Synthesis and Anticonvulsant Activity of Some Novel 3-Aminoquinazolines [1]

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A number of novel 3-aminoquinazolines were obtained *via* two synthetic pathways. In the first method *o*-aminobenzoylhydrazines were prepared either by reacting an isatoic anhydride and a hydrazine or by reacting *o*-nitrobenzoic acid with a hydrazine, followed by catalytic reduction. Subsequent cyclization with an appropriate orthoester provided 3-aminoquinazolines and 2-methyl-3-aminoquinazolines. The second pathway involved condensation of *o*-aminoacetophenone with a hydrazine to form hydrazones which were reduced to aminohydrazines and cyclized as above to yield 4-methyl-3-aminoquinazolines and 2,4-dimethyl-3-aminoquinazolines. The title compounds were evaluated in mice in MES and sc Met seizure models for anticonvulsant activity, and in the rotorod test for neurotoxicity. They were generally toxic. However, 4-methyl-3-(*N*-piperidino)-3,4-dihydroquinazoline hydrochloride exhibited activity comparable to that of methaqualone.

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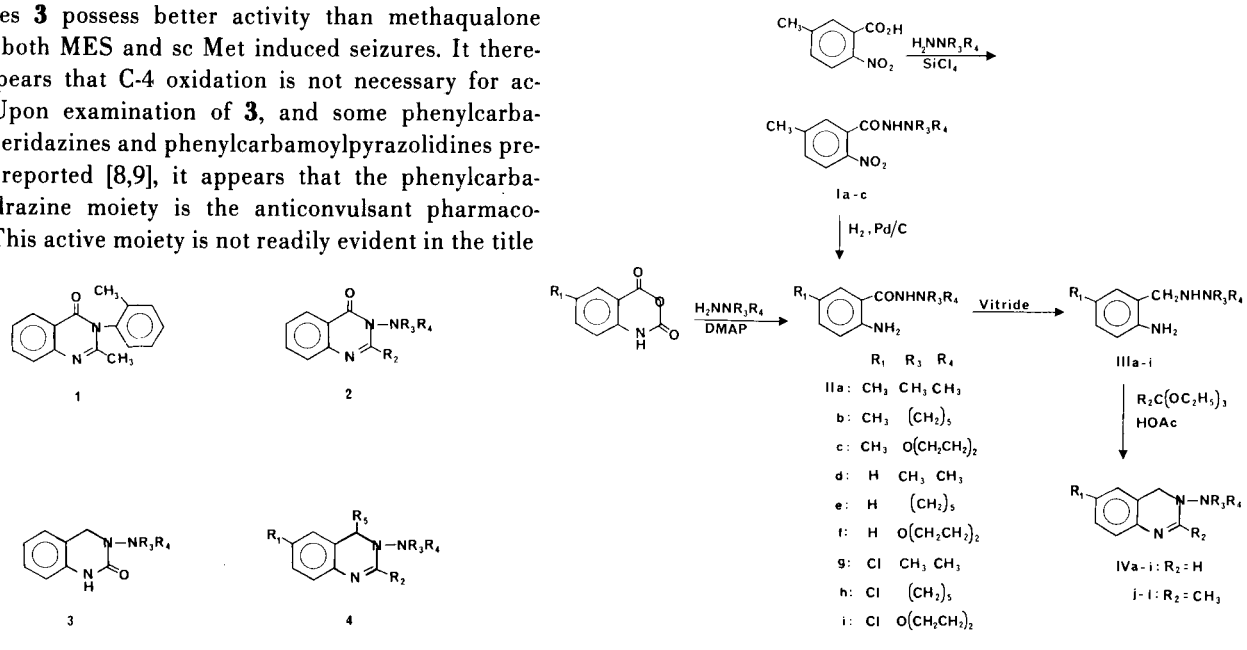
The anticonvulsant activity of quinazolines has not been explored as much as that of benzodiazepines, and none so far has found clinical application in antiepileptic therapy. However, quinazoline derivatives are known to be biologically versatile compounds, possessing several pharmacological properties including anticonvulsant. Methaqualone (**1**), a prototype of this class, is used clinically as a hypnotic, but has also demonstrated potency against major seizure types [2,3]. Recently it was reported [4] that some 4-quinazolines exhibit anticonvulsant activity comparable to **1** and with no neurotoxicity at doses up to 600 mg/kg. Very few 3-amino-4-quinazolinones **2** have been investigated for anticonvulsant activity as yet. Boltze [5] reported moderate activity with $R_2 = CH_3$, whereas Kornet [6] observed slightly better activity with $R_2 = H$. Previous work in our laboratories [7] has shown that 3-amino-2-quinazolones **3** possess better activity than methaqualone against both MES and sc Met induced seizures. It therefore appears that C-4 oxidation is not necessary for activity. Upon examination of **3**, and some phenylcarbamoylpiperidazines and phenylcarbamoylpyrazolidines previously reported [8,9], it appears that the phenylcarbamoylhydrazine moiety is the anticonvulsant pharmacophore. This active moiety is not readily evident in the title quinazolines **4**. Nevertheless, such compounds may be metabolically oxidized *in vivo* to 2-quinazolinones. To further test this hypothesis, compounds in which this metabolic pathway is blocked by substitution ($R_2 = CH_3$) were also evaluated. Thus the synthesis of a series of 3-aminoquinazolines **4** was undertaken in this investigation to study the validity of the suggested hypotheses, and to extend the general SAR scope in the quinazoline class. Substituent groups were varied in terms of lipophilicity in such a way as to impart a wide range of physicochemical properties to the molecules.

