SYNTHESIS OF 1,2,3,4-TETRAHYDROACRIDINE AND 5,6,7,8-TETRAHYDROQUINOLINE DERIVATIVES AS POTENTIAL ACETYLCHOLINESTERASE INHIBITORS

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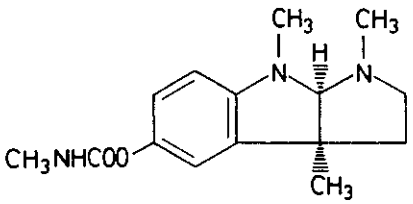
Abstract - This paper describes the synthesis of 1,3,4,5-tetrahydropyrazolo[3,4,5-*kl*]acridine (2) and 11-amino-1,3,4,5-tetrahydroazepino[3,2-*b*]quinolin-2-one (3) obtained by Schmidt reaction of 9-amino-3,4-dihydroacridin-1(2*H*)-one (1) and the preparation of 4,5-dihydro-3*H*-isoxazolo[3,4,5-*kl*]acridine (7) obtained in the same manner starting from 3,4-dihydroacridine-1,9(2*H*,10*H*)-dione (6). The corresponding pyrazolo[3,4,5-*de*]quinoline (20) and isoxazolo[5,4,3-*de*]quinoline (18) are also reported. The compounds have been prepared with the aim of studying their possible activity as acetylcholinesterase inhibitors.

The finding of a cholinergic deficit in the brain of patients with Alzheimer's disease, suggested that impaired cortical cholinergic transmission may be at least responsible for the symptoms of the disease.[1] In support of this suggestion it has been reported that physostigmine and 9-amino-1,2,3,4-tetrahydroacridine (Tacrine), which potentiate the action of acetylcholine by inhibiting the degrading enzyme cholinesterase, can bring about memory

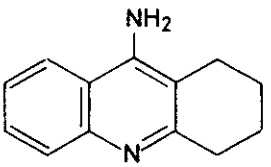
improvement in Alzheimer's patients.[2,3]

Physostigmine however shows serious, potentially lethal side effects (LD_{50} 0.6 mg/kg in mice) and is characterized by a short duration of action, while the main disadvantage of tacrine is its known liver toxicity.[4]

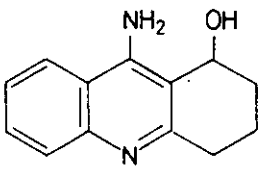
Considerable attention has been recently focused on 9-amino-(or 9-benzylamino)-1,2,3,4-tetrahydroacridin-1-ols (HP-029 and HP-128, Hoechst-Roussel), both significantly less toxic than tacrine, which are in phase II clinical trials for the Alzheimer's disease.[5]



