Synthesis and Analysis of 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole

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The synthesis of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole derivatives was carried out in one pot, by condensation of tryptamin with cycloalkanones in the presence of a polyphosphate ester as the catalyst in moderate to low yields, the aldol condensation being the main products. Reaction of tryptamine and cyclic ketones was also carried out in two stage through the imine intermediate with protic catalysis giving the tetrahydro-β-carbolines **8-14**, in good yields. 2-Methyl derivatives **15-21**, of the tetrahydro-β-carbolines, were obtained in good yields, using methyl iodide in dimethyl sulphoxide-potassium carbonate.

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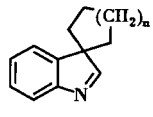
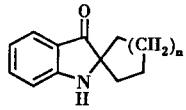
Tetrahydrocarbazoles bearing basic substituents at positions 1, 2, 3 or 4 have been the subject of a number of recent investigations. Members of this class are claimed to be hypoglycemic, analgesics, antiinflammatory, antidepressant [1a] and cardiotonic [1b].

Accordingly to the structural requirements for the antidepressant drugs, the synthesis of some spiro indole derivatives, such as 3,3-spiroindolenine [2], **1a**, 2,2-spiroindoxil [3], **1b**, was undertaken and now, this paper describes the synthesis of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole, **1c**, Scheme 1.

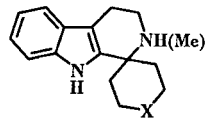
Scheme 1



1a



1b



X = $(CH_2)_n$, O, S, NMe
n = 0,1,2,3

1c

Modification of the bulk of the spiro ring in **1c** (n = 0, 1, 2, 3) and the heteroatom on the 4′ position (n = 1, X = O, S, NMe) was carried out to analyse the influence of these structures on biological activity.

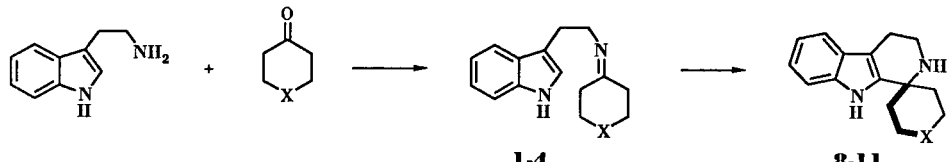
In an earlier patent [4a] was reported the preparation of the spirocyclohexane-β-carboline through the Schiff base intermediate which was cyclized in the presence of various catalysts. Recently, Cook [4b] prepared tetrahydro-β-carbolines by condensation of tryptophan methyl ester with aldehydes in refluxing benzene in the absence of a catalyst.

Thus, the synthesis of 1,2,3,4-tetrahydro-(9*H*)-pyrido-[3,4-*b*]indole was carried out starting with tryptamine and the appropriate cyclic ketone in one pot [5], in the presence of ethyl polyphosphate ester (PPE), as a weak and aprotic acid. Preparation of PPE was carried out as described previously [6]. The successful application of polyphosphate ester (PPE) as a reagent of Lewis acid type in dehydrating condensation reactions, such as the Fischer synthesis [7], polypeptide synthesis, polysaccharides, nucleosides and nucleic acids [6], prompted us to try this reagent in the Pictet-Spengler synthesis to prepare the tetrahydro-β-carbolines.

The condensation reaction of the tryptamine with the appropriate cycloalkanone in the presence of PPE as a dehydrating agent must give the corresponding imine derivative. In this first stage the water removed hydrolyzes the PPE [8] increasing the protic character which should permit the final cyclization of the intermediate imine to the β-carboline, Scheme 2.

The intermediate imine, was never detected and it permits us to suppose that the rate of the first stage of con-

Scheme 2



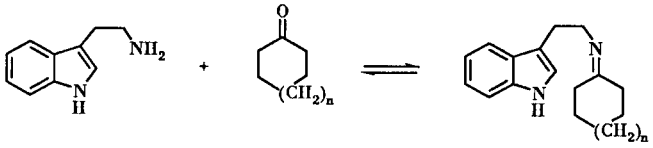
X = $(CH_2)_n$, n = 0,1,2,3,
For n = 1, X = O,S, NMe

1-4
5-7

8-11
12-14

densation of tryptamine with the cycloalkanone is lower than the electrophylic intramolecular reaction on the indole ring to give the 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]-indoles [8].

