Synthesis of 7,8-Dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones and Related Derivatives [1]

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This paper describes the synthesis of a new series of 4-amino-1-(unsubstituted and chloro or fluoro substituted benzyl)-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones **8** and the corresponding 7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-diones **13**. The derivatives obtained by reaction of these compounds with sodium azide in concentrated sulfuric acid are also reported.

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It has been reported in the patent literature [2,3] that fused heterocyclic aminoquinolinols **1** exhibited a considerable activity as anxiolytics and as memory enhancers. Furthermore, these compounds are related to 9-amino-1,2,3,4-tetrahydroacridin-1-ol **2**, a potential Alzheimer's disease therapeutic of low toxicity, which displayed a promising efficacy in the initiation of large-scale clinical trials [4].

1 2

x= =N-AlKyl, S,O.

y= =N- ,=CH-.

Figure 1

On the basis of these reports, as continuation of our programme directed to the preparation of fused-ring species derived from pyrazole [5], we here describe the synthesis of some 4-amino-1-(unsubstituted and chloro or fluoro substituted benzyl)-7,8-dihydro-6*H*-pyrazolo [3,4-*b*]quinolin-5-ones and of the corresponding 7,8-dihydro-6*H*-,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-diones and related derivatives, in order to verify their potential activity in cognitive disorders.

The syntheses are outlined in Scheme 1.

Our synthetic route to 4-amino derivatives **8** was similar in many respects to the one used for the synthesis of compound **2** [6]. The condensation of 5-amino-4-cyanopyrazoles **3** with 1,3-cyclohexanedione in refluxing toluene and in the presence of *p*-toluenesulfonic acid, afforded the enamino ketones **5**. The latter ones were then cyclized in refluxing tetrahydrofuran with potassium carbonate and copper chloride as catalyst, to give the 4-amino-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones **8**.

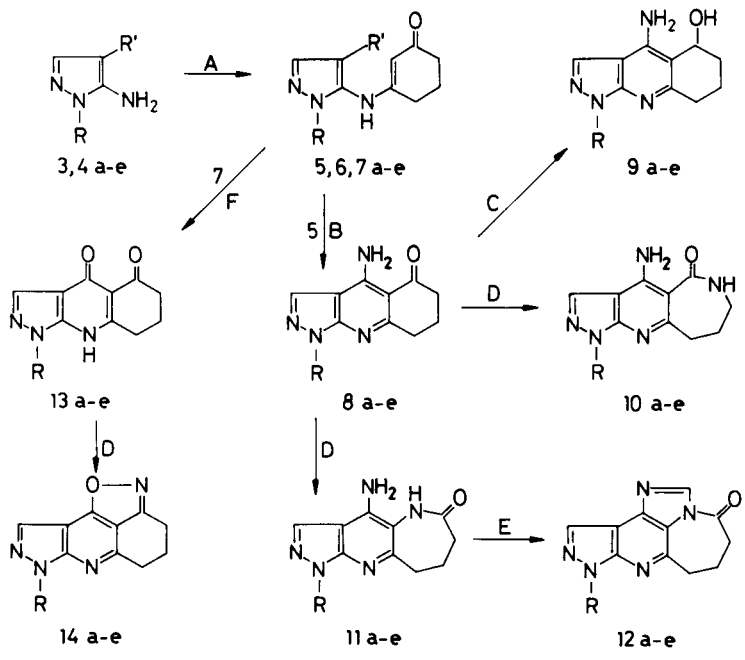
Reduction of **8** with sodium borohydride in warm aqueous dioxane gave the corresponding 5,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolinols **9**.

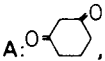
Ketones **8**, underwent the Schmidt reaction with sodium azide in chloroform and concentrated sulfuric acid affording a 1:3 mixture of the isomeric lactames **10** and **11**. The structure of these compounds was supported by chemical and spectral evidence. Comparison of their ir carbonyl absorption band showed a small but significant difference between **10** (ν, 1650 cm^{-1}) and **11** (ν, 1670 cm^{-1}) in agreement with the $\Delta\nu$ CO value between the anilides, with the carbonyl stretching band at higher frequency, and the corresponding benzamides. In the nmr spectra, the difference between chemical shifts of the C-7 methylene group of **10** (*ca* δ 2.95) and **11** (*ca* δ 2.15) was in agreement with the view that a methylene, next to the carbonyl function in a lactam group absorbs at a higher field when compared to a similar methylene group next to NH function of the lactam group. Moreover compounds **10** showed a broad amide NH signal at *ca* δ 7.95 shifted upfield from the signal observed at *ca* δ 8.40 in the other isomers **11**. The proposed structure for compounds **11** was further supported by the fact that, in our hands, cyclization of **11** with refluxing triethylorthoformate, easily provided the imidazo derivatives **12**, whose nmr spectra showed at *ca* δ 9.00 a sharp singlet, integrating for 1 H and representing the methinic proton in the 2 position.