Scheme I summarizes the synthetic pathways leading to 3-aminoquinazolines **IVa-i** and 2-methyl-3-aminoquinazolines **IVj-l**. The key intermediates **II** were prepared *via*

Scheme I



two routes, depending on the availability of starting materials. Thus **IIa-c** were obtained by the reaction of 5-methyl-2-nitrobenzoic acid with the corresponding hydrazine in the presence of silicon tetrachloride [10,11], followed by catalytic hydrogenation. Compounds **IId-i** were prepared by ring-opening of an appropriately substituted isatoic anhydride with the corresponding hydrazine. No significant difference in product yields was observed with 4-dimethylaminopyridine (DMAP) as catalyst and DMF as solvent [12]. Venuti [13] reported a yield improvement for such acylations with DMAP in pyridine. Reduction of **II**

Scheme II

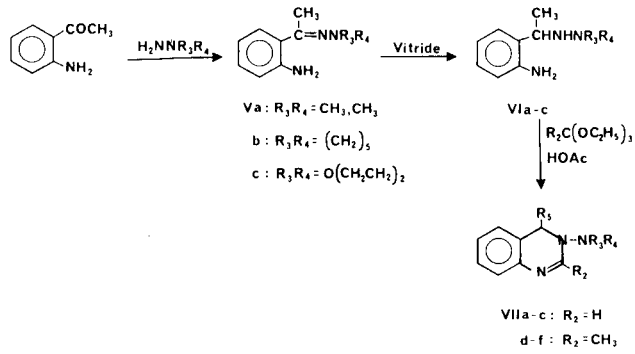


Table I

Properties of 3-Aminoquinazolines **IV** and **VII**

Compound	R_1	R_2	R_3 R_4	R_5	mp, °C	Yield, %	Formula	Analysis, % Calcd./Found C	H	N
IVa	CH_3	H	CH_3 CH_3		231-233 [a]	42	$C_{11}H_{16}ClN_3$ [b]	58.53 58.17	7.14 7.17	18.62 18.51
IVb	CH_3	H	$(CH_2)_5$		97-99 [c]	52	$C_{14}H_{19}N_3$	73.33 73.33	8.35 8.43	18.32 18.29
IVc	CH_3	H	$O(CH_2CH_2)_2$		144-146 [c]	50	$C_{13}H_{17}N_3O$	67.51 67.47	7.41 7.56	18.17 18.32
IVd	H	H	CH_3 CH_3		205-207 [d]	33	$C_{10}H_{14}ClN_3$ [b]	56.74 56.49	6.67 6.71	19.85 19.77
IVe	H	H	$(CH_2)_5$		75-77 [e]	43	$C_{13}H_{17}N_3$	72.52 72.78	7.96 8.02	19.52 19.39
IVf	H	H	$O(CH_2CH_2)_2$		122-124 [e]	70	$C_{12}H_{15}N_3O$	66.34 66.30	6.96 7.03	19.34 19.59
IVg	Cl	H	CH_3 CH_3		262-264 dec [f]	45	$C_{10}H_{13}Cl_2N_3$ [b]	48.80 48.78	5.32 5.35	17.07 17.23
IVh	Cl	H	$(CH_2)_5$		133-135 [e]	40	$C_{13}H_{16}ClN_3$	62.52 62.46	6.46 6.52	16.83 16.88
IVi	Cl	H	$O(CH_2CH_2)_2$		151-153 [e]	40	$C_{12}H_{14}ClN_3O$	57.26 57.52	5.61 5.64	16.69 16.79
IVj	H	CH_3	CH_3 CH_3		266-268 dec [d]	15	$C_{11}H_{16}ClN_3$ [b]	58.53 58.40	7.14 7.35	18.62 18.55
IVk	H	CH_3	$(CH_2)_5$		269-271 dec [f]	48	$C_{14}H_{20}ClN_3$ [b]	63.27 63.30	7.58 7.79	15.81 16.08
IVl	H	CH_3	$O(CH_2CH_2)_2$		153-155 [c]	51	$C_{13}H_{17}N_3O$	67.51 67.54	7.41 7.42	18.17 18.44
VIIa		H	CH_3 CH_3	CH_3	221-223 [a]	51	$C_{11}H_{16}ClN_3$ [b]	58.53 58.55	7.14 7.28	18.62 18.52
VIIb		H	$(CH_2)_5$	CH_3	216-218 [a]	42	$C_{15}H_{23}ClN_3O_{0.5}$ [g]	62.38 62.55	8.03 8.03	14.55 14.82
VIIc		H	$O(CH_2CH_2)_2$	CH_3	108-110 [c]	64	$C_{13}H_{17}N_3O$	67.51 67.86	7.41 7.57	18.17 18.17
VIId		CH_3	CH_3 CH_3	CH_3	144-146 [c]	73	$C_{18}H_{20}N_6O_7$ [h]	50.00 49.95	4.66 4.69	19.44 19.78
VIIe		CH_3	$(CH_2)_5$	CH_3	217-219 [f]	70	$C_{21}H_{24}N_6O_7$ [h]	53.39 53.57	5.12 5.15	17.79 17.87
VIIf		CH_3	$O(CH_2CH_2)_2$	CH_3	168-170 [i]	52	$C_{14}H_{19}N_3O$	68.54 68.68	7.81 7.92	17.13 17.19

[a] Absolute Ethanol/Ethyl acetate. [b] Hydrochloride. [c] Ethyl acetate. [d] Absolute Ethanol. [e] Toluene/Hexane. [f] 95% Ethanol. [g] Hydrochloride with one-half mole of ethanol. [h] Picrate. [i] Toluene.