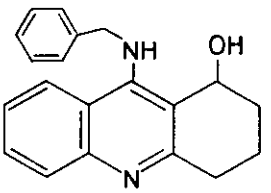
Physostigmine



Tacrine



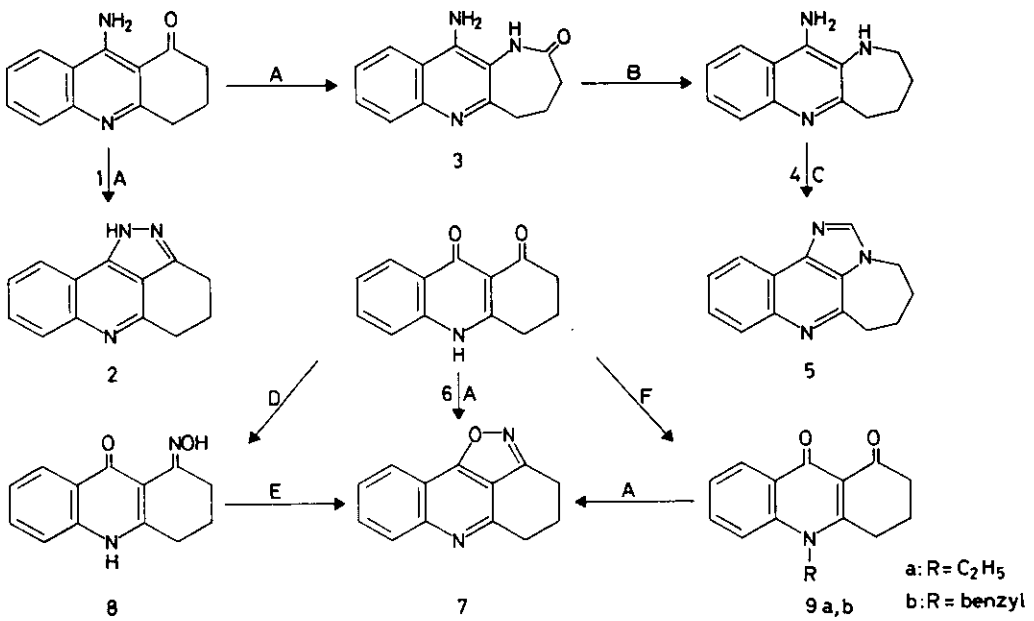
HP-029



HP-128

As continuation of our studies, directed towards the search of new tacrine-like compounds, in order to verify their activity as acetylcholinesterase inhibitors,[6] in this paper we describe the synthesis of some derivatives of 9-amino-3,4-dihydroacridin-1(2*H*)-one (1), 3,4-dihydroacridine-1,9(2*H*,10*H*)-dione (6) and 7,8-dihydroquinoline-4,5(1*H*,6*H*)-dione (16).

Key intermediates(1)[5] and (6)[7] to our syntheses outlined in Scheme 1 were prepared as reported in the literature. Compound (1), when subjected to the Schmidt reaction with sodium azide in concentrated sulfuric acid, gave, in addition to the expected lactam 11-amino-1,3,4,5-tetrahydroazepino[3,2-*b*]quinolin-2-one (3), also 1,3,4,5-tetrahydropyrazolo[3,4,5-*kl*]acridine (2), in approximate ratio of 4:1 (3/2). By the same reaction compound (6) afforded only the 4,5-dihydro-3*H*-isoxazolo[3,4,5-*kl*]acridine (7).



Reagents: A: NaN_3 / H_2SO_4 ; B: $LiAlH_4$; C: $CH(OC_2H_5)_3$; D: $NH_2OH \cdot HCl$ / Pyr. E: PPA ; F: C_2H_5I or $Ph\text{-}CH_2Br$ / $(nC_4H_9)_4N^+Br^-$

Scheme 1

The structural assignments of compounds (2), (3) and (7) were substantiated by their spectral data and elemental analysis.

In the ^1H nmr spectrum of 2 the NH appeared at δ 13.53 as a broad singlet, while the C-3 methylene group, next to C=N was shifted at lower field than the corresponding C-2 protons of 1, next to C=O.

The ^1H nmr spectrum of 3 showed the C-3 methylene group at δ 2.13 and the broad amide NH signal at δ 8.70, in full agreement with what previously observed for analogous moieties.[6] The structure of lactam (3) was further supported by its lithium aluminum hydride reduction, followed by condensation of the resulting diamine (4) with triethyl orthoformate. The expected imidazoderivative (5), whose ^1H nmr spectrum exhibited a sharp singlet at δ

7.93, integrating for one proton, and attributed to the bridgehead methinic CH in the position 2, was obtained.