The enamino ketones **6**, obtained from 5-amino-4-ethoxycarbonylpyrazoles **4** in the same manner as **5**, by heating with excess sodium hydroxide in aqueous ethanol gave the corresponding acids **7**, which were in turn cyclized with polyphosphoric esters (PPE) in acetonitrile to 7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-diones **13**.

When compounds **13** were allowed to react with sodium

Scheme 1



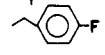
Reagents: A:  , p-TSA; B: K_2CO_3 - CuCl; C: $NaBH_4$; D: NaN_3/H_2SO_4; E: $CH(OEt)_3$; F: PPE

	R'
3,5	- CN
4,6	$-COOC_2H_5$
7	- COOH

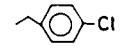
R

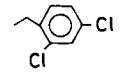
a : 

b : 

c : 

R

d : 

e : 

azide in the same conditions as previously described for ketones **8**, unexpectedly only the isoxazoles **14** were obtained in fair to excellent yields. The structure of **14** was confirmed and characterized by elemental analyses, ir (absence of NH and CO absorption), ^{1}H-nmr (absence of deuterium oxide exchangeable protons and shifting of C-3 methylene group of **14** at lower field than the corresponding protons of **13**), ^{13}C-nmr and mass spectra (see Experimental).

In the experimental, spectral data of the most significant compounds (R = benzyl) were reported. The ^{1}H-nmr spectra of the corresponding substituted benzyl compounds showed the same signals, except for the aromatic region.

All compounds were evaluated for enzymatic inhibitory activity versus acetylcholinesterase from *Electrophorus eel*, according to the procedure of Ellman [7]. Compounds **8b**, **12b** and **12c** were found to be the most potent ones. Further studies are under way and will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were determined on a T-60 Varian instrument with TMS as internal standard; the ^{13}C-nmr spectra were recorded on a Varian XL-100 spectrometer, operating at 25.2 MHz with broad-band proton decoupling; ir spectra were recorded on a Perkin-Elmer 580 spectrophotometer; electron ionization mass spectra were obtained on a Finnigan 5100 apparatus. Column chromatographic separations were accomplished on Merck silica gel (70-230 mesh). Purity of each compound was checked by tlc Carlo Erba silica gel plates. Sodium sulfate was used to dry organic solutions.

The synthesis of **3a** [8], **3e** [5], **4a** [9], and **4e** [5], has been reported elsewhere.

5-Amino-1-(2-fluorobenzyl)-4-cyanopyrazole **3b**.

This compound was prepared from 2-fluorobenzylhydrazine and ethoxymethylenemalononitrile, according to the synthetic

pathway described for the corresponding 1-benzyl derivative **3a** [8].

Compound **3b** had mp 149-151° (ethanol), 78%.

Anal. Calcd. for $C_{11}H_9FN_4$: C, 61.10; H, 4.20; N, 25.92. Found: C, 60.92; H, 4.22; N, 26.10.

5-Amino-1-(4-fluorobenzyl)-4-cyanopyrazole **3c**.

This compound was prepared from 4-fluorobenzylhydrazine and ethoxymethylenemalononitrile and had mp 170-172° (ethanol), 83%.

Anal. Calcd. for $C_{11}H_9FN_4$: C, 61.10; H, 4.20; N, 25.92. Found: C, 61.24; H, 4.18; N, 25.86.

5-Amino-1-(4-chlorobenzyl)-4-cyanopyrazole **3d**.

This compound was prepared from 4-chlorobenzylhydrazine and ethoxymethylenemalononitrile and had mp 171-173° (ethanol), 80%.

Anal. Calcd. for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; N, 24.08. Found: C, 56.78; H, 4.00; N, 24.18.

5-Amino-4-ethoxycarbonyl-1-(2-fluorobenzyl)pyrazole **4b**.

This compound was prepared from 2-fluorobenzylhydrazine and ethylethoxymethylenecyanoacetate as previously reported for the corresponding 1-benzyl derivative **4a** [9].

Compound **4b** had mp 98-100° (ethanol), 88%.

Anal. Calcd. for $C_{13}H_{14}FN_3O_2$: C, 59.31; H, 5.36; N, 15.96. Found: C, 59.44; H, 5.19; N, 15.71.

