SYNTHESES OF 1,2, AND 9-METHYL DERIVATIVES OF 4,9-DIHYDRO-6-METHOXY-3-METHYL-4-OXO-1*H*(2*H*)-PYRAZOLO-[3,4-*b*]QUINOLINE AND 4,9-DIHYDRO-6-HYDROXY-3-METHYL-4--OXO-1*H*(2*H*)-PYRAZOLO[3,4-*b*]QUINOLINE AND THEIR ANTIVIRAL ACTIVITY

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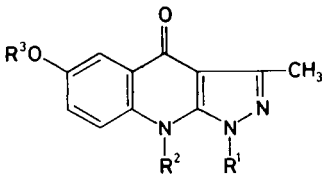
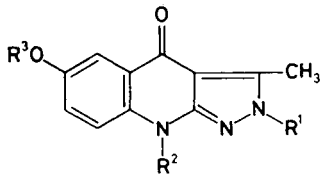
The paper describes syntheses of 4,9-dihydro-6-methoxy-3-methyl-4-oxo-1*H*(2*H*)-pyrazolo[3,4-*b*]-quinoline (*Ia*), its 1-methyl derivative (*Ic*), 1,9-dimethyl derivative (*Ie*), 2-methyl derivative (*IIa*), and 2,9-dimethyl derivative (*IIc*). Demethylation of these compounds with hydrobromic acid afforded 4,9-dihydro-6-hydroxy-3-methyl-4-oxo-1*H*(2*H*)-pyrazolo[3,4-*b*]quinoline (*Ib*), its 1--methyl derivative (*Id*), 1,9-dimethyl derivative (*If*), 2-methyl derivative (*IIb*), and 2,9-dimethyl derivative (*IId*) respectively. 4,9-Dihydro-6-hydroxy-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]-quinoline (*Ig*) was prepared by demethylation of *Ie* and/or *IIc* with pyridine hydrochloride. The compounds prepared were tested for antiviral activity *in vivo* in mice against influenza virus A2-Hongkong and encephalomyocarditis virus.

Some methyl derivatives of 4,9-dihydro-3-methyl-4-oxo-1*H*(2*H*)pyrazolo[3,4-*b*]-quinoline posses antiviral activity[1]. We describe now the preparation of their 6--methoxy and 6-hydroxy derivatives *Ia*–*Ig*, *IIa*–*IId*.

Compound *Ia* was obtained from 3-(4-methoxyanilino)-5-methyl-1*H*-pyrazole-4-



Ia, $R^1 = R^2 = H$; $R^3 = CH_3$
Ib, $R^1 = R^2 = R^3 = H$
Ic, $R^1 = R^3 = CH_3$; $R^2 = H$
Id, $R^1 = CH_3$; $R^2 = R^3 = H$
Ie, $R^1 = R^2 = R^3 = CH_3$
If, $R^1 = R^2 = CH_3$; $R^3 = H$
Ig, $R^1 = R^3 = H$; $R^2 = CH_3$



IIa, $R^1 = R^3 = CH_3$; $R^2 = H$
IIb, $R^1 = CH_3$; $R^2 = R^3 = H$
IIc, $R^1 = R^2 = R^3 = CH_3$
IId, $R^1 = R^2 = CH_3$; $R^3 = H$

-carboxylic acid by ring closure effected with polyphosphoric acid. Similarly, compound *IIa* was prepared from 3-(4-methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4--carboxylic acid[2]. 4-Chloro-6-methoxy-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline was obtained from 3-(4-methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylic acid by cyclization with phosphorus oxychloride. Methylation of this compound with dimethylsulphate in dimethyl sulphoxide in the presence of powdered potassium hydroxide yielded 4-chloro-6-methoxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]quinoline, which was converted into *Ic* by boiling in dilute hydrochloric acid. Methylation of the sodium salt of *Ic* with methyl iodide in dimethylformamide at room temperature gave *Ie*. Similarly, methylation of the sodium salt of *IIa* afforded *IIc*.