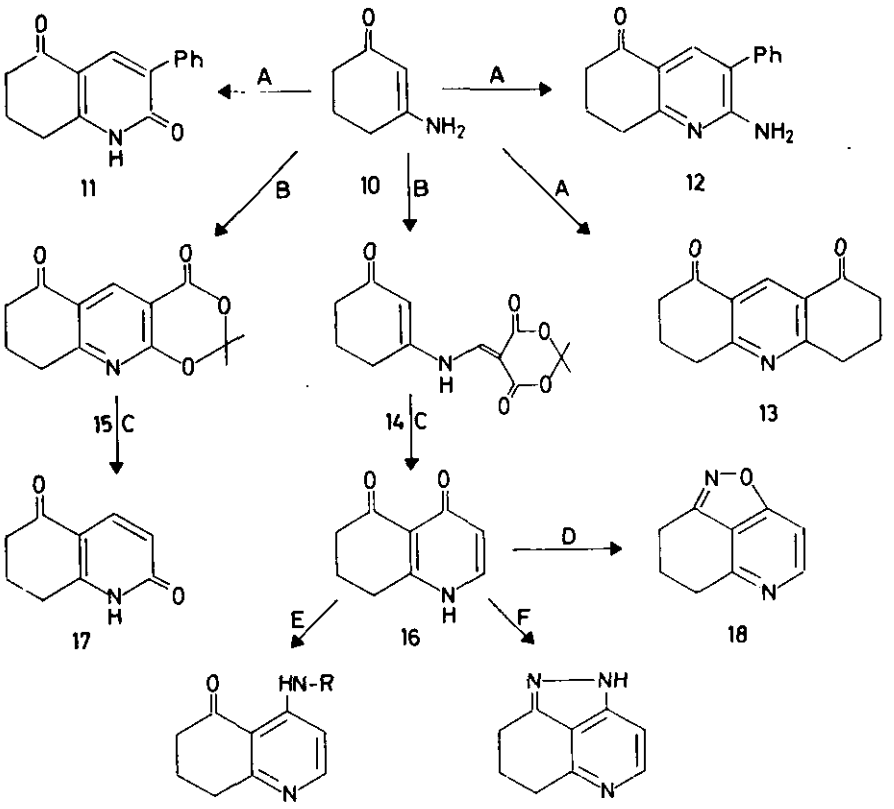
The structure of compound (7) was supported by mass and ^1H and ^{13}C nmr spectra: the mass spectrum showed an abundant molecular ion at m/z 210; no deuterium oxide exchangeable proton in the ^1H nmr spectrum was present and ^{13}C nmr spectrum was also consistent with the assigned structure (see Experimental). Furthermore the melting point and the nmr spectra were different from those reported for the isomeric isoxazolo[5,4,3-*kl*]acridine derivative.[8]

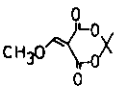
The treatment of ketoxime (8) with polyphosphoric acid and the Schmidt reaction of *10-ethyl-* or *10-benzyl-3,4-dihydroacridine-1,9(2H,10H)-diones* (9) led to the same compound (7).

Recently similar isoxazolo[3,4,5-*kl*]acridines, obtained by acid-catalyzed rearrangement of 1-oximinoacridine-1,9-diones, have been reported in the literature.[9]

The synthetic routes employed for the preparation of tetrahydroquinoline derivatives, summarized in Scheme 2, started from 1-amino-3-oxo-1-cyclohexene (10).[10] When allowed to react with α-formylphenylacetonitrile,[11] compound (10) yielded a mixture of 3-phenyl-7,8-dihydroquinoline-2,5(1*H*,6*H*)-dione (11), 2-amino-3-phenyl-7,8-dihydroquinolin-5(6*H*)-one (12) and 3,4,5,6-tetrahydroacridine-1,8(2*H*,7*H*)-dione (13). The latter compound resulted from the condensation of two molecules of 10 with methyl orthoformate, derived from a partial decomposition of α-formylphenylacetonitrile in the methanolic medium, and ammonia elimination. By reaction with methoxymethylene Meldrum's acid[12] compound (10) afforded a 1:1 mixture of 2,2-dimethyl-5-(3-oxo-1-cyclohexene)aminomethylene-1,3-dioxane-4,6-dione (14) and 2,2-dimethyl-8,9-dihydro-1,3-dioxino[4,5-*b*]quinoline-4,6(7*H*)-dione (15).

Compounds (14) and (15) in boiling diphenylether gave respectively the isomeric tetrahydroquinolinediones (16) and (17). The structure of these compounds was supported from a comparison of their ^1H nmr spectra in DMSO and CF_3COOH. In DMSO as solvent, compound (16) showed two doublets at δ 8.00 and 6.48 respectively for protons H-2 and H-3. Using CF_3COOH as solvent, a



Reagents : A: Ph $\overset{CN}{\underset{CHOH}{\diagup\!\!=}}$; B: CH_3O  ; C. Ph_2O, $\triangle$; D: NaN_3 / H_2SO_4 ;

E: 1) $POCl_3$. 2) NH_3/CH_3OH or benzylamine ; F: 1) $POCl_3$. 2) NH_2-$NH_2 \cdot H_2O$

Scheme 2

transformation of the original CH=N doublet into a triplet was observed,[13] while the AX pattern of compound (17) was not affected by changing the solvent to CF_3COOH. Furthermore the chemical shifts of C-2 and C-4 carbonyl in ^{13}C nmr spectra were in agreement with literature values found for isomeric fused 2-pyridones (162-165 ppm) and 4-pyridones (177-179 ppm).[14]

The 7,8-dihydroquinoline-4,5(1*H*,6*H*)-dione (16) underwent the Schmidt reaction, affording, as previously observed for the acridinedione (6), the

isoxazolo derivative (18). Reaction of (16) with phosphorus oxychloride followed by condensation of the resulting crude chloro derivative with methanolic ammonia, benzylamine or hydrazine hydrate gave the 4-amino-(or 4-benzylamino)-7,8-dihydroquinolin-5(6*H*)one (19) and 2,6,7,8-tetrahydropyrazolo[3,4,5-*de*]quinoline (20), respectively.