The reaction between tryptamine and the cycloalkanones of five and six members with PPE, occurs in moderate yields (32 and 38% respectively) of β-carboline together with an aldol condensation of the cycloalkanone, with considerable amounts of tryptamine remaining unchanged. For the reaction to tryptamine with cycloalkanones of seven and eight members the yields of β-carbolines are low (12 and 10% respectively) and the aldol condensation provides the main products. From these results one can propose that: a) the equilibrium of the imine formation in presence of PPE is shifted to the first member and this is more important with the bulk of the cycloalka-



X = $(CH_2)_n$, n = 0,1,2,3 **1-4**

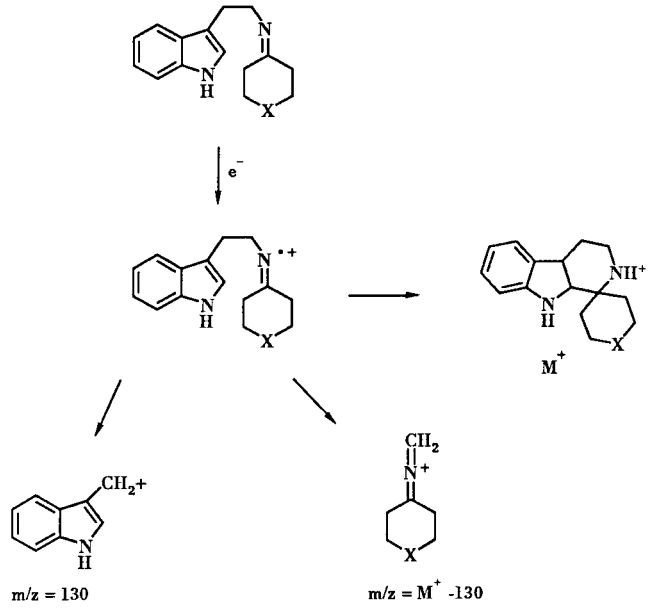
none; b) Under these reaction conditions the aldolic condensation of the cycloalkanone has the advantage of the tryptamine condensation; and then, c) the yield of the β-carboline decreases with the molar decrease of the ketone by the competing aldolic condensation. To avoid the cycloalkanone condensation, preparation of the tetrahydro-β-carbolines has been carried out by intramolecular cyclization of the imine intermediate in the presence of sulfuric acid. Thus, condensation of 1*H*-indole-3-ethanamine (tryptamine) with one equivalent of the appropriate cycloalkanone was carried out in refluxing benzene azeotropic conditions (Dean-Stark trap to remove water), in absence of an acid catalyst, provided the 3-[(*N*-cycloalkylidene)-2-aminoethyl]indoles **1-7**. The reaction time was variable (tlc) and the corresponding Schiff bases, **1-7**, were isolated in good yields. Ring closure to the β-carbolines was effected under Pictet-Spengler reaction conditions in which chloroform solutions of the imines **1-7**, were treated with sulfuric acid at room temperature. The kinetics of the reaction for cyclopentanone and cyclohexanone was fast up to the first 5 hours of the reaction, but after this was very low, except for the bulk cycloalkanones which seems to remove the water slowly, probably due to the steric hindrance near to the centers implicated in the formation of the new C=N bond. When the heterocycloalkanones were used, the behaviour with the tryptamine was similar to that of cyclohexanone so the yield was a function of the reaction rate.

The structural analysis of the Schiff bases **1-7**, was carried out by ^{1}H-nmr. The spectrum shows important analogies: the indole ring in all the Schiff bases, shows a similar proton spectrum; thus, the proton NH is always present as a broad singlet between 8.4 and 8.9 ppm; the proton on the 2-position appears as a doublet at 7.05 ppm (J = 2.4 to 2.2 Hz); the proton on the 4-position shows a multiplet always centered at 7.6 ppm. The remaining aromatic protons on positions 5, 6, and 7, appear at 7.35 to 7.05 ppm as a multiplet. The ethylenic bridge of the Schiff bases appears always as two triplets: the methylene of the benzylic type shows a triplet centered in the 3.70 to 3.50 ppm range (J = 7.40 to 8.20 Hz); the methylene on the iminic nitrogen appears centered in a range 3.08 to 3.15 ppm (J = 7.40 to 8.20 Hz). Differences appear on the carbocycle or heterocycle in Schiff base. Thus, the cycloalkane shows multiplets in the range 1.30 to 2.50 ppm. The O-, S- and NMe heterocyclohexanes, show the methylene groups as two multiplets centered at 2.33 and 2.97 for O, 3.65-3.80 and 2.15-2.50 for S, and 2.15 and 2.80 ppm for NMe. The methyl group in NMe derivative appears at 2.39 as a singlet.

b) The infrared spectra of the Schiff bases **1-7**, exhibits also important structural similarities. The more relevant absorption bands are the C=N stretching of the imine group and the aromatic substitution bands (*ortho* disubstitution). The first appears in the 1635-1620 cm^{-1} range for cycloalkane of six, seven and eight members and 1680 cm^{-1} for the cyclopentane ring. The same absorption C=N band for the heterocycloalkanes of O, S, and NMe, show higher frequency than for the cycloalkane at 1670, 1650 and 1675 cm^{-1} respectively. Moreover, the aromatic mono-substitution appears in the 750 and 735 cm^{-1} range.