with sodium bis(2-methoxyethoxy) aluminum hydride (Vitride) [14] gave the corresponding diamines **III** which were finally cyclized in glacial acetic acid with triethyl orthoformate to give **IVa-i** or triethyl orthoacetate to obtain **IVj-l** (Table I). Cyclization with acetic anhydride gave a poor yield because of diacetylation. The synthesis of 4-methyl-3-aminoquinazolines **VIIa-c** and 2,4-dimethyl-3-aminoquinazolines **VIId-f** is summarized in Scheme II. Condensation of *o*-aminoacetophenone with an appropriate hydrazine produced the corresponding hydrazones **Va-c**. For high boiling hydrazines such as *N*-aminopiperidine and *N*-aminomorpholine the mixtures were simply refluxed at 230° (oil bath temperature) over 16 hours in the manner previously described [7]. Since such high reaction temperatures could not be attained with the low boiling 1,1-dimethylhydrazine, titanium tetrachloride was used as catalyst in a method adapted from Martin [15]. It was observed that in the presence of titanium tetrachloride the condensation was complete after 5 hours at 100°, and afforded a better yield. Hydrazones **V** were reduced with Vitride to diamines **VI** and then cyclocondensed with the appropriate orthoesters to obtain **VII** (Table I).

All the title compounds were evaluated in the maximal electroshock (MES) seizure and pentylenetetrazole (scMET) seizure threshold tests for anticonvulsant activity in male Carworth Farm No. 1 mice by reported procedures [9]. Neurotoxicity was determined for each compound by the rotorod test [9]. Compounds **IVa-g**, **IVi-j** and **VIIa-c** could not be evaluated at doses greater than 100 mg/kg due to death by respiratory depression. It is significant that **IVd-f** (R_2 = H) exhibited some level of MES activity while **IVj-l** (R_2 = CH_3) were essentially inactive and toxic. An analogous comparison could be made between **VIIa-c** (R_2 = H) and **VIId-f** (R_2 = CH_3). These observations suggest that C-2 may indeed be oxidized *in vivo* to produce the active phenylcarbamoylhydrazine pharmacophore, whereas C-2 alkylation inhibits this metabolic pathway, resulting in inactive quinazolines. The most active compound in the series was **VIIb**. It had an MES ED_{50} of 48 mg/kg and TD_{50} of 76 mg/kg, compared to 52 mg/kg and 55 mg/kg respectively, for methaqualone. The preliminary results indicate that 4-methyl-3-(*N*-piperidino)-3,4-dihydroquinazoline hydrochloride (**VIIb**) may be a more potent and safer (therapeutic index: 1.58 *vs* 1.06) anticonvulsant agent than methaqualone (**1**). At the very least **VIIb** may serve as a lead for future SAR studies of anticonvulsant quinazolines.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as internal reference. Elemental analysis were performed by Micanal, Tucson, Arizona.