All the new compounds were tested as acetylcholine inhibitors "in vitro", by a modified micro Ellman method.[15] Compound (4) exhibited the strongest inhibition, almost four times as potent as tacrine. Further behavioural studies to establish the efficacy and toxicity of 4 are under way and will be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 580 spectrophotometer; ^{1}H nmr spectra were obtained on a Varian T-60 spectrometer with an internal TMS standard, except for the spectrum of compound (7) which was taken on a Bruker 400 instrument. Abbreviations are as follows: d=doublet; m=multiplet; t=triplet; s=singlet. ^{13}C Nmr spectra were recorded on a Varian XL 100 spectrometer, operating at 25.2 MHz with broad-band proton decoupling; electron ionization mass spectra were obtained on a Finnigan 5100 apparatus. Column chromatography was carried out using Merck silica gel (70-230 mesh). Purity of each compound was checked by silica gel plates (Merck GF_{254}). Anhydrous sodium sulfate was used as drying agent. Elemental analyses were performed by the Microanalytical Section of our Institute.

The synthesis of 1,[5] 6[7] and 10[10] has been reported elsewhere.

General procedure for the reaction of compounds (1) and (6) with hydrazoic acid.

Concentrated sulfuric acid (5 ml, 50 mmol) was added cautiously with cooling and stirring to a suspension of 1 or 6 (1 g, 4.7 mmol) in chloroform (5 ml). Sodium azide (1 g, 15.4 mmol) was then added gradually over 50-60 min. The

reaction was controlled by tlc and generally was complete after stirring for 8-10 h at room temperature. The reaction mixture was cooled, basified with diluted ammonium hydroxide and extracted with ethyl acetate. Drying and evaporation of the organic phase gave a solid which was chromatographed on a silica gel column by eluting with ethyl acetate (compound 7) or with ethyl acetate/methanol 9:1 (compounds 2 and 3; compound 2 was eluted first, followed by 3).

1,3,4,5-Tetrahydropyrazolo[3,4,5-*kl*]acridine (2).

This compound, obtained from 1 in a yield of 16%, was recrystallized from ethanol and had mp > 300 °C. ^{1}H Nmr (DMSO-d_6, δ, ppm): 13.53 (br s, 1H, exchangeable with deuterium oxide, NH), 8.33-7.50 (m, 4H, aromatic protons), 3.03 (t, J=6 Hz, 4H, 3 and 5-CH_2), 2.27 (m, 2H, 4-CH_2); ^{13}C nmr (DMSO-d_6): 158.1 (C-2a), 147.8 (C-5a), 146.5 (C-6a), 138.4 (C-10b), 129.3 (C-8), 128.2 (C-10), 125.0 (C-7), 122.3 (C-9), 116.1 (C-10c), 115.1 (C-10a), 30.0 (C-3), 24.7 (C-5), 22.1 (C-4); ms (m/z): 209 (M^+). Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.50; H, 5.31; N, 20.18.

11-Amino-1,3,4,5-tetrahydroazepino[3,2-*b*]quinolin-2-one (3).

This compound, obtained from 1 in a yield of 60%, was recrystallized from ethanol and had mp > 300 °C. ^{1}H Nmr (DMSO-d_6, δ, ppm): 8.70 (br s, 1H, exchangeable with deuterium oxide, NH), 8.08 (d, J=8 Hz, 1H, 7-CH), 7.95-7.20 (m, 3H, aromatic protons), 6.47 (br s, 2H, exchangeable with deuterium oxide, NH_2), 2.93 (t, J=6 Hz, 2H, 5-CH_2), 2.13 (m, 4H, 3-CH_2 and 4-CH_2); ^{13}C nmr (DMSO-d_6): 173.4 (C-2), 156.0 (C-5a), 145.8 (C-11), 142.2 (C-6a), 128.4 (C-8), 128.2 (C-7), 123.7 (C-10), 122.4 (C-9), 118.2 (C-11a), 113.3 (C-10a), 33.3 (C-3), 32.3 (C-5), 26.2 (C-4); ms (m/z): 227 (M^+); ir (nujol): νCO: 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.69; H, 5.72; N, 18.43.