c) Mass spectroscopy of the Schiff bases **1-7**, show the main pathway of fragmentation, consistent with cleavage

Scheme 3



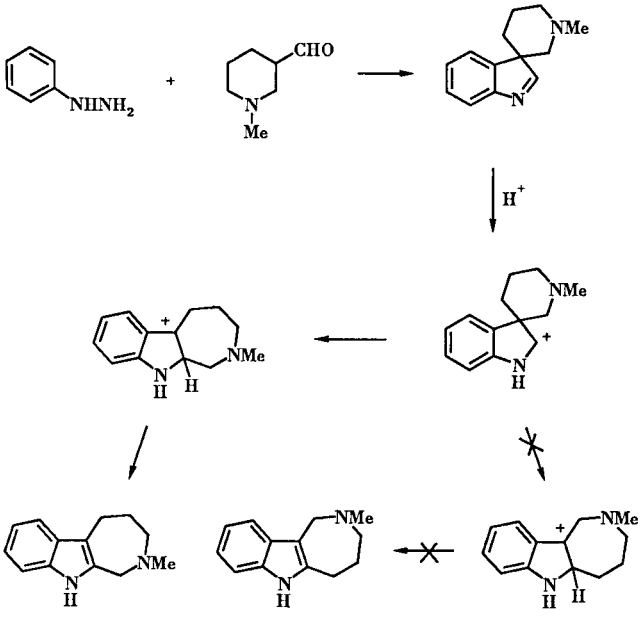
of the ethylenic bridge on position 3 of the indole ring, Scheme 3. The base peak corresponding in all the cases with the benzylic type cleavage and the resulting ion could be supported by the benzylic (m/z = 130) or the iminic type (m/z = M^+ -130) fragments. Moreover, the fragmentation pathway is identical to the β-carbolines and of low intensity. This fact indicates that the electronic impact occurs on the imine group of the Schiff base followed by the cyclization of the β-carboline due to the electrophilic character of the imine carbon atom, Scheme 3.

The 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1′-cycloalkanes were prepared by cyclization of the corresponding imine under Pictet-Spengler synthesis conditions. The cycloalkanoimines **1-7** were treated in the presence of acid at room temperature (except for **3** and **4**, at 50°). In all cases, carbolines **8-14** were obtained in good yields. The cyclization of the imines **1-7** to the tetrahydro-β-carbolines **8-14** in the presence of the catalyst, can be considered *via* two routes: a) electrophilic attack at position-2 of the intermediate carbocation, a geometrically favoured 6-endo cyclization, which seems more probable for the Pictet-Spengler or b) attack at position-3 through an indoleninium intermediate, which formally is an unfavorable 5-endo process [13] which rearranges to two carbocations, Scheme 4, that should afford to two different hexahydroazepino[3,4-*b*]indole derivatives. In our experience carried out with PPE or sulfuric acid catalyst only one carboline was detected. Study of the rearrangement of (3*H*)-indole-3-spiro-3′-methylpiperidine, under the same reaction conditions, afforded to only one rearranged indole product, Scheme 4.

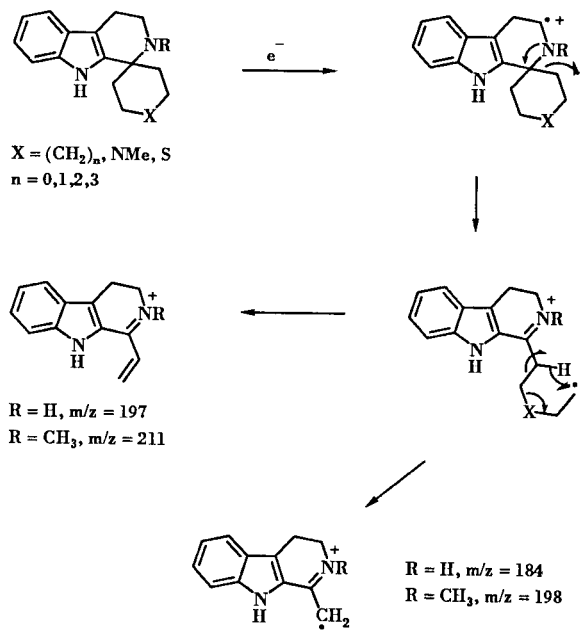
Rearrangement of the (3*H*)-indole-3-spiro-3′-methylpiperidine, can afford two indole derivatives, the 4-methyl-1,2,3,4,5,6-hexahydroazepino[3,4-*b*]indole, when the rearranged carbon atom is at position 2 of the (3*H*)-indole or the 2-methyl-1,2,3,4,5,6-hexahydroazepino[5,6-*b*]indole when the rearranged carbon atom is at position 4 of the (3*H*)-indole. The difference between both carbon atoms in the rearrangement is the stabilization of the low density charge of the carbon atom at position 2 by the vicinal nitrogen atom which is not possible on position 4.