5-Amino-4-ethoxycarbonyl-1-(4-fluorobenzyl)pyrazole **4c**.

This compound was prepared from 4-fluorobenzylhydrazine and ethylethoxymethylenecyanoacetate and had mp 122-124° (ethanol), 81%.

Anal. Calcd. for $C_{13}H_{14}FN_3O_2$: C, 59.31; H, 5.36; N, 15.96. Found: C, 59.33; H, 5.20; N, 15.70.

5-Amino-4-ethoxycarbonyl-1-(4-chlorobenzyl)pyrazole **4d**.

This compound was prepared from 4-chlorobenzylhydrazine and ethylethoxymethylenecyanoacetate and had mp 105-107° (ethanol), 79%.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.76; H, 4.98; N, 15.10.

General Procedure for the Preparation of 4-Cyano-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazoles **5** and 4-Ethoxycarbonyl-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazoles **6**.

A suspension of each compound **3** or **4** (0.1 mole), 1,3-cyclohexanedione (12.3 g, 0.11 mole) and *p*-toluenenesulfonic acid monohydrate (0.5 g) in toluene (300 ml) was stirred and refluxed for 24 hours with a Dean-Stark trap to remove water. The reaction mixture was cooled in an ice-water bath and the solid which had formed was collected by filtration, washed with ethyl ether and crystallized.

1-Benzyl-4-cyano-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **5a**.

This compound was prepared from **3a** and had mp 189-191° (benzene), 74%; ^{1}H-nmr (DMSO—d_6): δ 9.18 (bs, 1H, deuterium oxide-exchangeable, NH), 8.04 (s, 1H, 3-CH), 7.13 (s, 5H, phenyl protons), 5.13 (s, 2H, benzyl CH_2), 4.44 (s, 1H, 2'-CH), 2.55 (at, 2H, 6'-CH_2), 2.35-1.90 (m, 4H, 4' and 5'-CH_2).

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.17. Found: C, 69.77; H, 5.40; N, 19.08.

4-Cyano-1-(2-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **5b**.

This compound was prepared from **3b** and had mp 164-166° (ethyl acetate), 70%.

Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.79; H, 4.87; N, 18.06. Found: C, 65.91; H, 4.87; N, 17.94.

4-Cyano-1-(4-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **5c**.

This compound was prepared from **3c** and had mp 217-220° (ethyl acetate), 79%.

Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.79; H, 4.87; N, 18.06. Found: C, 66.11; H, 4.78; N, 18.29.

4-Cyano-1-(4-chlorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **5d**.

This compound was prepared from **3d** and had mp 200-202° (toluene), 84%.

Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.15. Found: C, 62.58; H, 4.60; N, 17.39.

4-Cyano-1-(2,4-dichlorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **5e**.

This compound was prepared from **3e** and had mp 193-195° (toluene), 86%.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.91; N, 15.51. Found: C, 56.44; H, 3.88; N, 15.73.

1-Benzyl-4-ethoxycarbonyl-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **6a**.

This compound was obtained from **4a** and had mp 122-124° (ethyl acetate/*n*-hexane), 68%; ^{1}H-nmr (DMSO-d_6): δ 8.83 (bs, 1H, deuterium oxide-exchangeable, NH), 7.96 (s, 1H, 3-CH), 7.25 (s, 5H, phenyl protons), 5.21 (s, 2H, benzyl CH_2), 4.60 (s, 1H, 2'-CH), 4.13 (q, 2H, CH_2-CH_3), 2.44 (at, 2H, 6'-CH_2), 2.30-1.75 (m, 4H, 4' and 5'-CH_2), 1.20 (t, 3H, CH_2-CH_3).

Anal. Calcd. for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 66.99; H, 6.20; N, 12.09.

4-Ethoxycarbonyl-1-(2-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **6b**.

This compound was obtained from **4b** and had mp 143-145° (ethyl acetate/*n*-hexane), 59%.

Anal. Calcd. for $C_{19}H_{20}FN_3O_3$: C, 63.85; H, 5.64; N, 11.76. Found: C, 64.03; H, 5.83; N, 11.75.

4-Ethoxycarbonyl-1-(4-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **6c**.

This compound was obtained from **4c** and had mp 145-147° (ethyl acetate/*n*-hexane), 74%.

Anal. Calcd. for $C_{19}H_{20}FN_3O_3$: C, 63.85; H, 5.64; N, 11.76. Found: C, 63.94; H, 5.77; N, 11.70.

1-(4-Chlorobenzyl)-4-ethoxycarbonyl-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **6d**.

