SYNTHESES OF SOME 4-DIALKYLAMINOALKYLAMINO DERIVATIVES OF 2,3-DIMETHYL-2*H*- AND 3,9-DIMETHYL-9*H*-PYRAZOLO[3,4-*b*]QUINOLINE

Stanislav RÁDL and Viktor ZIKÁN

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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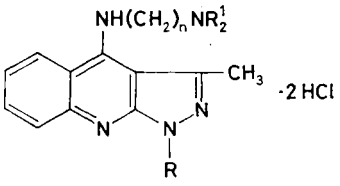
Reactions of 4-chloro-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline and 4-chloro-6-methoxy-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline with 3-dimethylaminopropylamine and/or 2-diethylaminoethylamine afforded 4-(3-dimethylaminopropylamino)-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline (*IIa*), its 6-methoxy derivative (*IIc*), 4-(2-diethylaminoethylamino)-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline (*IIb*) and its 6-methoxy derivative (*IId*). Reaction of 4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline with thionyl chloride gave an intermediate, whose reaction with 3-dimethylaminopropylamine afforded 4-(3-dimethylaminopropylamino)-3,9-dimethyl-9*H*-pyrazolo[3,4-*b*]quinoline (*III*). The compounds were tested *in vivo* in mice for efficacy against the A2-Hongkong influenza virus and the encephalomyocarditis virus.

Studying compounds with potential antiviral efficacy, we have also focussed our attention on a group of 4-dialkylaminoalkylamino derivatives of 1-alkyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline, of the general formula *I*, since such derivatives were reported to have induced interferon *in vivo* and to have exhibited antiviral activity[1-5]. Studies on the relation between structure and ability to induce the formation of interferon (or efficacy against interferon-sensitive viruses) reveal the key role of the substituents attached to position 1 of these compounds[1,5-7]. Compounds having hydrogen at this position proved to have no effect at all, the most efficacious ones had a methyl group at this position. With increasing bulkiness of the substituent attached to position 1 the efficacy steeply decreased. It seemed, therefore, interesting to us to synthetize such compounds as would have neither an acid hydrogen atom nor an alkyl group at this position. Compounds of types *II* and *III* comply with these requirements.

4-(3-Dimethylaminopropylamino)- (*IIa*) and 4-(2-diethylaminoethylamino)-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline (*IIb*) were obtained by the reaction of 4-chloro-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline with the corresponding dialkylaminoalkylamine in dimethylformamide, in the presence of anhydrous potassium carbonate.

Reaction of 4-(4-methoxyphenyl)thiosemicarbazide with ethyl 2-chloroacetatoacetate gave ethyl 3-(4-methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylate. Methyl-

ation of its sodium salt with methyl iodide produced ethyl 3-(4-methoxyanilino)--1,5-dimethyl-1*H*-pyrazole-4-carboxylate. The acid released by hydrolysis of this ester was cyclized by the action of phosphorus oxychloride to 4-chloro-6-methoxy--2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline which was used to obtain compounds *IIc* and *IId*.



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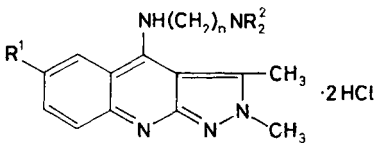
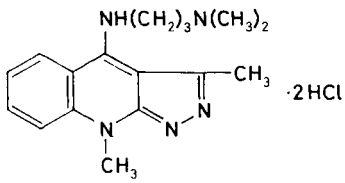


II a, R^1= H; R^2= CH_3; n = 3
II b, R^1= H; R^2= C_2H_5; n = 2
II c, R^1= OCH_3; R^2= CH_3; n = 3
II d, R^1= OCH_3; R^2= C_2H_5; n = 2



III

The intermediate formed by heating 4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo-[3,4-*b*]quinoline with thionyl chloride reacted with 3-dimethylaminopropylamine to 4-(3-dimethylaminopropylamino)-3,9-dimethyl-9*H*-pyrazolo[3,4-*b*]quinoline (*III*). The starting 4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline[8,9] was obtained by reaction of 4-phenyl-4-methylthiosemicarbazide with ethyl 2-chloro-acetoacetate, followed by cyclization of the formed 3-(N-methylanilino)-5-methyl--1*H*-pyrazole-4-carboxylic acid by the action of polyphosphoric acid. The starting 4-phenyl-4-methylthiosemicarbazide was obtained from N-methylaniline *via* 2-(N--phenyl-N-methyl-thiocarbamoylthio)acetic acid.