The 6-methoxy derivatives *Ia*, *Ic*, *Ie*, *IIa*, and *IIc* were demethylated with hydrobromic acid to the corresponding 6-hydroxy derivatives *Ib*, *Id*, *If*, *IIb*, and *IId* respectively. This reagent removes aromatic methoxy groups without affecting N-methyl groups. It is well known[3,4] that both aromatic methoxy groups and N--methyl groups on the pyrazole nucleus are demethylated with pyridine hydrochloride. The reagent proved to be useful for the preparation of 4,9-dihydro-3,9--dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline from 4,9-dihydro-1,3,9-trimethyl-4--oxo-1*H*-pyrazolo[3,4-*b*]quinoline and/or from 4,9-dihydro-2,3,9-trimethyl-4-oxo--2*H*-pyrazolo[3,4-*b*]quinoline[1]. Application of this method to the demethylation of *Ie* and *IIc* gave only poor yields of *Ig* (34%, 22% respectively); tar products prevailed. The yields of *Ig* were no better when the demethylation was performed with *If* or *IId*[5].

The presence of an absorption band in the region 334–340 nm is characteristic of 4,9-dihydro-3-methyl-4-oxo-1*H*(2*H*)-pyrazolo[3,4-*b*]quinoline derivatives alkylated in the position 1. Derivatives having an alkyl group in the position 2 have this maximum at 365–370 nm refs[1,6]. Introduction of methoxy or hydroxy group into the position 6 shifts this band to 365–375 nm (1-methyl derivatives), or 394–398 nm (2-methyl derivatives).

The compounds *Ia–Ig*, *IIa–IId* were tested *in vivo* for their effects against influenza virus A2-Hongkong and encephalomyocarditis virus (EMC) after peroral and subcutaneous administration to mice[1]. These tests were performed at the Virology Department of our Institute (Head: Dr F. Šmejkal). Significant effect was found only for *Ia* which, administered s.c. to mice infected with 50 LD_{50} of EMC virus, extended the survival time by 80–100%. The efficacy of this compound is comparable with that of 4-(3-dimethylaminopropylamino)-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]-quinoline dihydrochloride (BL-20803) in the same test.

EXPERIMENTAL

The melting points were determined in a Mettler apparatus FP 5, those higher than 300°C were determined on a Kofler block and are not corrected. The UV spectra were taken with a spectro-

photometer Perkin–Elmer 550 S in ethanol, molar absorption coefficients are given in $m^2\ mol^{-1}$. The mass spectra were measured on MCH 1320 and MAT 44 S spectrometers.

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

To a solution of ethyl 3-(4-methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylate (ref.[2]) (6·9 g, 25 mmol) in ethanol (100 ml) a solution of sodium hydroxide (10 g) in water (125 ml) was added. The mixture was refluxed for 8 h, cooled and acidified with conc. hydrochloric acid. The solid was filtered off and washed with water; yield 5·1 g (82%), m.p. 181—183°C. For $C_{12}H_{13}N_3O_4$ (247·25) calculated: 58·29% C, 5·30% H, 16·99% N; found: 57·95% C, 5·54% H, 16·90% N.

4,9-Dihydro-6-methoxy-3-methyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ia*)

A mixture of 3-(3-methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylic acid (7·4 g, 30 mmol) and polyphosphoric acid (50 g, 85% P_2O_5) was stirred for 4 h at 90°C. After addition of water (300 ml) the mixture was cooled and the separated solid was collected by filtration, washed with water and crystallized from 50% aqueous dimethylformamide. Yield 6·6 g (96%), not melting up to 360°C. For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 62·73% C, 4·92% H, 17·93% N. UV spectrum: λ_{max} 212 nm (log ε 3·10), 241 (3·73), 285 (2·93), 356 (sh), 372 (2·77).

4,9-Dihydro-6-methoxy-2,3-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIa*)

This compound was obtained from 3-(4-methoxyanilino)-1,5-dimethyl-1*H*-pyrazole-4-carboxylic acid according to the procedure described for the preparation of *Ia*; yield 79%, m.p. 326—328°C. For $C_{13}H_{13}N_3O_2$ (243·3) calculated: 64·19% C, 5·38% H, 17·27% N; found: 63·81% C, 5·52% H, 17·33% N. UV spectrum: λ_{max} 210 nm (log ε 3·10), 241 (3·72), 286 (sh), 292 (3·07), 394 (2·88).

4-Chloro-6-methoxy-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline

A mixture of 3-(4-methoxyanilino)-5-methyl-1*H*-pyrazole-4-carboxylic acid (4·5 g, 18 mmol) and phosphorus oxychloride (40 ml) was refluxed for 1 h. The cooled mixture was concentrated under reduced pressure to a syrup which was poured on ice. The mixture was basified with 4M-NaOH, cooled and washed with water. Recrystallization from chloroform gave 4·25 g of yellow crystals (94%), m.p. 232—236°C. For $C_{12}H_{10}ClN_3O$ (247·7) calculated: 58·19% C, 4·07% H, 16·96% N, 14·31% Cl, found: 58·60% C, 4·11% H, 17·08% N, 14·25% Cl.