Preparation of *N*′-methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido-[3,4-*b*]indole-1-spiro-1′-cycloalkanes **15-21**, can be obtained selectively by methylation of the NH derivatives with methyl iodide in DMSO-potassium carbonate in good yields. Structural analysis was made as follows: a) the ^{1}H-nmr spectra show important similarities for the NH of the 2-methyl derivatives. The indole ring in compounds **8-21** show the same proton spectrum. The NH proton appears as a broad singlet ranging from 8.60 to 7.65 ppm. The hydrogen on position 5 shows a centered multiplet at 7.60 ppm. The remaining aromatic protons appear at 7.60-7.00 as a multiplet. The ethylenic bridge is shown as two isolated triplets. The methylene on position 3 appears centered on the range at 2.74 to 2.67 ppm for NH derivatives, J = 5.77 to 5.82 Hz, and at 2.80 to 2.70, J = 5.77 to 5.82 Hz for the NMe derivatives. The methylene on position 4 ranges from 3.17 to 3.11 ppm for NH derivatives and at 3.25 to 3.15 ppm for the *N*-methyl derivatives (J = 5.69 to 5.82 Hz for NH and 5.77 to 5.82 Hz for NMe). In compounds **8-14** the aminic H-2 appears as a broad singlet at 1.25 ppm. The *N*-methyl derivatives **15-21** show the methyl signal on position 2 as a singlet at 2.38 to 2.36

Scheme 4



Scheme 5



ppm. Moreover, in compound **21** this signal integrated for six protons by superposition with the methyl group on position 4'. The methylene protons appears as multiplets ranging among 2.50 to 1.30 ppm. The heterocycloalkanes with oxygen, **12**, and sulfur, **13**, show the methylenes as three triplets at 1.66-1.73, 2.18-2.26, 3.80-4.02 (**12**), and 2.00-2.20, 2.34-2.46 and 3.20-3.36 (**13**). The methyl derivatives **19** and **20** show only one signal as a multiplet.

b) The mass spectrum of the NH and *N*-methyl derivatives of the carbolines **8-14** show the same fragment peaks and the only difference is the molecular ion. The electronic impact seems to happen on the aminic nitrogen which produces cleavage of the spiranic ring. The open chain gave the same peak m/z = 197, by a fragmentation of the McLafferty type and the cleavage of the alkyl residue gave m/z = 184. Both fragments have high intensity in all cases and are the base peak of the spectrum, Scheme 5.

EXPERIMENTAL

Melting points were determined using a Reichert stage microscope and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 681 spectrophotometer. Nuclear magnetic resonance spectra were recorded at 200 MHz using a Bruker WM-200-SY spectrometer. Chemical shifts are given relative to internal tetramethylsilane. Mass spectra were recorded using a Hewlett-Packard SP85 spectrometer. Elemental analysis were performed with a Model 240 Perkin-Elmer analyzer.

A. Condensation of Tryptamine with Cycloalkanone in the Presence of Polyphosphate Ester (PPE): Synthesis of the 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cycloalkanes **8-14**.

a/1. Synthesis of the 1,2,3,4-Tetrahydro-(9*H*)pyrido[3,4-*b*]indole-1-spiro-1'-cycloalkanes **8**.

A solution of 1 g (6 mmoles) of tryptamine in 10 ml of cyclopentanone (freshly distilled) was added to 0.6 ml of PPE prepared previously following Schramm's procedure [6]. The reaction was warmed at 140° with magnetic stirring for 12 hours. After cooling excess cyclohexanone was distilled under vacuum to give a residual brown oil which was purified by column chromatography using ethyl acetate:hexane (1:2) as the eluent. Cyclopentanone condensation products were identified and 0.44 g (32%) as a brown solid, mp 138-140° of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]-indole-1-spiro-1'-cyclopentane, **8** was obtained.

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.23; H, 8.33; N, 12.12.

a/2. Synthesis of 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclohexane, **9**.

Compound **9** was prepared following the procedure referred in a/1. Thus, 1 g (6 mmoles) of tryptamine in 10 ml of cyclohexanone (freshly distilled) was added 0.6 ml of PPE at reflux for 12 hours. Cyclohexanone was removed and the residual dark oil was chromatographed on a column of silica gel using ethyl acetate:hexane (1:2) as eluent. Cyclohexanone condensation products were identified and 0.56 g (38%) of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]-indole-1-spiro-1'-cyclohexane as a brown solid, mp 133-134°, was obtained.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.55; H, 8.23; N, 11.42.

a/3. Synthesis of 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cycloheptane, **10**.