4,5-Dihydro-3*H*-isoxazolo[3,4,5-*kl*]acridine (7).

This compound, obtained from 6 in a yield of 86%, was recrystallized from ethyl acetate and had mp 136-138 °C. ^{1}H Nmr ($CDCL_3$, δ, ppm): 8.25 (d, J=8 Hz, 1H, 10-CH), 8.18 (d, J=8 Hz, 1H, 7-CH), 7.80 (t, J=8 Hz, 1H, 8-CH), 7.62 (t, 1H, 9-CH), 3.17 (t, J=6 Hz, 2H, 3-CH_2), 3.14 (t, J=6 Hz, 2H, 5-CH_2), 2.37 (quintet, J=6 Hz, 2H, 4-CH_2); ^{13}C nmr (DMSO-d_6): 162.3 (C-5a), 158.6, 158.1 (C-2a, C-10b, interchangeable), 148.6 (C-6a), 130.6 (C-10), 129.2 (C-8) 126.3 (C-7), 121.3 (C-9), 114.5 (C-10c), 113.9 (C-10a), 28.7 (C-3), 23.7 (C-5), 20.7 (C-4); ms (m/z): 210 (M^+). Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.44; H, 4.95; N, 13.07. The same product resulted from the Schmidt reaction of 9a and 9b in a yield of 74% and 60% respectively or by treating the oxime (8) with polyphosphoric acid at 80 °C for 2 h, according to the experimental conditions of the Beckmann rearrangement, in a yield of 68%.

11-Amino-2,3,4,5-tetrahydro-*1H-azepino[3,2-b]quinoline* (4).

To a well stirred dispersion of lithium aluminium hydride (0.75 g, 20 mmol) in anhydrous tetrahydrofuran (150 ml), a suspension of 3 (2.3 g, 10 mmol) in the same solvent (100 ml) was added slowly. The resulting mixture was allowed to reflux for 12 h, cooled at 0 °C, and water (1 ml) followed by 40% sodium hydroxide (4 ml) carefully added. The precipitated oxides were separated by filtration and washed thoroughly with warm tetrahydrofuran. The organic solution was concentrated "in vacuo" and the residue was crystallized from ethyl acetate/n-hexane; 1.5 g (70%), mp 178-177 °C. ^{1}H Nmr ($CDCl_3$, δ, ppm): 7.98-7.18 (m, 4H, aromatic protons), 5.10 (br s, 2H, exchangeable with deuterium oxide, NH_2), 3.00 (m, 4H, 2-CH_2), 2.47 (br s, 1H, exchangeable with deuterium oxide, NH), 1.78 (m, 4H, 3-CH_2 and 4-CH_2); ms (m/z): 213 (M^+). Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.27; H, 7.08; N, 19.76.

3,4,5,6-Tetrahydro-1,2a,7-triazacyclohept[*cd*]benz[e]indene (5).

Compound 4 (1 g, 4.7 mmol) in triethyl orthoformate (20 ml, 120 mmol) was

heated under reflux until tlc (ethyl acetate/methanol 9:1) indicated that the starting material has been converted. The solvent was removed and the residue was crystallized from ethyl acetate/n-hexane; 0.75 g (72%), mp 152-154 °C. ^{1}H Nmr ($CDCl_3$, δ, ppm): 8.48 (m, 1H, 11-CH), 8.05 (m 1H, 8-CH), 7.93 (s, 1H, 2-CH), 7.62 (m, 2H, 9-CH and 10-CH), 4.36 (m, 2H, 3-CH_2), 3.40 (m, 2H, 6-CH_2), 2.12 (m, 4H, 4-CH_2 and 5-CH_2); ms (m/z): 222 (M^+). Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.40; H, 6.13; N, 18.94.

3,4-Dihydroacridine-1,9(2*H*,10*H*)-dione, 1-oxime (8).

A mixture of 3,4-dihydroacridine-1,9(2*H*,10*H*)-dione (6) (2.1 g, 10 mmol) and hydroxylamine hydrochloride (3.5 g, 50 mmol) in pyridine (30 ml) was heated at 100 °C for 4 h. The mixture was poured into ice-water and the solid was collected and washed with water. The precipitate was tritured in hot ethanol, then filtered to give 1.9 g (83%) of 8, mp > 300 °C. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.29; H, 5.24; N, 12.08.