4-Chloro-6-methoxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]quinoline

To a suspension of 4-chloro-6-methoxy-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline (9·9 g, 40 mmol) in dimethyl sulphoxide (100 ml) powdered potassium hydroxide was added (2·5 g, 45 mmol) and the mixture was stirred for 4 h at room temperature. Dimethyl sulphate (5·6 g, 45 mmol) was added and the mixture was stirred for 8 h at room temperature. The mixture was poured into water and the separated solid was filtered off and washed with water. The crude product was purified by sublimation *in vacuo*; yield 8·0 g (76%), m.p. 128—133°C (sublim.). For $C_{13}H_{12}ClN_3O$ (261·7) calculated: 59·66% C, 4·62% H, 16·06% N, 13·55% Cl; found: 59·74% C, 4·60% H, 15·66% N, 13·43% Cl.

4,9-Dihydro-6-methoxy-1,3-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ic*)

A mixture of 4-chloro-6-methoxy-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]quinoline (2·6 g, 10 mmol) and 2M-hydrochloric acid (25 ml) was stirred under reflux for 6 h. After cooling the solid was

filtered off and crystallized from ethanol; yield 1·95 g (75%), m.p. 306–310°C. For $C_{13}H_{13}N_3O_2 \cdot .H_2O$ (261·3) calculated: 59·76% C, 5·79% H, 16·08% N; found: 59·44% C, 5·44% H, 16·29% N. UV spectrum: λ_{max} 211 nm (log ε 3·17), 242 (3·62), 289 (2·80), 335 (2·76), 369 (2·75).

4,9-Dihydro-6-methoxy-1,3,9-trimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ie*)

Sodium hydride (80%, 2·2 g, 73 mmol) was added to a stirred suspension of *Ic* (thoroughly dried under reduced pressure; 16·6 g, 68 mmol) in dimethylformamide (330 ml) and the mixture was stirred under nitrogen for 1 h. Methyl iodide (14·5 g, 0·1 mol) was added dropwise and the stirring was continued at room temperature for 4 h. The mixture was poured into water and left to stand overnight in a refrigerator. The separated solid was filtered off, washed with water and crystallized from ethanol; yield 10·9 g (63%), m.p. 227–228°C. For $C_{14}H_{15}N_3O_2$ (257·3) calculated: 65·38% C, 5·88% H, 16·33% N; found: 65·40% C, 5·91% H, 16·33% N. UV spectrum: λ_{max} 219 nm (log ε 3·24), 245 (3·65), 294 (2·75), 358 (2·84), 372 (2·84).

4,9-Dihydro-6-methoxy-2,3,9-trimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIc*)

The title compound was obtained from *IIa* according to the procedure described for the preparation of *Ie*; yield 94%, m.p. 191–193°C. For $C_{14}H_{15}N_3O_2$ (257·3) calculated: 65·38% C, 5·88% H, 16·33% N; found: 65·67% C, 5·99% H, 16·65% N. UV spectrum: λ_{max} 210 nm (log ε 3·07), 243 (3·73), 287 (*sh*), 294 (3·05), 395 (2·89).

General Procedure for Demethylation of *Ia*, *Ic*, *Ie*, *IIa*, and *IIc* by Hydrobromic Acid

A mixture of the 6-methoxy derivative (7·5 mmol) and 48% hydrobromic acid (25 ml) was refluxed for 8 h, poured into water and cooled. The separated product was filtered off and crystallized from an appropriate solvent.

4,9-*Dihydro*-6-*hydroxy*-3-*methyl*-4-*oxo*-1*H*-*pyrazolo*[3,4-*b*]*quinoline* (Ib) was prepared from *Ia*; yield 53%; not melting up to 360°C (50% aqueous dimethylformamide). For $C_{11}H_9N_3O_2$ (215·2) calculated: 61·39% C, 4·21% H, 19·53% N; found: 60·97% C, 4·42% H, 19·14% N. UV spectrum: λ_{max} 210 nm (log ε 3·04), 237 (3·71), 273 (2·76), 285 (2·90), 355 (sh), 395 (sh).