1-(5-Methyl-2-nitrobenzoyl)-2,2-dialkylhydrazines **Ia-c**.

The preparation of **Ia** is representative of the general procedure.

1-(5-Methyl-2-nitrobenzoyl)-2,2-dimethylhydrazine (**Ia**).

To a stirred and ice-cooled solution containing 11.0 g (0.06 mole) of 5-methyl-2-nitrobenzoic acid and 4.68 g (0.078 mole) of 1,1-dimethylhydrazine in 75 ml of dry pyridine was added 6.00 g (0.035 mole) of silicon tetrachloride dropwise. A precipitate formed instantly. The reaction mixture was allowed to attain room temperature over 1 hour and then slowly heated at reflux for 3 hours. The resulting solution was cooled to room temperature, poured onto crushed ice and the slurry was filtered. After thoroughly washing the silica residue with hot ethanol, the combined filtrates were concentrated under reduced pressure. The pyridine was azeotroped with toluene leaving a viscous oil which was adjusted to *p*H 8 with 5% sodium hydroxide and extracted into chloroform. The organic layer was dried (magnesium sulfate), and evaporated *in vacuo* to leave a solid residue. Recrystallization from ethyl acetate yielded 9.02 g (67%) of a pale yellow powder, mp 133-135° (lit [16] mp 133.5-134.5°).

1-(5-Methyl-2-nitrobenzamido)piperidine (**Ib**).

A mixture of 11.0 g (0.06 mole) of 5-methyl-2-nitrobenzoic acid, 6.6 g (0.066 mole) of *N*-aminopiperidine, and 6.0 g (0.034 mole) of silicon tetrachloride in 75 ml of anhydrous pyridine yielded 8.80 g (56%) of a yellow powder. Recrystallization from ethyl acetate afforded the product, mp 154-156° (lit [6] mp 153-155°).

1-(5-Methyl-2-nitrobenzamido)morpholine (**Ic**).

From 11.0 g (0.06 mole) of 5-methyl-2-nitrobenzoic acid, 6.73 g (0.066 mole) of *N*-aminomorpholine and 6.0 g (0.034 mole) of silicon tetrachloride in 75 ml of dry pyridine there was obtained 7.50 g (47%) of a pale yellow solid. Recrystallization from ethyl acetate gave the pure product, mp 192-194°; nmr (deuteriochloroform): 2.5 (s, 3H, Ar-CH_3), 2.6-2.8 and 2.9-3.1 (two m, 4H, $N(CH_2)_2$), 3.3-3.6 and 3.7-4.0 (two m, 4H, $O(CH_2)_2$), 7.3-8.1 (m, 3H, ArH), 7.8 (broad s, 1H, CONH, deuterium oxide exchangeable).

1-(5-Methyl-2-aminobenzoyl)-2,2-dialkylhydrazines **IIa-c**.

Compounds **IIa** and **IIb** were prepared as previously described [16].

Compound **IIc** was obtained by catalytic reduction [16] of **Ic** as white flakes in quantitative yield, mp 220-223°, and was used directly in the orthoester cyclization step.

1-(2-Aminobenzoyl)-2,2-dialkylhydrazines **IId-i**.

The preparation of **IId** is representative of this general method.

1-(2-Aminobenzoyl)-2,2-dimethylhydrazine (**IId**).