This compound was obtained from **4d** and had mp 152-154° (ethyl acetate), 82%.

Anal. Calcd. for $C_{19}H_{20}ClN_3O_3$: C, 61.04; H, 5.39; N, 11.24. Found: C, 61.23; H, 5.38; N, 11.40.

1-(2,4-Dichlorobenzyl)-4-ethoxycarbonyl-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **6e**.

This compound was obtained from **4e** and had mp 163-165° (toluene), 77%.

Anal. Calcd. for $C_{19}H_{19}Cl_2N_3O_3$: C, 55.89; H, 4.69; N, 10.29. Found: C, 55.78; H, 4.88; N, 10.04.

General Procedure for the Preparation of 4-Carboxy-5-[3-oxo-1-cyclohexen-1-yl)amino]pyrazoles **7**.

The corresponding ethyl ester **6** (5 g) in 15% sodium hydroxide (80 ml) was refluxed for 4 hours. After cooling, the reaction mixture was poured into ice and acidified with 10% hydrochloric acid to *p*H 5-6. The separate product was filtered, washed with water, and crystallized.

1-Benzyl-4-carboxy-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **7a**.

This compound was obtained from **6a** and had mp 163-165° (ethanol), 92%; ^{1}H-nmr (DMSO-d_6): δ 8.76 (broad, 1H, deuterium oxide-exchangeable, COOH), 7.83 (s, 1H, 3-CH), 7.23 (s, 5H, phenyl protons), 6.20 (bs, 1H, deuterium oxide-exchangeable, NH), 5.20 (s, 2H, benzyl CH_2), 4.72 (s, 1H, 2'-CH), 2.37 (at, 2H, 6'-CH_2), 2.03 (at, 2H, 4'-CH_2), 1.90 (m, 2H, 5'-CH_2).

Anal. Calcd. for $C_{17}H_{17}N_3O_3 \cdot H_2O$: C, 61.99; H, 5.82; N, 12.76. Found: C, 62.21; H, 5.77; N, 12.99.

4-Carboxy-1-(2-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]-pyrazole **7b**.

This compound was obtained from **6b** and had mp 147-150° (ethanol), 80%.

Anal. Calcd. for $C_{17}H_{16}FN_3O_3 \cdot H_2O$: C, 58.78; H, 5.22; N, 12.09. Found: C, 58.53; H, 5.19; N, 11.96.

4-Carboxy-1-(4-fluorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]-pyrazole **7c**.

This compound was obtained from **6c** and had mp 133-135° (ethanol), 94%.

Anal. Calcd. for $C_{17}H_{16}FN_3O_3 \cdot H_2O$: C, 58.78; H, 5.22; N, 12.09. Found: C, 58.87; H, 5.48; N, 12.24.

4-Carboxy-1-(4-chlorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]-pyrazole **7d**.

This compound was obtained from **6d** and had mp 162-165° (ethanol), 74%.

Anal. Calcd. for $C_{17}H_{16}ClN_3O_3 \cdot H_2O$: C, 56.12; H, 4.99; N, 11.55. Found: C, 56.34; H, 5.12; N, 11.80.

4-Carboxy-1-(2,4-dichlorobenzyl)-5-[(3-oxo-1-cyclohexen-1-yl)amino]pyrazole **7e**.

This compound was obtained from **6e** and had mp 177-180° (ethanol), 68%.

Anal. Calcd. for $C_{17}H_{15}Cl_2N_3O_3 \cdot H_2O$: C, 51.26; H, 4.30; N, 10.55. Found: C, 51.18; H, 4.04; N, 10.85.

General Procedure for the Preparation of 4-Amino-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-ones **8**.

A suspension of each compound **5** (0.01 mole), anhydrous potassium carbonate (2.5 g) and rameous chloride (1 g) in tetrahydrofuran (250 ml) was refluxed with stirring for 3 hours. The hot reaction mixture was treated with decolorizing carbon, filtered and evaporated to dryness. The residue was chromatographed on a short column of silica gel by eluting with an ethyl acetate-*n*-hexane (2:1) mixture, then crystallized.

4-Amino-1-benzyl-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **8a**.

This compound was obtained from **5a** and had mp 210-212° (ethyl acetate), 65%; ^{1}H-nmr (DMSO-d_6): δ 9.43 (broad, 1H, deuterium oxide-exchangeable, hydrogen bonded NH), 8.34 (bs, 1H, deuterium oxide-exchangeable, NH), 8.22 (s, 1H, 3-CH), 7.20 (s, 5H, phenyl protons), 5.47 (s, 2H, benzyl CH_2), 2.93 (t, 2H, 8-CH_2), 2.52 (t, 2H, 6-CH_2), 1.98 (m, 2H, 7-CH_2).