Compounds *IIa–d* and *III* were tested *in vivo* in mice for their efficacy against the A2-Hongkong influenza virus and the encephalomyocarditis (EMC) virus after *p.o.* and *s.c.* administration. The tests were carried out as described before[8] at the Virological Department of the Institute (head: Dr F. Šmejkal). None of the compounds tested exhibited any significant antiviral effect.

EXPERIMENTAL

The melting points, determined in an apparatus Mettler FP5, are not corrected. The IR spectra were measured in an apparatus Perkin–Elmer 577, the UV spectra in Perkin–Elmer 550 S. The ^{1}H NMR spectra were measured in an apparatus BS-487 C (Tesla Brno) 80 MHz; the standard was tetramethylsilane, unless otherwise stated.

4-(3-Dimethylaminopropylamino)-2,3-dimethyl-2*H*-pyrazolo-[3,4-*b*]quinoline Dihydrochloride (*IIa*)

A suspension of 4-chloro-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline (1·6 g, 7 mmol), anhydrous potassium carbonate (1·0 g, 7 mmol), and 3-dimethylaminopropylamine (0·8 g, 7·8 mmol) in 30 ml of dimethylformamide was stirred for 12 h at 100°C. The insoluble portion was removed by filtration, the filtrate was taken to dryness, the residue was dissolved in ethanol and acidified with an ethanolic solution of hydrogen chloride. The crystals that separated after cooling were collected on a filter and recrystallized from 90% aqueous ethanol; yield 2·1 g (81%), m.p. 262·3–264·6°C. For $C_{17}H_{23}N_5 \cdot 2\,HCl$ (370·3) calculated: 55·14% C, 6·60% H, 18·91% N, 19·17% Cl; found: 55·09% C, 6·60% H, 19·20% N, 18·90% Cl. UV spectrum (ethanol): λ_{max} 213 nm ($\log \varepsilon$ = 4·21), 248 nm (4·70), 300 nm (4·15). ^{1}H NMR spectrum (^2H_2O): 7·10–8·00 (m, 4 H, 5,6,7,8-H), 4·00 (s, 3 H, NCH_3), 3·98 (m, 2 H, $NHCH_2$), 3·10 (s, 6 H, $N(CH_3)_2$), 2·80 (s, 3 H, CH_3), 2·50 (m, 2 H, CH_2).

4-(2-Diethylaminoethylamino)-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]-quinoline Dihydrochloride (*IIb*)

This was prepared by a procedure analogous to that for *IIa*, with the use of 2-diethylaminoethylamine; yield 78%, m.p. 234·8–239·2°C. For $C_{18}H_{25}N_5 \cdot 2\,HCl \cdot 2\,H_2O$ (418·4) calculated: 51·55% C, 7·21% H, 16·70% N, 16·91% Cl; found: 51·25% C, 7·07% H, 16·85% N, 16·84% Cl.

4-(4-Methoxyphenyl)thiosemicarbazide

To a stirred solution of 4-methoxyaniline (369·5 g, 3 mol) in 500 ml of ethanol was added 240 ml of conc. aqueous ammonia, then carbon disulphide (228 g, 3 mol) was added dropwise in the course of 15 min. The mixture was stirred for 1 h at room temperature. A solution obtained by dissolving chloroacetic acid (283·5 g, 3 mol) in 600 ml of water and neutralized with sodium carbonate (159 g, 1·5 mol) was added. The mixture was stirred 1 h at room temperature, then 80% hydrazine hydrate (225 ml, 3·6 mol) was added dropwise and the stirring was continued for additional 4 h. The crystals obtained after cooling were collected on a filter and recrystallized from ethanol; yield 508·5 g (86%), m.p. 152·1–153·9°C. Reported m.p. 144°C (ref.[10]) and 154°C (ref.[11]). For $C_8H_{11}N_3OS$ (197·3) calculated: 48·71% C, 5·62% H, 21·30% N, 16·25% S; found: 49·24% C, 5·74% H, 21·40% N, 16·41% S. IR spectrum (KBr): 3 300 (ArNH), 3 180 (NH, NH_2), 2 820 (OCH_3), 1 640 (NH_2), 1 575, 1 550, 1 535 (aromat. vibration), 1 240 (Ar—O—C), 1 038 (R—O—C), 830 cm^{-1} (*para*-subst. aromate).