A mixture containing 20.4 g (0.12 mole) of isatoic anhydride, 1.47 g (0.012 mole) of 4-dimethylaminopyridine (DMAP) and 80 ml of dry DMF was warmed to 45°. The solution was stirred at this temperature while a solution of 7.92 g (0.0132 mole) of 1,1-dimethylhydrazine in 40 ml of DMF was added dropwise over 30 minutes under nitrogen. Stirring was continued at 45-50° until tlc indicated complete disappearance of isatoic anhydride (3 hours). The reaction mixture was cooled to room temperature, poured into 100 ml of water, adjusted to *p*H 9 with 50% sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with 100 ml of saturated brine, dried (magnesium sulfate) and concentrated *in vacuo* to leave a brownish solid. Recrystallized from toluene afforded 17.7 g (82%) of an off-white crystalline solid, mp 142-144° (lit [6a] mp 143-144°).

1-(2-Aminobenzamido)piperidine (**IIe**).

Isatoic anhydride (17.0 g, 0.10 mole), *N*-aminopiperidine (11.0 g, 0.11 mole) and DMAP (1.20 g, 0.01 mole) were reacted. Recrystallization from 1:1 ethyl acetate/toluene gave 16.80 g (77%) of pale yellow crystals, mp 163-165° (lit [6a] mp 168.5-169°).

1-(2-Aminobenzamido)morpholine (**IIf**).

Reaction of 16.3 g (0.10 mole) of isatoic anhydride, 11.2 g (0.11 mole)

of *N*-aminomorpholine and 1.20 (0.01 mole) of DMAP yielded 14.30 g (65%) of white flakes from 2:1 ethyl acetate/toluene, mp 204-206° (lit [16] mp 204-205°).

1-(5-Chloro-2-aminobenzoyl)-2,2-dimethylhydrazine (**IIg**).

5-Chloroisatoic anhydride (20.0 g, 0.10 mole), 1,1-dimethylhydrazine (6.6 g, 0.11 mole) and DMAP (1.20 g, 0.01 mole) were reacted to produce 21.0 g (98%) of crystals from toluene, mp 158-160° (lit [6a] mp 159.5-161.5°).

1-(5-Chloro-2-aminobenzamido)piperidine (**IIh**).

Reaction of 10.0 g (0.05 mole) of 5-chloroisatoic anhydride, 5.5 g (0.055 mole) of *N*-aminopiperidine and 0.61 g (0.005 mole) of DMAP afforded 8.10 g (64%) of a white fluffy crystalline solid. After recrystallization from 2:1 ethyl acetate/toluene, the purified product had mp 208-210° (lit [16] mp 208-210.5°).

1-(5-Chloro-2-aminobenzamido)morpholine (**IIi**).

Treatment of 10.0 g (0.05 mole) of 5-chloroisatoic anhydride with 5.61 g (0.055 mole) of *N*-aminomorpholine and 0.61 g (0.005 mole) of DMAP and subsequent recrystallization from 2:1 ethanol/toluene yielded 8.75 g (69%) of white crystals, mp 226-228° (lit [16] mp 227.5-229.5°).

3-Aminoquinazolines and 2-Methyl-3-aminoquinazolines **IVa-l**.

General Procedure.

To an efficiently stirred solution containing 28 ml (0.10 mole) of Vitride and 28 ml of toluene in a 3-neck round-bottom flask fitted with a reflux condenser was added 0.025 mole of the hydrazide **IIa-i** portionwise under nitrogen at room temperature. After addition was complete the reaction mixture was refluxed for 1-5 hours. The solution was allowed to cool to room temperature and added dropwise *via* a separatory funnel to 20 ml of a 20% aqueous sodium hydroxide solution with magnetic stirring and ice-bath cooling. The organic layer was decanted and the aqueous slurry was washed twice with toluene. The combined organic extracts were dried (magnesium sulfate), concentrated *in vacuo* and azeotroped several times with absolute ethanol to leave the diamine **IIa-i**.

To this residue was added 9.6 ml (0.15 mole) of glacial acetic acid and either 22.20 g (0.15 mole) of triethyl orthoformate or 24.30 g (0.15 mole) of triethyl orthoacetate. The reaction mixture was refluxed under nitrogen until tlc indicated complete disappearance of the dianine (2-4 hours). The resulting solution was concentrated, basified (*p*H 9) with 5% sodium hydroxide and extracted with chloroform. The organic layer was dried (magnesium sulfate) and evaporated to dryness under reduced pressure. Solid products were simply recrystallized whereas oils were converted to the hydrochloride salts with ethereal hydrogen chloride. The yields given are overall yields for reduction, cyclization and recrystallization. Properties of these products are summarized in Table I.

3-Dimethylamino-6-methyl-3,4-dihydroquinazoline Hydrochloride (**IVa**).