10-Ethyl-3,4-dihydroacridine-1,9(2*H*,10*H*)-dione (9a).

10-Benzyl-3,4-dihydroacridine-1,9(2*H*,10*H*)-dione (9b).

Compound 6 (4.2 g, 20 mmol) was dissolved in a biphasic mixture of toluene (150 ml) and 50% potassium hydroxide (75 ml, 670 mmol) to which benzyltrimethylammonium chloride (1.6 g, 5 mmol) had been added. Ethyl iodide (3.8 g, 24 mmol for 9a) or benzyl bromide (4.1 g, 24 mmol for 9b) was then added and the reaction mixture was stirred vigorously for 2 h. After cooling the organic phase was separated, washed with water and evaporated. The residue was chromatographed on a silica gel column by eluting with an ethyl acetate/n-hexane 1:1 mixture.

Compound 9a, 1.4 g (29%) was recrystallized from cyclohexane, mp, 84-86 °C. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.61; H, 6.25; N, 5.90.

Compound 9b, 2.4 g (40%) was recrystallized from cyclohexane, mp, 104-106 °C. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 79.29; H, 5.40;

N, 4.39.

3-Phenyl-7,8-dihydroquinoline-2,5(1*H*,6*H*)-dione (11).

2-Amino-3-phenyl-7,8-dihydroquinolin-5(6*H*)-one (12).

3,4,5,6-Tetrahydroacridine-1,8(2*H*,7*H*)-dione (13).

An intimate mixture of 1-amino-3-oxo-1-cyclohexene 10[10] (3.3 g, 30 mmol) and α-formylphenylacetonitrile[11] (4.4 g, 30 mmol) was heated with stirring in an oil bath at 130 °C for 5 h. After cooling methanol (100 ml) was added and the suspension was boiled gently for 5 min. The undissolved orange solid was removed from the hot suspension by filtration. The filter cake was recrystallized from dimethylformamide/ethanol to give 2.2. g (31%) of 11, mp 284-286 °C. ^{1}H Nmr (DMSO-d_6, δ, ppm): 12.10 (br s, 1H, exchangeable with deuterium oxide, NH), 7.92 (s, 1H, 4-CH), 7.75-7.10 (m, 5H, aromatic protons), 2.83 (t, J=6 Hz, 2H, 8-CH_2), 2.47 (t, J=6 Hz, 2H, 6-CH_2), 2.03 (m, 2H, 7-CH_2). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.52; H, 5.73; N, 5.71.

The methanolic solution was allowed to cool to room temperature, after which a yellow precipitate formed. The solid was collected by filtration and twice recrystallized from methanol to give 2.4 g (34%) of 12, mp 208-210 °C. ^{1}H Nmr (DMSO-d_6, δ, ppm): 7.63 (s, 1H, 4-CH), 7.40 (s, 5H, aromatic protons), 6.53 (br s, 2H, exchangeable with deuterium dioxide, NH_2), 2.80 (t, J=6 Hz, 2H, 8-CH_2), 2.47 (t, J=6 Hz, 2H, 6-CH_2), 2.07 (m, 2H, 7-CH_2). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.44; H, 5.81; N, 11.55.

The resulting methanolic solution was evaporated to dryness and the residue was purified by chromatography on silica gel and elution with ethyl acetate/n-hexane 2:1 mixture gave 0.7 g (11%) of 13, mp 148-151 °C (lit.,[16] 144 °C). ^{1}H Nmr ($CDCl_3$, δ, ppm): 8.70 (s, 1H, 9-CH), 3.20 (t, J=6 Hz, 4H, 4-CH_2 and 5-CH_2), 2.64 (t, J=6 Hz, 4H, 2-CH_2 and 7-CH_2), 2.24 (m, 4H, 3-CH_2 and 6-CH_2). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.61; H, 6.17; N, 6.51.

2,2-Dimethyl-5-(3-oxo-1-cyclohexen-1-yl)aminomethylene-1,3-dioxane-4,6-dione (14)

2,2-Dimethyl-8,9-dihydro-1,3-dioxino[4,5-*b*]quinoline-4,6(7*H*)-dione (15).