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.17. Found: C, 69.87; H, 5.24; N, 19.30.

4-Amino-1-(2-fluorobenzyl)-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **8b**.

This compound was obtained from **5b** and had mp 198-201° (ethyl acetate), 74%.

Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.79; H, 4.87; N, 18.05. Found: C, 65.54; H, 5.00; N, 17.90.

4-Amino-1-(4-fluorobenzyl)-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **8c**.

This compound was obtained from **5c** and had mp 208-210° (ethyl acetate), 58%.

Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.79; H, 4.87; N, 18.05. Found: C, 65.74; H, 5.04; N, 18.34.

4-Amino-1-(4-chlorobenzyl)-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]quinolin-5-one **8d**.

This compound was obtained from **5d** and had mp 203-205° (ethyl acetate), 70%.

Anal. Calcd. for $C_{17}H_{15}ClN_4O$: C, 62.48; H, 4.63; N, 17.14. Found: C, 62.68; H, 4.72; N, 17.07.

4-Amino-1-(2,4-dichlorobenzyl)-7,8-dihydro-6*H*-pyrazolo[3,4-*b*]-quinolin-5-one **8e**.

This compound was obtained from **5e** and had mp 270-273° (dimethylformamide/ethanol), 61%.

Anal. Calcd. for $C_{17}H_{14}Cl_2N_4O$: C, 56.52; H, 3.90; N, 15.51. Found: C, 56.46; H, 3.97; N, 15.40.

General Procedure for the Reduction of Ketones **8** with Sodium Borohydride.

To a suspension of **5** (0.01 mole) in 20% aqueous dioxane (100 ml) kept at 40-45°, sodium borohydride (1.1 g, 0.03 mole) was added in several portions during 10 minutes. The mixture was heated and stirred until tlc (ethyl acetate) indicated that the starting material was disappeared (about 1 hour). After cooling, water (200 ml) was added and the mixture extracted with ethyl acetate. The residue obtained after solvent evaporation, was purified by chromatography on a silica gel column by eluting with ethyl acetate.

4-Amino-1-benzyl-5,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolin-5-ol **9a**.

This compound was obtained from **8a** and had mp 210-213° (ethyl acetate), 72%; ^{1}H-nmr (DMSO-d_6): δ 8.10 (s, 1H, 3-CH), 7.20 (s, 5H, phenyl protons), 6.60 (bs, 2H, deuterium oxide-exchangeable, NH_2), 5.13 (s, 2H, benzyl CH_2), 4.80 (as, 2H, 5-CH and 1H deuterium oxide-exchangeable, OH), 2.82 (m, 2H, 8-CH_2), 1.83 (m, 4H, 6 and 7-CH_2).

Anal. Calcd. for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16; N, 19.04. Found: C, 69.53; H, 5.90; N, 19.10.

4-Amino-1-(2-fluorobenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]-quinolin-5-ol **9b**.

This compound was obtained from **8b** and had mp 157-159° (ethyl acetate/*n*-hexane), 58%.

Anal. Calcd. for $C_{17}H_{17}FN_4O$: C, 65.37; H, 5.48; N, 17.94. Found: C, 65.23; H, 5.62; N, 18.04.

4-Amino-1-(4-fluorobenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]-quinolin-5-ol **9c**.

This compound was obtained from **8c** and had mp 165-167° (ethyl acetate/*n*-hexane), 66%.

Anal. Calcd. for $C_{17}H_{17}FN_4O$: C, 65.37; H, 5.48; N, 17.94. Found: C, 65.25; H, 5.70; N, 17.97.

4-Amino-1-(4-chlorobenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]-quinolin-5-ol **9d**.

This compound was obtained from **8d** and had mp 168-170° (ethyl acetate/*n*-hexane), 60%.

Anal. Calcd. for $C_{17}H_{17}ClN_4O \cdot \frac{1}{2}H_2O$: C, 60.44; H, 5.37; N, 16.59. Found: C, 60.29; H, 5.48; N, 16.32.

4-Amino-1-(2,4-dichlorobenzyl)-5,6,7,8-tetrahydropyrazolo[3,4-*b*]-quinolin-5-ol **9e**.

This compound was obtained from **8e** and had mp 209-212° (ethyl acetate), 68%.

Anal. Calcd. for $C_{17}H_{16}Cl_2N_4O$: C, 56.21; H, 4.44; N, 15.42. Found: C, 56.35; H, 4.40; N, 15.60.