Ethyl 3-(4-Methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylate

To a stirred suspension of 4-(4-methoxyphenyl)thiosemicarbazide (197 g, 1 mol) in 700 ml of ethanol was added a solution of ethyl 2-chloroacetoacetate (170 g, 1·03 mol) in 250 ml of ethanol. The mixture was stirred 2 h at room temperature, then left standing overnight in a refrigerator. The insoluble portion was collected on a filter and recrystallized from ethanol, the separated sulphur was removed by filtration; yield 170·5 g, m.p. 151·4–151·6°C. The mother liquor was concentrated to a third of its volume and the separated crystals were collected on a filter (30·5 g,

m.p. 150·4—151·4°C). The overall yield was 73%. For $C_{14}H_{17}N_3O_3$ (275·3) calculated: 61·08% C, 6·23% H, 15·26% N; found: 60·98% C, 6·29% H, 15·39% N. ^{1}H NMR spectrum (C^2HCl_3): 10·85 (bs, 1 H, pyrazole NH), 7·98 (bs, 1 H, NH), 7·30 (d, 2 H, J = 8·5 Hz, 2,6-H of aniline), 6·75 (d, 2 H, J = 8·5 Hz, 3,5-H of aniline), 4·20 (q, 2 H, J = 7·0 Hz, CH_2), 3·70 (s, 3 H, CH_3O), 2·22 (s, 3 H, CH_3), 1·35 (t, 3 H, J = 7·0 Hz, CH_3CH_2).

Ethyl 3-(4-Methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylate

To a stirred solution of ethyl 3-(4-methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylate (20·65 g, 75 mmol) in 100 ml of dimethylformamide under nitrogen was added 80% sodium hydride (2·5 g, 83 mmol) and the mixture was stirred 1 h at room temperature. Methyl iodide (11·8 g, 83 mmol) was then added dropwise in the course of 30 min and the stirring at room temperature was continued for 2 more h. The solvent was removed and the residue was recrystallized from ethanol; yield 20·6 g (95%), m.p. 121·2—121·6°C. For $C_{15}H_{19}N_3O_3$ (289·3) calculated: 62·27% C, 6·62% H, 14·52% N; found: 62·22% C, 6·77% H, 14·57% N. ^{1}H NMR spectrum (C^2HCl_3): 8·02 (bs, 1 H, NH), 7·41 (d, 2 H, J = 8·5 Hz, 2,6-H of aniline), 6·80 (d, 2 H, J = = 8,5 Hz, 3,5-H of aniline), 4·28 (q, 2 H, J = 7·0 Hz, CH_2), 3·70 (s, 3 H, CH_3O), 3·65 (s, 3 H, NCH_3), 2·40 (s, 3 H, CH_3), 1·35 (t, 3 H, J = 7·0 Hz, CH_3CH_2).

3-(4-Methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylic Acid

To a stirred solution of ethyl 3-(4-methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylate (7·2 g, 25 mmol) in 100 ml of ethanol was added at 50°C a solution of sodium hydroxide (10 g) in 125 ml of water and the mixture was refluxed for 2 h. After cooling to 50°C the solution was acidified with concentrated hydrochloric acid. The crystals that separated from the cold solution were collected on a filter and washed with water; yield 5·4 g (83%),m.p. 190·5—191·0°C. For $C_{13}H_{15}N_3O_3$ (261·3) calculated: 59·76% C, 5·79% H, 16·08% N; found: 59·79% C, 5·86% H, 16·22% N. IR spectrum (KBr): 3 320 (NH), 2 830 (NCH_3, OCH_3), 2 550 (COOH), 1 650 (CO), 1 595, 1 550, 1 505 (aromat. vibration), 1 240 (C—O—Ar), 1 030 (C—O—R), 810 cm^{-1} (*para*-subst. aromate).