A suspension of 1-amino-3-oxo-1-cyclohexene (10) (5.6 g, 50 mmol) and methoxymethylene Meldrum's acid[12] (9 g, 50 mmol) in ethanol (100 ml) was refluxed for 2 h. After few minutes of heating a precipitate began to separate from the initially clear solution. The mixture was filtered, while still hot, and the solid obtained in this manner was rinsed with ethanol to afford 3.1 g (24%) of pure 14 as orange needles, mp 195-197 °C. ^{1}H Nmr ($CDCl_3$, δ, ppm): 10.90 (br d, J=13 Hz, 1H, exchangeable with deuterium oxide, NH), 8.33 (d, J=13 Hz, 1H, NH=CH), 5.91 (s, 1H, CH-CO), 2.93-1.95 (m, 6H, cyclohexene CH_2), 1.70 (s, 6H, CH_3). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.12; H, 5.84; N, 5.15.

The ethanol filtrate, from above, upon standing overnight at room temperature deposited more solid which was collected by filtration, washed with a small amount of ice-cold ethanol to yield 3.3 g (27%) of pure 15, as yellow needles, mp 138-141 °C (decomp.). ^{1}H Nmr ($CDCl_3$, δ, ppm): 8.87 (s, 1H, 10-CH), 3.13 (t, J=6 Hz, 2H, 9-CH_2), 2.70 (t, J=6 Hz, 2H, 7-CH_2), 2.26 (m, 2H, 8-CH_2), 1.84 (s, 6H, CH_3). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.16; H, 5.55; N, 5.79.

7,8-Dihydroquinoline-4,5(1*H*,6*H*)-dione (16).

7,8-Dihydroquinoline-2,5(1*H*,6*H*)-dione (17).

Each compound 14 or 15 (20 mmol) and diphenyl ether (100 ml) were placed in a flask fitted with a Dean-Stark trap. The mixture was heated rapidly to reflux temperature with vigorous stirring and then maintained until the starting material had disappeared (about 30 min). The reaction was controlled by tlc (ethyl acetate/methanol 9:1). The reaction mixture was allowed to cool to room temperature and n-hexane (100 ml) was added. The crude pale yellow solid was collected by filtration and thoroughly washed with additional n-hexane. Compound (16), obtained from 14 in a yield of 65%,

was recrystallized from isopropanol/light petroleum ether and had mp 192-104 °C. ^{1}H Nmr (DMSO-d_6, δ, ppm): 12.00 (br s, 1H, exchangeable with deuterium oxide, NH), 8.00 (d, J=7 Hz, 1H, 2-CH), 6.48 (d, J=7 Hz, 1H, 3-CH), 2.90 (t, J=6 Hz, 2H, 8-CH_2), 2.57 (t, J=6 Hz, 2H, 6-CH_2), 1.96 (m, 2H, 7-CH_2); ^{13}C nmr (DMSO-d_6): 205.9 (C-5), 176.7 (C-4), 164.3 (C-8a), 145.5 (C-2), 117.1 (C-3), 116.2 (C-4a), 38.1 (C-6), 28.8 (C-8), 21.2 (C-7). Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.97; H, 5.48; N, 8.34.

Compound (17), obtained from 15 in a yield of 72%, was recrystallized from methanol and had mp 285-288 °C (lit.,[10] 289-291 °C). ^{1}H Nmr (DMSO-d_6, δ, ppm): 12.00 (br s, 1H, exchangeable with deuterium oxide, NH), 7.78 (d, J=9 Hz, 1H, 4-CH), 6.23 (d, J=9 Hz, 1H, 3-CH), 2.80 (t, J=6 Hz, 2H, 8-CH_2), 2.47 (t, J=6 Hz, 2H, 6-CH_2), 2.05 (m, 2H, 7-CH_2); ^{13}C nmr (DMSO-d_6): 201.5 (C-5), 167.5 (C-2), 160.1 (C-8a), 145.6 (C-4), 121.2 (C-3), 117.1 (C-4a), 38.3 (C-6), 28.4 (C-8), 21.8 (C-7). Anal. Calcd for $C_9H_9NO_2$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.01; H, 5.53; N, 8.53.

