7** on thermolysis. The IR and ^{1}H NMR spectra of **8** are consistent with their structures.

Acknowledgement

The authors are grateful to Professor Dr. *H. Sterk*, Institut für Organische Chemie der Karl-Franzens-Universität Graz, Austria, for recording the IR and NMR spectra.

Experimental

Melting points are uncorrected. IR spectra: Beckman 4210. ^{1}H NMR spectra: Varian EM360 with *TMS* as internal standard.

1. *2-Acetamidonicotinic acid* (**2**)

This was prepared by reacting 2-aminonicotinic acid (**1**) with acetic anhydride as previously reported[18].

2. *3-Aryl-2-methyl-pyrido[2,3-d]pyrimidin-4(3H)-ones* (**4**)

An intimate mixture of 2-acetamidonicotinic acid (**2**) (1.38 g, 10.0 mmol) and the appropriate amine **3** (10.5 mmol) was heated at 180 °C for 15 min in an oil bath. After cooling, the dark brown mixture was treated with ethanol and the insoluble 2-aminonicotinic acid (**1**) was filtered and washed with ethanol. Subsequently, the combined filtrate and washing were evaporated to dryness and the resulting crude product was recrystallized from benzene-petroleum ether (b. p. 40-60 °C).

2-Methyl-3-(2-methylphenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**4a**)

M. p. 174 °C (Ref.[17]: 109-110°; Ref.[18]: 178-179°); yield 31%. IR (nujol): 1690 s (C=O), 1595 s (C=N, C=C and aromatics) cm^{-1}. $C_{15}H_{13}N_3O$ (251.3)*.

3-(4-Bromophenyl)-2-methyl-pyrido[2,3-d]pyrimidin-4(3H)-one (**4b**)

M. p. 195-196 °C (Ref.[17]: 192-193 °); yield 46%. $C_{14}H_{10}BrN_3O$ (316.7).

3-(2-Chlorophenyl)-2-methyl-pyrido[2,3-d]pyrimidin-4(3H)-one (**4c**)

M. p. 181-182 °C (Ref.[18]: 194-195 °); yield 28%. IR (nujol): 1685 s (C=O), 1595 s shouldered at 1580 (C=N, C=C and aromatics) cm^{-1}. $C_{14}H_{10}ClN_3O$ (271.7).

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* Here and subsequently all compounds gave satisfactory elemental analyses (C, H, N).

3. *3-(2-Methylphenyl)-2-substituted styryl-pyrido[2,3-d]pyrimidin-4(3H)-ones* (**6a-6C**)

Method A. A solution of **4a** (0.251 g, 1 mmol) and the appropriate aldehyde **5** (1 mmol) in glacial acetic acid (10 ml) containing drops of concentrated sulfuric acid was refluxed for 4 h. The reaction mixture was then concentrated, neutralized with aqueous 10% sodium carbonate and the separated semi solid product was crystallized as yellow crystals from the proper solvent. The following compounds were prepared:

3-(2-Methylphenyl)-2-styryl-pyrido[2,3-d]pyrimidin-4(3H)-one (**6a**)

Recrystallized from aqueous methanol, m. p. 187–188 °C; yield 90%. IR (nujol): 1675 s (C=O), 1630 w, 1550 s shouldered at 1580 and at 1525 (C=N, C=C and aromatics) cm^{-1}. $C_{22}H_{17}N_3O$ (339.4).

2-(3,4-Methylenedioxystyryl)-3-(2-methylphenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**6b**)

Recrystallized from benzene, m. p. 187–188 °C; yield 33%. IR (nujol): 1685 s (C=O), 1630 w, 1595 m and 1545 s (C=N, C=C and aromatics), 1250 s and 1035 (C—O—C) cm^{-1}. $C_{23}H_{17}N_3O_3$ (383.4).

^{1}H NMR (*DMSO-d_6*): 2.1 (s, CH_3-tolyl), 6.1 (s, O—CH_2—O). 6.15 (d, J = 16 Hz, N=C(—)—CH=), 6.7–7.65 (m, 8 aromatic H), 7.05 (d, J = 16 Hz, =CH—), 8.5 (dd, J = 2 and 7 Hz, H at 5-5), 8.95 (q, H at C-7).