Isolated as a white crystalline solid; nmr (deuterium oxide): δ 2.4 (s, 3H, Ar-CH_3), 2.9 (s, 6H, $N(CH_3)_2$), 5.03 (s, 2H, Ar-CH_2), 6.9-7.5 (m, 3H, ArH), 8.6 (s, 1H, N = CH).

6-Methyl-3-(*N*-piperidino)-3,4-dihydroquinazoline (**IVb**).

Isolated as yellowish transparent needles; nmr (deuteriochloroform): δ 1.1-2.0 (m, 6H, $(CH_2)_3$), 2.3 (m, 3H, Ar-CH_3), 2.7-3.0 (m, 4H, $N(CH_2)_2$), 4.63 (s, 2H, Ar-CH_2), 6.8-7.03 (m, 3H, ArH), 7.7 (s, 1H, N = CH).

6-Methyl-3-(*N*-morpholino)-3,4-dihydroquinazoline (**IVc**).

Isolated as white crystals, nmr (deuteriochloroform): δ 2.3 (s, 3H, Ar-CH_3), 2.73-3.1 (m, 4H, $N(CH_2)_2$), 3.67-4.0 (m, 4H, $O(CH_2)_2$), 4.63 (s, 2H, Ar-CH_2), 6.8-7.1 (m, 3H, ArH).

3-Dimethylamino-3,4-dihydroquinazoline Hydrochloride (**IVd**).

Isolated as orange crystals; nmr (deuterium oxide): δ 2.9 (s, 6H, $N(CH_3)_2$), 5.03 (s, 2H, Ar-CH_2), 7.0-7.6 (m, 4H, ArH), 8.5 (s, 1H, N = CH).

3-(*N*-Piperidino)-3,4-dihydroquinazoline (**IVe**).

Isolated as a yellowish crystalline solid; nmr (deuteriochloroform): δ 1.1-2.0 (m, 5H, $(CH_2)_3$), 2.7-3.0 (m, 4H, $N(CH_2)_2$), 4.7 (s, 2H, Ar-CH_2), 6.8-7.3 (m, 4H, ArH), 7.4 (s, 1H, N = CH).

3-(*N*-Morpholino)-3,4-dihydroquinazoline (**IVf**).

Isolated as pale yellow crystals; nmr (deuteriochloroform): δ 2.6-3.0 (m, 4H, $N(CH_2)_2$), 3.6-3.9 (m, 4H, $O(CH_2)_2$), 4.63 (s, 2H, Ar-CH_2), 6.8-7.3 (m, 4H, ArH), 7.37 (s, 1H, N = CH).

6-Chloro-3-dimethylamino-3,4-dihydroquinazoline Hydrochloride (**IVg**).

Isolated as a pale orange crystalline solid; nmr (deuterium oxide): δ 2.9 (s, 6H, $N(CH_3)_2$), 5.1 (s, 2H, Ar-CH_2), 7.0-7.7 (m, 3H, ArH), 8.6 (s, 1H, N = CH).

6-Chloro-3-(*N*-piperidino)-3,4-dihydroquinazoline (**IVh**).

Isolated as white needles; nmr (deuteriochloroform): δ 1.1-2.0 (m, 6H, $(CH_2)_3$), 2.7-3.0 (m, 4H, N $(CH_2)_2$), 4.67 (s, 2H, Ar-CH_2), 6.8-7.2 (m, 3H, ArH), 7.37 (s, 1H, N = CH).

6-Chloro-3-(*N*-morpholino)-3,4-dihydroquinazoline (**IVi**).

Isolated as white crystals; nmr (deuteriochloroform): δ 2.8-3.1 (m, 4H, $N(CH_2)_2$), 3.8-4.1 (m, 4H, $O(CH_2)_2$), 4.7 (s, 2H, Ar-CH_2), 6.8-7.2 (m, 3H, ArH), 7.37 (s, 1H, N = CH).

2-Methyl-3-(*N*-piperidino)-3,4-dihydroquinazoline Hydrochloride (**IVk**).

Isolated as white needles; nmr (deuterium oxide): δ 1.1-2.1 (m, 6H, $(CH_2)_3$), 2.5 (s, 3H, N = C-CH_3), 2.7-3.1 (m, 4H, $N(CH_2)_2$), 4.9 (s, 2H, Ar-CH_2), 6.9-7.6 (m, 4H, ArH).

2-Methyl-3-(*N*-morpholino)-3,4-dihydroquinazoline (**IVl**).