4,9-*Dihydro*-6-*hydroxy*-1,3-*dimethyl*-4-*oxo*-1*H*-*pyrazolo*[3,4-*b*]*quinoline* (Id) was prepared from *Ic*; yield 68%; not melting up to 360°C (50% aqueous dimethylformide). For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 62·57% C, 5·03% H, 18·61% N. UV spectrum: λ_{max} 238 nm (log ε 3·66), 285 (2·84), 355 (2·80), 369 (2·80).

4,9-*Dihydro*-6-*hydroxy*-1,3,9-*trimethyl*-4-*oxo*-1*H*-*pyrazolo*[3,4-*b*]*quinoline* (If) was prepared from *Ie*; yield 80%; m.p. 336–340°C (ethanol). For $C_{13}H_{13}N_3O_2$ (243·2) calculated: 64·19% C, 5·28% H, 17·27% N; found: 63·87% C, 5·47% H, 17·14% N. UV spectrum: λ_{max} 219 nm (log ε 3·20), 294 (3·66), 364 (2·89), 375 (2·89).

4,9-*Dihydro*-6-*hydroxy*-2,3-*dimethyl*-4-*oxo*-2*H*-*pyrazolo*[3,4-*b*]*quinoline* (IIb) was prepared from *IIa*; yield 83%; not melting up to 360°C (50% aqueous dimethylformamide). For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 62·56% C, 4·72% H, 17·92% N. UV spectrum: λ_{max} 210 nm (log ε 3·19), 242 (3·71), 286 (sh), 293 (3·05), 396 (2·84).

4,9-*Dihydro*-6-*hydroxy*-2,3,9-*trimethyl*-4-*oxo*-2*H*-*pyrazolo*[3,4-*b*]*quinoline* (IId) was prepared from *IIc*; yield 79%, m.p. 338–341°C (ethanol). For $C_{13}H_{13}N_3O_2$ (243·2) calculated: 64·19% C, 5·38% H, 17·27% N; found: 64·59% C, 5·60% H, 17·27% N. UV spectrum: λ_{max} 210 nm (log ε 3·08), 242 (3·74), 287 (sh), 298 (3·05), 398 (2·90). Mass spectrum (*m/z*): 243 (M^+).

4,9-Dihydro-6-hydroxy-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ig*)

A) A stirred mixture of pyridine (20 g) and conc. hydrochloric acid (30 ml) was gradually heated to 160°C to remove water. At this temperature *IIc* (5·1 g, 20 mmol) was added and the mixture was stirred at 220°C for 10 h. The mixture was poured into water (150 ml), boiled with charcoal and filtered. The filtrate was cooled and the separated crystals were collected by filtration, washed with cold water and crystallized from ethanol; yield 1·1 g (22%), m.p. 343—348°C. For $C_{12}H_{11}N_3O_2$ (247·2) calculated: 58·29% C, 5·30% H, 16·99% N; found: 57·99% C, 5·34% H, 17·15% N. UV spectrum: λ_{max} 211 nm (log ε 2·99), 242 (3·67), 292 (2·84), 377 (2·74), 402 (2·75).

B) A mixture of anhydrous pyridine hydrochloride (40 g), obtained according to ref.[7], and *Ie* (2·0 g, 7·8 mmol) was stirred under nitrogen at 220°C for 4 h. The work-up procedure described under *A*) gave 0·65 g of *Ig* (34%), m.p. 343—348°C.

The elemental analyses were carried out by Mrs J. Komancová and Mrs V. Šmídová (Head: Dr J. Körbl). The UV *spectra were interpreted by Dr B. Kakáč, the mass spectra were measured and interpreted by Drs M. Ryska and I. Koruna.*

REFERENCES

1. Rádl S., Zikán V., Šmejkal F.: This Journal *50*, 1057 (1985).
2. Rádl S., Zikán V.: This Journal *51*, 1692 (1986).
3. Royer R., Demerseman P.: Bull. Soc. Chim. Fr. *1968*, 2633.
4. Rádl S.: Chem. Listy *79*, 1233 (1985).
5. Rádl S.: unpublished results.
6. Rádl S., Zikán V., Šmejkal F.: This Journal *50*, 2010 (1985).
7. Fieser M., Fieser L. F.: *Reagents for Organic Synthesis*, Vol. 3, p. 352. Wiley, New York 1960.

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