General Procedure for the Reaction of Compounds **8** with Hydrazoic Acid.

Concentrated sulfuric acid (5 ml) was added cautiously with cooling and stirring to a suspension of **8** (1 g) in chloroform (5 ml), then sodium azide (1 g) was added gradually over 50-60 minutes. Generally the reaction was complete after 3 hours at room temperature. The reaction mixture was cooled, basified with diluted ammonium hydroxide and finally extracted exhaustively with ethyl acetate. After removal of the solvent, the crude residue was chromatographed on a silica gel column by eluting with ethyl acetate. Compounds **10** were eluted first, followed by **11**.

4-Amino-1-benzyl-6,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*c*]azepin-5(1*H*)-one **10a** and 4-Amino-1-benzyl-5,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*b*]azepin-6(1*H*)-one **11a**.

These compounds were obtained from **8a**.

Compound **10a** had mp 248-251° (methanol), 18%; ^{1}H-nmr (DMSO-d_6): δ 8.20 (s, 1H, 3-CH), 7.95 (broad, 1H, deuterium oxide-exchangeable, NH), 7.37 (bs, 2H, deuterium oxide-exchangeable, NH_2), 7.23 (s, 5H, phenyl protons), 5.50 (s, 2H, benzyl CH_2), 2.95 (m, 4H, 7 and 9-CH_2), 2.00 (m, 2H, 8-CH_2); ir (nujol): CO 1650 cm^{-1}; ms: (m/z) 307 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.41; H, 5.60; N, 22.77.

Compound **11a** had mp 236-238° (ethyl acetate), 50%; ^{1}H-nmr (DMSO-d_6): δ 8.40 (bs, 1H, deuterium oxide-exchangeable, NH), 8.07 (s, 1H, 3-CH), 7.20 (s, 5H, phenyl protons), 6.64 (bs, 2H, deuterium oxide-exchangeable, NH_2), 5.50 (s, 2H, benzyl CH_2), 2.80 (m, 2H, 9-CH_2), 2.15 (m, 4H, 7 and 8-CH_2); ir (nujol): CO 1670 cm^{-1}; ms: (m/z) 307 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.66; H, 5.62; N, 22.72.

4-Amino-1-(2-fluorobenzyl)-6,7,8,9-tetrahydropyrazolo[4',3':5,6]-pyrido[3,2-*c*]azepin-5(1*H*)-one **10b** and 4-Amino-1-(2-fluorobenzyl)-5,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*b*]azepin-6-(1*H*)-one **11b**.

These compounds were obtained from **8b**.

Compound **10b** had mp 255-257° (methanol), 22%.

Anal. Calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found: C, 62.73; H, 5.07; N, 21.25.

Compound **11b** had mp 253-255° (methanol), 54%.

Anal. Calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found: C, 62.66; H, 5.09; N, 21.80.

4-Amino-1-(4-fluorobenzyl)-6,7,8,9-tetrahydropyrazolo[4',3':5,6]-pyrido[3,2-*c*]azepin-5(1*H*)-one **10c** and 4-Amino-1-(4-fluorobenzyl)-5,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*b*]azepin-6(1*H*)-one **11c**.

These compounds were obtained from **8c**.

Compound **10c** had mp 273-275° (ethanol), 20%.

Anal. Calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found: C, 63.01; H, 5.15; N, 21.49.

Compound **11c** had mp 282-285° (ethyl acetate), 66%.

Anal. Calcd. for $C_{17}H_{16}FN_5O$: C, 62.76; H, 4.96; N, 21.53. Found: C, 62.64; H, 5.04; N, 21.57.

4-Amino-1-(4-chlorobenzyl)-6,7,8,9-tetrahydropyrazolo[4',3':5,-6]pyrido[3,2-*c*]azepin-5(1*H*)-one **10d** and 4-Amino-1-(4-chlorobenzyl)-5,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*b*]azepin-6(1*H*)-one **11d**.

These compounds were obtained from **8d**.

Compound **10d** had mp 270-272° (ethyl acetate), 15%.

Anal. Calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found: C, 59.47; H, 4.72; N, 20.21.

Compound **11d** had mp 283-285° (ethyl acetate), 61%.

Anal. Calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found: C, 59.48; H, 4.73; N, 20.22.