Isolated as a yellowish crystalline solid; nmr (deuteriochloroform): δ 2.25 (s, 3H, N = C-CH_3), 2.4-3.3 (m, 4H, $N(CH_2)_2$), 3.4-4.1 (m, 4H, $O(CH_2)_2$), 4.6 (s, 2H, Ar-CH_2), 6.8-7.3 (m, 4H, ArH).

3-Dimethylamino-2-methyl-3,4-dihydroquinazoline Hydrochloride (**IVj**).

The reduction of **IId** (7.00 g, 0.039 mole) was effected with Vitride as described in the general procedure. To the diamine residue **IIId** thus obtained was added 4 ml (0.042 mole) of acetic anhydride and the reaction mixture was refluxed for 22 hours. The mixture was cooled, poured onto crushed ice, basified (*p*H 9) with 50% sodium hydroxide and extracted with methylene chloride. The organic layer was dried (magnesium sulfate) and concentrated *in vacuo* to a viscous oil. Tlc of the oil indicated more than one product. The oil was acidified (*p*H 2) with 5% hydrochloric acid and extracted with ether. Tlc of the ether layer corresponded to the diacetylated compound by comparison to an authentic sample, hence it was discarded. The aqueous layer was readjusted to *p*H 9 with 50% sodium hydroxide, extracted with ether, and the organic layer was dried over magnesium sulfate. Concentration under reduced pressure left an oil which was precipitated with ethereal hydrogen chloride and recrystallized from absolute alcohol to yield 1.3 g (15%) of a yellow powder; nmr (deuterium oxide): δ 2.6 (s, 3H, N = C-CH_3), 2.8 (s, 6H, $N(CH_3)_2$), 5.0 (s, 2H, Ar-CH_2), 7.03-7.65 (m, 4H, ArH).

o-Aminoacetophenone-*N,N*-(3-oxapentamethylene)hydrazone (**Vc**).

A 100 ml 3-neck flask was charged with 6.75 g (0.05 mole) of *o*-aminoacetophenone and 20.4 g (0.20 mole) of *N*-aminomorpholine. The reaction flask was fitted with a molecular sieve column surmounted by a reflux condenser and the system was thoroughly purged with nitrogen. The reaction mixture was refluxed at 220-230° (metal bath temperature) for 16 hours then vacuum distilled. The product was collected at 151-154° (0.08 mm) as a yellow viscous oil which solidified upon cooling and trituration with ether. Recrystallization from ether yielded 7.73 g (71%) of a yellow crystalline solid, mp 81-83°; nmr (deuteriochloroform): δ 2.47 (s, 3H, N = C-CH_3), 2.7-3.1 (m, 4H, $N(CH_2)_2$), 3.8-4.1 (m, 4H, $O(CH_2)_2$), 5.7-6.6 (broad s, 2H, Ar-NH_2, deuterium oxide exchangeable), 6.6-7.7 (m, 4H, ArH).

Anal. Calcd. for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.94; H, 7.97; N, 19.27.

o-Aminoacetophenone-*N,N*-pentamethylenehydrazone (**Vb**).

The procedure was similar to that described for **Vc**. A mixture of 10.6 g (0.078 mole) of *o*-aminoacetophenone and 31.2 g (0.312 mole) of *N*-aminopiperidine yielded 13.0 g (77%) of a pale yellow solid, mp 48-51°; nmr (deuteriochloroform): δ 1.1-2.0 (m, 6H, $(CH_2)_3$), 2.4 (s, 3H, N=C-CH_3), 2.6-3.2 (m, 5H, $N(CH_2)_2$), 5.6-6.5 (broad s, 2H, Ar-NH_2, deuterium oxide exchangeable), 6.57-7.67 (m, 4H, ArH).

All attempts to obtain an analytically pure sample were unsuccessful.

o-Aminoacetophenone-*N,N*-dimethylhydrazone Dihydrochloride (**Va**).