4-Chloro-6-methoxy-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline

A mixture of 3-(4-methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylic acid (7·8 g, 30 mmol) and phosphorus oxychloride (70 ml) was refluxed for 30 min. The excessive phosphorus oxychloride was distilled off, the sirupy residue was mixed with ice and alkalinized with 20% NaOH. The insoluble portion was collected on a filter, washed with water and recrystallized from ethyl acetate; yield 6·1 g (78%), m.p. 218·0—219·5°C. For $C_{13}H_{12}ClN_3O$ (261·7) calculated: 59·66% C, 4·62% H, 13·54% Cl, 16·05% N; found: 59·80% C, 4·65% H, 13·29% Cl, 16·19% N.

4-(3-Dimethylaminopropylamino)-6-methoxy-2,3-dimethyl-2*H*-pyrazolo-[3,4-*b*]quinoline Dihydrochloride (*IIc*)

A mixture of 4-chloro-6-methoxy-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline (1·8 g, 7 mmol), anhydrous potassium carbonate (1 g, 7 mmol) and 3-dimethylaminopropylamine (0·8 g, 7·8 mmol) in 30 ml of dimethylformamide was stirred for 12 h at 130°C. The solid portion was filtered off, the filtrate was taken to dryness, the residue was dissolved in ethanol and acidified with an ethanolic solution of hydrogen chloride. The product, which crystallized after cooling, was twice recrystallized from 90% aqueous ethanol; yield 1·1 g (39%), m.p. 198·9—202·3°C. For $C_{18}H_{25}N_5O \cdot 2\,HCl \cdot H_2O$ (418·4) calculated: 51·67% C, 6·99% H, 16·95% Cl, 16·74% N; found: 51·37% C, 6·91% H, 16·58% Cl, 16·41% N.

4-(2-Diethylaminoethylamino)-6-methoxy-2,3-dimethyl-2*H*-pyrazolo[3,4-*b*]quinoline Dihydrochloride (*IId*)

This was obtained, with the use of 2-diethylaminoethylamine, by a procedure analogous to that for *IIc*; yield 38%, m.p. 199·5–206·0°C. For $C_{19}H_{27}N_5O \cdot 2\,HCl \cdot H_2O$ (432·4) calculated: 52·78°C, 7·23% H, 16·40% Cl, 16·20% N; found: 52·37% C, 6·87% H, 16·21% Cl, 15·76% N.

2-(N-Phenyl-N-methyl-thiocarbamoylthio)acetic Acid

To a stirred solution of N-methylaniline (214 g, 2 mol), 640 ml of ethanol, and 320 ml of concentrated aqueous ammonia was added carbon disulphide (152 g, 2 mol) and the mixture was stirred 4 h at room temperature. A solution obtained by neutralization of chloroacetic acid (189 g, 2 mol) in 400 ml of water with sodium carbonate (106 g, 1 mol) was then added to the mixture and stirring was continued for 8 h at room temperature. After acidification with concentrated hydrochloric acid and cooling the separated product was collected on a filter and washed with water; yield 283 g (59%), m.p. 188·6–189·4°C. For $C_{10}H_{11}NS_2O_2$ (241·2) calculated: 49·77% C, 4·59% H, 5·80% N, 26·57% S; found: 49·64% C, 4·58% H, 5·90% N, 26·11% S. IR spectrum (KBr): 2 600 (COOH), 1 720, 1 695 (CO), 1 580 cm^{-1} (aromatic vibration).

4-Phenyl-4-methyl-thiosemicarbazide

To a solution of 2-(N-phenyl-N-methyl-thiocarbamoylthio)acetic acid (193 g, 0·8 mol) in 300 ml of ethanol and 160 ml of concentrated aqueous ammonia was added 80% hydrazine hydrate (82 g, 1·3 mol). The mixture was stirred 8 h at room temperature and left standing overnight. The separated crystals were collected on a filter (104 g), the filtrate was left standing for a fortnight and another crop of crystals (21 g) was obtained. The combined portions were recrystallized from ethanol; yield 111 g (76%), m.p. 116·8–117·2°C. For $C_8H_{11}N_3S$ (181·3) calculated: 53·01% C, 6·12% H, 23·18% N, 17·69% S; found: 52·73% C, 6·20% H, 22·93% N, 17·28% S. IR spectrum (KBr): 3 200 (NH, NH_2), 2 860 (NCH_3), 1 630 (NH_2), 1 580 cm^{-1} (aromatic vibration).