4-Amino-1-(2,4-dichlorobenzyl)-6,7,8,9-tetrahydropyrazolo-[4',3':5,6]pyrido[3,2-*c*]azepin-5(1*H*)-one **10e** and 4-Amino-1-(2,4-dichlorobenzyl)-5,7,8,9-tetrahydropyrazolo[4',3':5,6]pyrido[3,2-*b*]azepin-6(1*H*)-one **11e**.

These compounds were obtained from **8e**.

Compound **10e** had mp 256-259° (methanol), 14%.

Anal. Calcd. for $C_{17}H_{15}Cl_2N_5O$: C, 54.26; H, 4.02; N, 18.61. Found: C, 54.03; H, 4.10; N, 18.71.

Compound **11e** had mp 297-300° (ethyl acetate), 52%.

Anal. Calcd. for $C_{17}H_{15}Cl_2N_5O \cdot H_2O$: C, 51.79; H, 4.34; N, 17.76. Found: C, 52.06; H, 4.36; N, 17.60.

General Procedure for the Preparation of 4,5,6,8-Tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-ones **12**.

A suspension of each compound **11** (2 g) in triethylorthoformate (20 ml) was heated under reflux with vigorous stirring until tlc (ethyl acetate) indicated that all the starting material has been converted (about 40 hours). The solvent was removed and the residue crystallized.

8-Benzyl-4,5,6,8-tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-one **12a**.

This compound was obtained from **11a** and had mp 165-167° (ethanol), 78%; ^{1}H-nmr (DMSO-d_6): δ 8.97 (s, 1H, 2-CH), 8.33 (s, 1H, 10-CH), 7.20 (s, 5H, phenyl protons), 5.70 (s, 2H, benzyl CH_2), 3.33 (m, 4H, 4 and 6-CH_2), 2.16 (m, 2H, 5-CH_2); ms: (m/z) 317 (M^+, 54), 288 (46), 240 (41), 91 (100), 65 (38), 55 (34).

Anal. Calcd. for $C_{18}H_{15}N_5O$: C, 68.12; H, 4.76; N, 22.07. Found: C, 68.22; H, 4.88; N, 22.04.

8-(2-Fluorobenzyl)-4,5,6,8-tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-one **12b**.

This compound was obtained from **11b** and had mp 173-176° (ethanol), 66%.

Anal. Calcd. for $C_{18}H_{14}FN_5O \cdot \frac{1}{2}H_2O$: C, 62.78; H, 4.39; N, 20.34. Found: C, 62.68; H, 4.44; N, 20.39.

8-(4-Fluorobenzyl)-4,5,6,8-tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-one **12c**.

This compound was obtained from **11c** and had mp 174-176° (ethanol), 80%.

Anal. Calcd. for $C_{18}H_{14}FN_5O$: C, 64.47; H, 4.21; N, 20.88. Found: C, 64.07; H, 4.12; N, 20.56.

8-(4-Chlorobenzyl)-4,5,6,8-tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-one **12d**.

This compound was obtained from **11d** and had mp 193-195° (ethanol), 72%.

Anal. Calcd. for $C_{18}H_{14}ClN_5O$: C, 61.45; H, 4.01; N, 19.91. Found: C, 61.29; H, 4.10; N, 19.72.

8-(2,4-Dichlorobenzyl)-4,5,6,8-tetrahydro-3*H*-1,2a,7,8,9-pentaazacyclohept[*cd*]-*as*-indacen-3-one **12e**.

This compound was obtained from **11e** and had mp 196-199° (ethanol), 84%.

Anal. Calcd. for $C_{18}H_{13}Cl_2N_5O$: C, 55.98; H, 3.39; N, 18.13. Found: C, 56.00; H, 3.36; N, 17.96.

General Procedure for the Preparation of 7,8-Dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-diones **13**.

To a suspension of the appropriate carboxylic acid **7** (2 g) in acetonitrile (25 ml), polyphosphoric esters (PPE) (8 g) were added and the mixture was refluxed for 2 hours. The solvent was removed *in vacuo*, cracked ice and water were added to the residue, and the whole was basified by adding excess of powdered sodium bicarbonate. After 1 hour, the mixture was extracted with ethyl acetate and the extract washed with water, 10% hydrochloric acid, water and then dried. The solvent was evaporated and the residue crystallized.

1-Benzyl-7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-dione **13a**.

This compound was prepared from **7a** and had mp 188-200° (ethanol), 86%; ^{1}H-nmr (DMSO-d_6): δ 14.23 (broad, 1H, deuterium oxide-exchangeable, NH), 8.08 (s, 1H, 3-CH), 7.28 (s, 5H, phenyl protons), 5.62 (s, 2H, benzyl CH_2), 3.13 (t, 2H, 8-CH_2), 2.73 (t, 2H, 6-CH_2), 2.14 (quintet, 2H, 7-CH_2).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.57; H, 5.43; N, 14.47.