4,5-Dihydro-3*H*-isoxazolo[5,4,3-*de*]quinoline (18)

This compound was obtained from 16 by Schmidt reaction in the same manner as for 7. mp 48-50 °C, from ethyl acetate/n-hexane (55%). Maleate: mp 149-151 °C from isopropanol. ^{1}H Nmr ($CDCl_3$, δ, ppm): 8.48 (d, J=6 Hz, 1H, 7-CH), 7.25 (d, J=6 Hz, 1H, 8-CH), 3.12 (m, 4H, 3-CH_2 and 5-CH_2), 2.30 (m, 2H, 4-CH_2); ^{13}C Nmr ($CDCl_3$): 164.0 (C-5a), 159.2 (C-2a), 157.8 (C-8a), 149.6 (C-7), 118.2 (C-8b), 103.4 (C-8), 28.8 (C-3), 24.3 (C-5), 21.6 (C-4). Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.44; H, 4.38; N, 9.98.

4-Amino-7,8-dihydroquinolin-5(6*H*)-one (19a)

4-Benzylamino-7,8-dihydroquinolin-5(6*H*)-one (19b)

4,5-Dihydro-3*H*-pyrazolo[3,4,5-*de*]quinoline (20)

Compound (16) (2 g, 13 mmol) was cautiously added with stirring to phosphorus oxychloride (20 ml, 215 mmol), cooled externally with ice-water. The mixture

was heated at 100° for 2 h, then evaporated to dryness under reduced pressure. The residue was made alkaline with diluted sodium hydroxide and extracted with ethyl acetate. The solvent was removed and the residue was treated with a saturated methanolic ammonia solution (20 ml), to obtain 19a, or with a 10% ethanolic benzylamine solution (30 ml, 28 mmol), to obtain 19b, or with hydrazine hydrate (2 g, 40 mmol) in ethanol (20 ml) to obtain 20. The reaction mixture was heated at 60 °C for 3 h (compound 19a was obtained by heating in a sealed flask for 20 h). The solvent was evaporated and the crude residue, was purified by column chromatography by eluting with an ethyl acetate/methanol 9:1 mixture. Compounds (19a) and (19b) were converted to their maleic acid salts in isopropanol.

19a Maleate: 0.9 g (26%); mp 199-201 °C, from isopropanol. ^{1}H Nmr (free base, $CDCl_3$, δ, ppm): 8.05 (d, J=6 Hz, 1H, 2-CH), 7.04 (br s, 2H, exchangeable with deuterium oxide, NH_2), 6.37 (d, J=6 Hz, 1H, 3-CH), 3.00 (t, J=6 Hz, 2H, 8-CH_2), 2.68 (t, J=6 Hz, 2H, 6-CH_2), 2.04 (m, 2H, 7-CH_2). Anal. Calcd for $C_9H_{10}N_2O.C_4H_4O_4$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.90; H, 5.10; N, 9.99.

19b Maleate: 1.5 g (33%); mp 165-167 °C, from isopropanol. ^{1}H Nmr (free base, $CDCl_3$, δ, ppm): 9.83 (br s, 1H, exchangeable with deuterium oxide, NH), 8.07 (d, J=6 Hz, 1H, 2-CH), 7.26 (s, 5H, aromatic protons), 6.37 (d, J=6 Hz, 1H, 3-CH), 4.43 (d, J=5 Hz, 2H, benzylic CH_2), 3.00 (t, J=6 Hz, 2H, 8-CH_2), 2.63 (t, J=6 Hz, 2H, 6-CH_2), 2.06 (m, 2H, 7-CH_2). Anal. Calcd for $C_{16}H_{16}N_2O.C_4H_4O_4$: C, 65.21; H, 5.47; N, 7.61. Found: C, 65.44; H, 5.67; N, 7.51.

20: 1.3 g (67%); mp 218-220 °C, from H_2O. ^{1}H Nmr ($CDCl_3$, δ, ppm): 12.95 (br s, 1H, exchangeable with deuterium oxide,), 8.18 (d, J=6 Hz, 1H, 7-CH), 7.25 (d, J=6 Hz, 1H, 8-CH), 3.05 (m, 4H, 3-CH_2 and 5-CH_2), 2.20 (m, 2H, 6-CH_2); ^{13}C nmr (*DMSO-d_6*): 157.3 (C-2a), 146.9 (C-5a), 144.4 (C-7), 140.7 (C-8a), 118.5 (C-8b), 103.1 (C-8), 29.1 (C-3), 24.7 (C-5), 22.3 (C-4); ms (m/z: 159 (M^+). Anal. Calcd for $C_9H_9N_3$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.12; H, 5.77; N, 26.28.

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