Compound **10** was prepared following the procedure referred in a/1. Thus, 1 g (6 mmoles) of tryptamine in 10 ml of cycloheptanone (freshly distilled) was added to 0.6 ml of PPE and warmed at the reflux temperature for 12 hours. Cycloheptanone was removed under vacuum and the residual dark oil was chromatographed on a silica gel column using ethyl acetate:hexane as eluent (1:2). Cycloheptanone condensation products were identified and 0.20 g (12%) of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cycloheptane, as a brown solid, mp 135-137°, was obtained.

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.05; H, 8.58; N, 10.82.

a/4. Synthesis of 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclooctane, **11**.

This compound was prepared following the procedure referred in a/1. Thus, 1 g (6 mmoles) of tryptamine in 10 ml of cycloheptanone (freshly distilled) was added to 0.6 ml of PPE and warmed at the reflux temperature for 12 hours. Cyclooctanone was removed under vacuum and the residual dark oil was chromatographed in a silica gel column using ethyl acetate:hexane as eluent (1:2). Cyclooctanone condensation products were identified and 0.17 g (10%) of 1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclooctane, as a brown solid, mp 138-140°, was obtained.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.25; H, 8.87; N, 10.27.

B. Condensation of Tryptamine with Cycloalkanone (or Heterocyclohexanone) with a Protic Catalyst: a/ Preparation of 3-[(*N*-cycloalkyliden)-2-aminoethyl]indoles, **1-7**.

a/. A solution of 0.025 mole of tryptamine and 0.030 mole of the appropriate cycloalkanone in dry benzene was boiled 5 hours with a Dean-Stark, to remove water azeotropically. The mixture was concentrated up to half volume and then cooled in an ice bath giving a brown solid, which was filtered off and recrystallized from benzene to give a crystalline yellow solid with the following yields and spectral data.

a/1. 3-[(*N*-Cyclopentyliden)-2-aminoethyl]indole, **1**.

This compound had mp 110-112°, 85% yield; ^{1}H nmr (deuteriochloroform): 8.50 (s broad, 1H, ArH-1), 7.00 (d, J = 2.39 Hz, 1H, ArH-2), 7.36-7.10 (m, 4H, ArH), 3.55 (t, J = 7.7 Hz, 2H, CH_2-A), 3.12 (t, J = 7.7 Hz, 2H, CH_2-B), 2.45-1.65 (m, 8H, CH_2-cyclic); ir (potassium bromide): 1680 (st C=N), 735 (*ortho* substituted Ar); ms: (70 eV) 226 (M^+, 35%), 130 (100), 96 (87).

Anal. Calcd. for $C_{15}H_{19}N_2$: C, 79.25; H, 8.42; N, 12.32. Found: C, 79.30; H, 8.27; N, 12.45.

a/2. 3-[(*N*-Cyclohexyliden)-2-aminoethyl]indole, **2**.

This compound had mp 109-110°, 80% yield; ^{1}H nmr (deuteriochloroform): 8.40 (s broad, 1H, ArH-1), 7.00 (d, J = 2.4 Hz, 1H, ArH-2), 7.68-7.60 (m, 4H, ArH), 3.66 (t, J = 7.7 Hz, 2H, CH_2-A), 3.08 (t, J = 7.7 Hz, 2H, CH_2-B), 2.33-1.43 (m, 10H, CH_2-cyclic); ir (potassium bromide): 1620 (st C=N), 740 (*ortho* substituted Ar); ms: (70 eV) 240 (M^+, 21%), 130 (100), 110 (93).

Anal. Calcd. for $C_{16}H_{21}N_2$: C, 79.62; H, 8.77; N, 11.61. Found:

C, 79.41; H, 8.56; N, 11.32.

a/3. 3-[(*N*-Cycloheptyliden)-2-aminoethyl]indole, **3**.

This compound had mp 125-126°, 83% yield; ^{1}H nmr (deuteriochloroform): 8.85 (s broad, 1H, ArH-1), 6.98 (d, J = 2.2 Hz, 1H, ArH-2), 7.65-7.60 (m, 4H, ArH), 3.54 (t, J = 8.2 Hz, 2H, CH_2-A), 3.14 (t, J = 8.2 Hz, 2H, CH_2-B), 2.51-1.52 (m, 12H, CH_2-cyclic); ir (potassium bromide): 1630 (st C=N), 740 (*ortho* substituted Ar); ms: (70 eV) 254 (M^+, 10%), 124 (100), 130 (11).

Anal. Calcd. for $C_{17}H_{23}N_2$: C, 79.95; H, 9.08; N, 10.97. Found: C, 79.77; H, 8.86; N, 10.65.

a/4. 3-[(*N*-Cyclooctyliden)-2-aminoethyl]indole, **4**.