4,9-Dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline

Ethyl 2-chloroacetoacetate (51 g, 0·31 mol) was added to a stirred suspension of 4-phenyl-4-methyl-thiosemicarbazide (54 g, 0·3 mol) in 1·5 l of ethanol and the mixture was stirred 1 h at room temperature, then refluxed for 30 min. Five g of activated carbon was added and the mixture was refluxed for additional 15 min. The filtrate was taken to dryness and the residue was mixed with 450 g of polyphosphoric acid containing 85% of phosphorus pentoxide. The mixture was stirred for 1 h at 95°C, poured into 4 l of water and briefly boiled with 10 g of activated carbon. The filtrate was cooled down and left standing overnight in a refrigerator. The separated product was collected on a filter and recrystallized from ethanol; yield 16·7 g (26%), m.p. 248·5–249·2°C. The IR and UV spectra were identical with those of another sample of the compound, obtained in a different way[8].

4-(3-Dimethylaminopropylamino)-3,9-dimethyl-9*H*-pyrazolo[3,4-*b*]-quinoline Dihydrochloride (*III*)

A mixture of 4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (1·6 g, 7·5 mmol) and thionyl chloride (25 ml) was refluxed for 1 h. After evaporation of thionyl chloride the residue was taken into 25 ml of tetrachloromethane and the mixture was taken to dryness again. The residue was dissolved in 25 ml of dimethylformamide, anhydrous potassium carbonate

(1·6 g, 11 mmol) and 3-dimethylaminopropylamine (0·9 g, 9 mmol) were added and the mixture was stirred 2 h at 120°C. The insoluble solid was removed by filtration and the filtrate was taken to dryness. The residue was dissolved in ethanol, briefly boiled with activated carbon and acidified with an ethanolic solution of hydrogen chloride. The crystals that separated after cooling were collected on a filter and twice recrystallized from ethanol; yield 0·95 g (34%), m.p. 282·5–286·5°C (decomp.). For $C_{17}H_{23}N_5 \cdot 2\,HCl$ (370·3) calculated: 55·14% C, 6·80% H, 19·15% Cl, 18·91% N; found: 54·81% C, 6·76% H, 18·75% Cl, 18·67% N. ^{1}H NMR spectrum (^2H_2O, 85°C, sodium salt of 3-trimethylsilylpropionic acid): 7·40–8·40 (m, 4 H, 5, 6, 7, 8-H), 4·10 (t, 2 H, J = 7·0 Hz, $NHCH_2$), 3·85 (s, 3 H, NCH_3), 3·45 (t, 2 H, J = 7·0 Hz, CH_2N), 3·10 (s, 6 H, $N(CH_3)_2$), 2·90 (s, 3 H, CH_3), 2·50 (m, 2 H, CH_2).

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REFERENCES

1. Crenshaw R. R., Luke G. M., Siminoff P.: J. Med. Chem. *19*, 262 (1976).
2. Siminoff P., Crenshaw R. R.: Antimicrob. Agents Chemother. *11*, 571 (1977).
3. Kern E. R., Hamilton J. R., Overall J. C., Glasgow L. A.: Antimicrob. Agents Chemother. *10*, 691 (1976).
4. Siminoff P., Bernard A. M., Hursky V. S., Price K. E.: Antimicrob. Agents Chemother. *3*, 742 (1973).
5. Rádl S., Roubínek F., Šmejkal F., Zikán V.: Česk. Farm. *34*, 190 (1985).
6. Rádl S., Zikán V.: Česk. Farm. *32*, 257 (1983).
7. Rádl S., Zikán V.: Drugs Fut. *10*, 215 (1985).
8. Rádl S., Zikán V., Šmejkal F.: This Journal *50*, 1057 (1985).
9. De Wald H. A.: J. Heterocycl. Chem. *11*, 1061 (1974).
10. Busch M., Ulmer T.: Ber. Dtsch. Chem. Ges. *35*, 1710 (1902).
11. Tišler M.: Croat. Chem. Acta *28*, 147 (1956).

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