1-(2-Fluorobenzyl)-7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-dione **13b**.

This compound was prepared from **7b** and had mp 164-166° (ethanol), 80%.

Anal. Calcd. for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.46; H, 4.65; N, 13.30.

1-(4-Fluorobenzyl)-7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-dione **13c**.

This compound was prepared from **7c** and had mp 143-145° (ethanol), 86%.

Anal. Calcd. for $C_{17}H_{14}FN_3O_2$: C, 65.59; H, 4.53; N, 13.50. Found: C, 65.49; H, 4.76; N, 13.80.

1-(4-Chlorobenzyl)-7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-dione **13d**.

This compound was prepared from **7d** and had mp 191-193° (ethanol), 72%.

Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.29; H, 4.30; N, 12.82. Found: C, 62.09; H, 4.60; N, 12.99.

1-(2,4-Dichlorobenzyl)-7,8-dihydro-6*H*,9*H*-pyrazolo[3,4-*b*]quinoline-4,5-dione **13e**.

This compound was prepared from **7e** and had mp 149-151° (ethanol), 85%.

Anal. Calcd. for $C_{17}H_{13}Cl_2N_3O_2$: C, 56.37; H, 3.62; N, 11.60. Found: C, 56.21; H, 3.70; N, 11.53.

General Procedure for the Reaction of Compounds **13** with Hydrazoic Acid.

Compounds **13** were allowed to react with sodium azide/concentrated sulfuric acid, according to the procedure described for compounds **10** and **11**. The crude residue obtained after the solvent evaporation was directly crystallized.

7-Benzyl-4,5-dihydro-3*H*-isoxazolo[5,4,3-*de*]pyrazolo[3,4-*b*]quinoline **14a**.

This compound was obtained from **13a** and had mp 122-124° (ethanol), 79%; ^{1}H-nmr (DMSO-d_6): δ 8.37 (s, 1H, 9-CH), 7.20 (s, 5H, phenyl protons), 5.73 (s, 2H, benzyl CH_2), 3.13 (m, 4H, 3 and 5-CH_2), 1.37 (quintet, 2H, 4-CH_2); ^{13}C-nmr (DMSO-d_6): 158.77 (C-5a), 158.68, 158.23 (C-2a, C-9b, interchangeable), 136.91 (C-1'), 129.83 (C-9), 128.31 (C-3' and C-5'), 127.35 (C-4'), 127.26 (C-2' and C-6'), 112.25 (C-9c), 99.82 (C-9a), 50.77 (benzyl CH_2), 28.92 (C-3), 24.02 (C-5), 20.78 (C-4); ms: (m/z) 290 (M^+-28, 20), 262 (13), 213 (19), 91 (100), 65 (21).

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.36; H, 4.86; N, 19.31.

7-(2-Fluorobenzyl)-4,5-dihydro-3*H*-isoxazolo[5,4,3-*de*]pyrazolo-[3,4-*b*]quinoline **14b**.

This compound was obtained from **13b** and had mp 148-150° (ethanol), 84%.

Anal. Calcd. for $C_{17}H_{13}FN_4O$: C, 66.22; H, 4.25; N, 18.17. Found: C, 66.43; H, 4.35; N, 18.25.

7-(4-Fluorobenzyl)-4,5-dihydro-3*H*-isoxazolo[5,4,3-*de*]pyrazolo-[3,4-*b*]quinoline **14c**.

This compound was obtained from **13c** and had mp 134-136° (ethanol), 88%.

Anal. Calcd. for $C_{17}H_{13}FN_4O$: C, 66.22; H, 4.25; N, 18.17. Found: C, 66.01; H, 4.49; N, 18.28.

7-(4-Chlorobenzyl)-4,5-dihydro-3*H*-isoxazolo[5,4,3-*de*]pyrazolo-[3,4-*b*]quinoline **14d**.

This compound was obtained from **13d** and had mp 163-165° (ethanol), 80%.

Anal. Calcd. for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; N, 17.25. Found: C, 63.07; H, 4.17; N, 17.07.

7-(2,4-Dichlorobenzyl)-4,5-dihydro-3*H*-isoxazolo[5,4,3-*de*]pyrazolo[3,4-*b*]quinoline **14e**.

This compound was obtained from **13e** and had mp 185-187° (ethanol), 80%.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_4O$: C, 56.84; H, 3.37; N, 15.60. Found: C, 56.58; H, 3.47; N, 15.49.

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