This compound had mp 122-124°, 72% yield; ^{1}H nmr (deuteriochloroform): 8.55 (s broad, 1H, ArH-1), 7.00 (d, J = 2.2 Hz, 1H, ArH-2), 7.66-7.59 (m, 4H, ArH), 3.67 (t, J = 7.89 Hz, 2H, CH_2-A), 3.15 (t, J = 7.89 Hz, 2H, CH_2-B), 2.50-1.31 (m, 14H, CH_2-cyclic); ir (potassium bromide): 1635 (st C=N), 740 (*ortho* substituted Ar); ms: (70 eV) 268 (M^+, 9%), 138 (100), 130 (37).

Anal. Calcd. for $C_{18}H_{25}N_2$: C, 80.25; H, 9.35; N, 10.40. Found: C, 80.23; H, 9.18; N, 10.12.

a/5. 3-[(*N*-Tetrahydropyran-4'-yliden)-2-aminoethyl]indole, **5**.

This compound had mp 122-124°, 74% yield; ^{1}H nmr (deuteriochloroform): 8.40 (s broad, 1H, ArH-1), 6.98 (d, J = 2.3 Hz, 1H, ArH-2), 7.65-7.60 (m, 4H, ArH), 3.69 (t, J = 7.3 Hz, 2H, CH_2-A), 3.09 (t, J = 7.3 Hz, 2H, CH_2-B), 2.97-2.33 (m, 8H, CH_2-cyclic); ir (potassium bromide): 1670 (st C=N), 750 (*ortho* substituted Ar); ms: (70 eV) 242 (M^+, 16%), 130 (100), 112 (45).

Anal. Calcd. for $C_{15}H_{19}N_2O$: C, 74.04; H, 7.87; N, 11.51. Found: C, 73.85; H, 7.56; N, 11.24.

a/6. 3-[(*N*-Tetrahydrothiopyran-4'-yliden)-2-aminoethyl]indole, **6**.

This compound had mp 114-115°, 78% yield; ^{1}H nmr (deuteriochloroform): 8.75 (s broad, 1H, ArH-1), 6.95 (d, J = 2.2 Hz, 1H, ArH-2), 7.65-7.58 (m, 4H, ArH), 3.60 (t, J = 7.2 Hz, 2H, CH_2-A), 3.10 (t, J = 7.2 Hz, 2H, CH_2-B), 3.80-3.65 and 2.50-2.15 (m, 8H, CH_2-cyclic); ir (potassium bromide): 1650 (st C=N), 750 (*ortho* substituted Ar); ms: (70 eV) 258 (M^+, 20%), 130 (100), 128 (49).

Anal. Calcd. for $C_{15}H_{19}N_2S$: C, 69.46; H, 7.38; N, 10.80; S, 12.36. Found: C, 69.29; H, 7.24; N, 10.65; S, 11.98.

a/7. 3-[(*N*-(4'-Methyl)pyperidino-4'-yliden)-2-aminoethyl]indole, **7**.

This compound had mp 105-106°, 70% yield; ^{1}H nmr (deuteriochloroform): 8.90 (s broad, 1H, ArH-1), 6.95 (d, J = 2.2 Hz, 1H, ArH-2), 7.65-7.60 (m, 4H, ArH), 3.69 (t, J = 7.4 Hz, 2H, CH_2-A), 3.08 (t, J = 7.4 Hz, 2H, CH_2-B), 2.80-2.15 (m, 8H, CH_2-cyclic), 2.39 (s, 3H, CH_3); ir (potassium bromide): 1675 (st C=N), 740 (*ortho* substituted Ar); ms: (70 eV) 255 (M^+, 15%), 130 (51), 125 (100).

Anal. Calcd. for $C_{16}H_{22}N_3$: C, 74.96; H, 8.65; N, 16.39. Found: C, 74.67; H, 8.55; N, 16.12.

b) Preparation of the 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclo(or heterocyclo)alkanes, **8-14**.

To a solution of 0.020 mole of the 3-[(*N*-cycloalkyliden)-2-aminoethyl]indole in 80 ml of methanol, cooled in an ice bath, were added dropwise 20 ml of concentrated sulfuric acid. The mixture was stirred at room temperature for 5 hours and finally was poured into ice-water, made basic with aqueous sodium hydroxide (30%) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and after the solvent was removed, a yellow solid was obtained which was recrystallized from hexane with the following yields and spectral data.

b/1. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclopentane, **8**.

This compound, as yellow crystals, had mp 138-140° (hydrochloride, mp 250-252° dec), 80% yield; ^{1}H nmr (deuteriochloroform): 7.75 (s broad, 1H, NH-9), 7.50-7.05 (m, 4H, ArH), 3.17 (t, J = 5.8 Hz, 2H, CH_2-4), 2.74 (t, J = 5.8 Hz, 2H, CH_2-3), 2.10-1.80 (m, 8H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 226 (M^+, 30%), 199 (100), 184 (31).

Anal. Calcd. for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.46; H, 8.22; N, 12.18.

b/2. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclohexane, **9**.