A solution of 17.6 g (0.13 mole) of *o*-aminoacetophenone in 260 ml of toluene was cooled to −40° (dry ice/acetone). To the stirred solution was added 31.2 g (0.52 mole) of *N,N*-dimethylhydrazine dropwise. After stirring for 15 minutes a solution of titanium tetrachloride (7.8 ml, 0.065 mole) in 73 ml of toluene was introduced dropwise. A brick-red precipitate was formed instantaneously. The reaction mixture was allowed to attain room temperature over 30 minutes, then refluxed at 100° (oil bath temperature) for 5 hours, at the end of which time tlc indicated complete disappearance of *o*-aminoacetophenone. The resulting white suspension was filtered and concentrated under reduced pressure leaving a wine-red liquid which was vacuum distilled and afforded 21.4 g (93%) of a yellow oil. The dihydrochloride salt was precipitated with ethanolic hydrogen chloride and recrystallized from absolute ethanol to give yellowish crystals, mp 189-192° dec; nmr of free base (deuteriochloroform): δ 2.4 (s, 3H, N=C-CH_3), 2.6 (s, 6H, $N(CH_3)_2$), 5.8-6.3 (broad s, 2H, Ar-NH_2, deuterium oxide exchangeable), 6.6-7.6 (m, 4H, ArH).

Anal. Calcd. for $C_{10}H_{17}Cl_2N_3$: C, 48.01; H, 6.85; N, 16.80. Found: C, 48.09; H, 6.92; N, 16.81.

4-Methyl-3-aminoquinazolines and 2,4-Dimethyl-3-aminoquinazolines **VIIa-f**.

General Procedure.

Diamines **VIa-c** were obtained by the reduction of hydrazones **Va-c** using 4 equivalents of Vitride in the same manner as for diamines **IIIa-i**. Cyclization was achieved with 6 equivalents each of glacial acetic acid and either triethyl orthoformate or triethyl orthoacetate by the procedure described for **IVa-l**. Oily products were converted in the usual way to either hydrochloride salts or picrates.

3-Dimethylamino-4-methyl-3,4-dihydroquinazoline Hydrochloride (**VIIa**).

Isolated as pale yellow crystals; nmr (deuterium oxide): δ 1.7 (d, 3H, CH_3), 3.0 (s, 6H, $N(CH_3)_2$), 5.5 (q, 1H, Ar-CH), 7.3-7.8 (m, 4H, ArH), 8.9 (s, 1H, N=CH).

4-Methyl-3-(*N*-piperidino)-3,4-dihydroquinazoline Hydrochloride (**VIIb**).

Isolated as a white crystalline solid; nmr (deuterium oxide): δ 1.5-2.1 (m, 9H, $(CH_2)_3$ and CH_3), 2.8-3.6 (m, 4H, $N(CH_2)_2$), 5.4 (q, 1H, Ar-CH), 7.2-7.7 (m, 4H, ArH), 8.85 (s, 1H, N=CH).

4-Methyl-3-(*N*-morpholino)-3,4-dihydroquinazoline (**VIIc**).

Isolated as white crystals after charcoal treatment; nmr (deuteriochloroform): δ 1.5 (d, 3H, CH_3), 2.8-3.3 (m, 4H, $N(CH_2)_2$), 3.7-4.1 (m, 4H, $O(CH_2)_2$), 4.95 (q, 1H, Ar-CH), 6.7-7.4 (m, 4H, ArH), 7.5 (s, 1H, N=CH).

2,4-Dimethyl-3-dimethylamino-3,4-dihydroquinazoline Picrate (**VIId**).

Isolated as yellow crystals; nmr (DMSO-d_6): δ 1.4 (d, 3H, CH_3), 2.57 (s, 3H, N=C-CH_3), 2.67 and 2.9 (two s, 6H, $N(CH_3)_2$), 5.5 (q, 1H, Ar-CH), 7.1-7.6 (m, 4H, ArH), 8.7 (s, 2H, ArH of Picrate).

2,4-Dimethyl-3-(*N*-piperidino)-3,4-dihydroquinazoline Picrate (**VIIe**).

Isolated as orange crystals; nmr (DMSO-d_6): δ 1.2-2.1 (m, 9H, $(CH_2)_3$ and CH_3), 2.6 (s, 3H, N=C-CH_3), 2.8-3.4 (m, 4H, $N(CH_2)_2$), 5.65 (q, 1H, Ar-CH), 7.2-7.7 (m, 4H, ArH), 8.7 (s, 2H, ArH or picrate).

2,4-Dimethyl-3-(*N*-morpholino)-3,4-dihydroquinazoline (**VIIf**).

Isolated at white crystals; nmr (deuteriochloroform): δ 1.3 (d, 3H, CH_3), 2.3 (s, 3H, N=C-CH_3), 2.8-3.3 (m, 4H, $N(CH_3)_2$), 3.6-4.1 (m, 4H, $O(CH_2)_2$), 4.9 (q, 1H, Ar-CH), 6.9-7.4 (m, 4H, ArH).

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