2-(4-Hydroxy-3-methoxystyryl)-3-(2-methylphenyl)pyrido[2,3-d]pyrimidin-4(3H)-one (**6c**)

Recrystallized from ethanol, m. p. 211–212 °C; yield 65%. IR (nujol): 1680 s (C=O), 1625 m, 1580 s, 1545 s (C=N, C=C and aromatics), 1260 s and 1035 s (C—O—C) cm^{-1}. $C_{23}H_{19}N_3O_3$ (385.4).

^{1}H NMR (*DMSO-d_6*): 2.1 (s, CH_3-tolyl), 3.65 (s, CH_3O—), 6.0 (d, J = 16 Hz, N=C(—)—CH=), 6.7–7.6 (m. 8 aromatic H), 7.9 (d, J = 16 Hz, =CH—styryl), 8.45 (dd, J = 2 and 7 Hz, H at C-5), 8.9 (q, H at C-7), 9.55 (s, OH).

Method B for **6a**. A solution of **4a** (0.63 g, 2.5 mmol), benzaldehyde (0.27 g, 2.5 mol) and potassium hydroxide (0.14 g) in methanol (15 ml) was refluxed for 3 h and coold. The end product was precipitated with water and recrystallized; yield 0.35 g (41%).

4. *Bis-2,4,6-trichlorophenyl malonates* (**7**)

These were prepared according to the reported method[23].

5. *10-Aza-5,6-dihydro-2-ethyl-3-hydroxy-5-substituted-1H-pyrido-[1,2-a]quinazoline-1,6-dione* (**8**)

A mixture of **4a** (0.251 g, 1 mmol) and **7** (1 mmol) was placed in an oil bath at 200 °C for 25 min. The cooled dark brown raction mixture was mixed with benzene and the separated product was filtered, washed with benzene and recrystallized from ethanol as yellow crystals. The following compounds were prepared:

10-Aza-5,6-dihydro-2-ethyl-3-hydroxy-5-(2-methylphenyl)-1H-pyrido-[1,2-a]quinazoline-1,6-dione (**8a**)

M. p. 277–278 °C; yield 0.12 g (34.6%). IR (KBr): 3300–2800 m (OH and CH), a broad band splitted at 1675 s (C=O), 1640 s (C=O), 1620 s and at 1600 s (C=N, C=C and aromatics) cm^{-1}. $C_{20}H_{17}N_3O_3$ (347.4).

^1H NMR (*DMSO-d_6*): 1.0 (t, $J = 7$ Hz, CH_3-ethyl, 2.15 (s, CH_3-tolyl), 2.15 (q, CH_2-ethyl), 4.85 (s, H at C-4), 7.2–7.6 (m, 5 aromatic H), 8.37 (dd, $J = 2$ and 7 Hz, H at C-7), 8.75 (q, H at C-9), 10.25 (s, OH).

10-Aza-5,6-dihydro-3-hydroxy-2-isopropyl-5-(2-methylphenyl)-1H-pyrido-[1,2-a]quinazoline-1,6-dione (**8b**)

M. p. 259–260 °C; yield 0.2 g (55.3%). IR (KBr): 3000–2800 m (OH, CH), a broad band splitted at 1690 m (C=O), 1640 s (C=O), 1620 s and at 1600 s (C=N, C=C and aromatics) cm^{-1}. $C_{21}H_{19}N_3O_3$ (361.4).

^1H-NMR (*DMSO-d_6*): 1.2 (d, $J = 7$ Hz, two CH_3-isopropyl), 2.1 (s, CH_3-tolyl), 3.1 (q, CH_3-isopropyl), 4.8 (s, H at C-4), 7.25–7.6 (m, 5 aromatic H), 8.35 (dd, $J = 2$ and 7 Hz, H at C-7), 8.7 (q, H at C-9), 10.2 (s, OH).

10-Aza-5,6-dihydro-3-hydroxy-5-(2-methylphenyl)-2-phenyl-1H-pyrido-[1,2-a]quinazoline-1,6-dione (**8c**)

M. p. 252–253 °C; yield 0.13 g (33%). IR (KBr): 3300–2800 m (OH), a broad band splitted at 1690 s (C=O), 1650 s (C=O), 1600 s (C=N, C=C and aromatics cm^{-1}. $C_{24}H_{17}N_3O_3$ (395.4).

^1H NMR (*DMSO-d_6*): 2.15 (s, CH_3-tolyl), 5.0 (s, H at C-4), 7.2–7.65 (m, 10 aromatic H), 8.5 (dd, $J = 2$ and 7 Hz, H at C-7), 8.8 (q, H at C-9).

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