This compound, as yellow crystals, had mp 133-134° (hydrochloride, 260-262 dec), 72% yield; ^{1}H nmr (deuteriochloroform): 7.72 (s broad, 1H, NH-9), 7.45-7.05 (m, 4H, ArH), 3.14 (t, J = 5.7 Hz, 2H, CH_2-4), 2.71 (t, J = 5.7 Hz, 2H, CH_2-3), 1.80-1.45 (m, 10H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 240 (M^+, 31%), 197 (100), 184 (19).

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.63; H, 8.45; N, 11.42.

b/3. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cycloheptane, **10**.

This compound, as yellow crystals, had mp 135-137° (hydrochloride, 240-242° dec), 70% yield; ^{1}H nmr (deuteriochloroform): 7.85 (s broad, 1H, NH-9), 7.50-7.00 (m, 4H, ArH), 3.14 (t, J = 5.8 Hz, 2H, CH_2-4), 2.69 (t, J = 5.8 Hz, 2H, CH_2-3), 1.90-1.80 (m, 12H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 254 (M^+, 28%), 197 (100), 184 (26).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.15; H, 8.66; N, 10.85.

b/4. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclooctane, **11**.

This compound, as yellow crystals, had mp 138-140° (hydrochloride, 238-240° dec), 62% yield; ^{1}H nmr (deuteriochloroform): 8.10 (s broad, 1H, NH-9), 7.50-7.00 (m, 4H, ArH), 3.13 (t, J = 5.8 Hz, 2H, CH_2-4), 2.67 (J = 5.8 Hz, 2H, CH_2-3), 1.90-1.30 (m, 14H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms; (70 eV) 268 (M^+, 28%), 197 (97), 184 (100).

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.34; H, 8.79; N, 10.12.

b/5. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-tetrahydropyran, **12**.

This compound, as yellow crystals, had mp 182-184° (hydrochloride, 255-256° dec), 74% yield; ^{1}H nmr (deuteriochloroform): 8.30 (s broad, 1H, NH-9), 7.60-7.10 (m, 4H, ArH), 3.15 (t, J = 5.7 Hz, 2H, CH_2-4), 2.72 (t, J = 5.7 Hz, 2H, CH_2-3), 4.02-3.88, 2.26-2.18, and 1.73-1.66 (m, 8H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 242 (M^+, 31%), 197 (44), 184 (100).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.30; H, 7.29; N, 11.45.

b/6. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-tetrahydrothiopyran, **13**.

This compound, as yellow crystals, had mp 165-167° (hydrochloride, 220-222° dec), 75% yield; ^{1}H nmr (deuteriochloroform): 7.80 (s broad, 1H, NH-9), 7.55-6.95 (m, 4H, ArH), 3.11 (t, J = 5.7

Hz, 2H, CH_2-4), 2.69 (t, J = 5.7 Hz, 2H, CH_2-3), 3.36-3.20, 2.46-2.34, and 2.20-2.00 (m, 8H, CH_2-cyclic), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 258 (M^+, 8%), 197 (100), 184 (41).

Anal. Calcd. for $C_{15}H_{18}N_2S$: C, 69.73; H, 7.02; N, 10.84; S, 12.41. Found: C, 69.35; H, 7.21; N, 10.65; S, 12.04.

b/7. 1,2,3,4-Tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-(*N*'-methyl)piperidine, **14**.

This compound, as yellow crystals, had mp 188-190° (hydrochloride, 235-237° dec), 65% yield; ^1H nmr (deuteriochloroform): 8.60 (s broad, 1H, NH-9), 7.50-6.95 (m, 4H, ArH), 3.12 (t, J = 5.8 Hz, 2H, CH_2-4), 2.70 (t, J = 5.8 Hz, 2H, CH_2-3), 2.80-2.00 (m, 8H, CH_2-cyclic), 2.38 (s, 3H, CH_3), 1.25 (s broad, 1H, NH-2); ms: (70 eV) 255 (M^+, 45%), 197 (100), 184 (48).

Anal. Calcd. for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46. Found: C, 75.23; H, 8.38; N, 16.25.

c/ Preparation of the 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclo(or heterocyclo)alkanes, **15-21**.

Potassium carbonate (0.55 g, 4 mmoles) in 15 ml of dimethyl sulphoxide (DMSO) was stirred at room temperature for 30 minutes. A solution of 4 mmoles of 1,2,3,4-tetrahydro-(9*H*)-pyrido-[3,4-*b*]indole-1-spiro-1'-cycloalkane in 10 ml of DMSO was added and then 0.57 g (4 mmoles) of methyl iodide was added dropwise. The mixture was stirred at room temperature for 3 hours. The DMSO was distilled under vacuum and the residual oil was washed with water and extracted with dichloromethane. The solution was dried over magnesium sulfate and evaporated to give a yellow solid with the following yields and spectral data:

c/1. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclopentane, **15**.

This compound had mp 125-126°, 72% yield; ^1H nmr (deuteriochloroform): 7.80 (s broad, 1H, NH-9), 7.65-7.05 (m, 4H, ArH), 3.15 (t, J = 5.8 Hz, 2H, CH_2-4), 2.80 (t, J = 5.8 Hz, 2H, CH_2-3), 2.40-1.90 (m, 8H, CH_2-cyclic), 2.38 (s, 3H, CH_3); ms: (70 eV) 240 (M^+, 43%), 211 (100), 198 (35).

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.96; H, 8.39; N, 11.66. Found: C, 79.79; H, 8.15; N, 11.46.

c/2. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclohexane, **16**.

This compound had mp 115-117°, 70% yield; ^1H nmr (deuteriochloroform): 8.10 (s broad, 1H, NH-9), 7.55-7.05 (m, 4H, ArH), 3.20 (t, J = 6.0 Hz, 2H, CH_2-4), 2.80 (t, J = 6.0 Hz, 2H, CH_2-3), 2.20-1.65 (m, 10H, CH_2-cyclic), 2.38 (s, 3H, CH_3); ms: (70 eV) 254 (M^+, 31%), 211 (100), 198 (20).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.27; H, 8.27; N, 11.01. Found: C, 80.15; H, 8.68; N, 11.10.

c/3. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cycloheptane, **17**.

This compound had mp 110-112°, 65% yield; ^1H nmr (deuteriochloroform): 7.95 (s broad, 1H, NH-9), 7.60-7.05 (m, 4H, ArH), 3.25 (t, J = 6.1 Hz, 2H, CH_2-4), 2.80 (t, J = 6.1 Hz, 2H, CH_2-3), 2.60-1.90 (m, 12H, CH_2-cyclic), 2.38 (s, 3H, CH_3); ms: (70 eV) 268 (M^+, 100%), 211 (57), 198 (83).

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.42; H, 8.73; N, 10.32.

c/4. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-1'-cyclooctane, **18**.

This compound had mp 105-106°, 60% yield; ^1H nmr (deuteriochloroform): 7.90 (s broad, 1H, NH-9), 7.65-6.95 (m, 4H, ArH), 3.25 (t, J = 6.1 Hz, 2H, CH_2-4), 2.80 (t, J = 6.1 Hz, 2H, CH_2-3), 2.40-1.65 (m, 14H, CH_2-cyclic), 2.36 (s, 3H, CH_3); ms: (70 eV) 282 (M^+, 5%), 211 (29), 198 (100).

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.67; H, 9.20; N, 9.72.

c/5. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-tetrahydropyrane, **19**.

This compound had mp 152-154°, 68% yield; ^1H nmr (deuteriochloroform): 7.90 (s broad, 1H, NH-9), 7.75-7.10 (m, 4H, ArH), 3.20 (t, J = 6.1 Hz, 2H, CH_2-4), 2.75 (t, J = 6.1 Hz, 2H, CH_2-3), 2.30-1.75 (m, 8H, CH_2-cyclic), 2.38 (s, 3H, CH_3); ms: (70 eV) 256 (M^+, 35%), 211 (42), 198 (100).

Anal. Calcd. for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.87; H, 7.68; N, 10.79.

c/6. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-tetrahydrothiopyrane, **20**.

This compound had mp 157-158°, 70% yield; ^1H nmr (deuteriochloroform): 7.85 (s broad, 1H, NH-9), 7.55-7.10 (m, 4H, ArH), 3.25 (t, J = 6.1 Hz, 2H, CH_2-4), 2.75 (t, J = 6.1 Hz, 2H, CH_2-3), 2.25-1.90 (m, 8H, CH_2-cyclic), 2.35 (s, 3H, CH_3); ms: (70 eV) 272 (M^+, 15%), 211 (100), 198 (28).

Anal. Calcd. for $C_{16}H_{20}N_2S$: C, 70.55; H, 7.40; N, 10.28. Found: C, 70.33; H, 7.42; N, 10.07.

c/7. 2-Methyl-1,2,3,4-tetrahydro-(9*H*)-pyrido[3,4-*b*]indole-1-spiro-4'-(*N*'-methyl)piperidine, **21**.

This compound had mp 160-162°, 65% yield; ^1H nmr (deuteriochloroform): 8.10 (s broad, 1H, NH-9), 7.55-7.10 (m, 4H, ArH), 3.15 (t, J = 6.1 Hz, 2H, CH_2-4), 2.70 (t, J = 6.1 Hz, 2H, CH_2-3), 2.50-1.90 (m, 8H, CH_2-cyclic), 2.38 (s, 3H, CH_3); ms: (70 eV) 269 (M^+, 20%), 211 (100), 198 (31).

Anal. Calcd. for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60. Found: C, 75.66; H, 8.43; N, 15.56.

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