Alkylation of Cycloalkano[*b*]indoles *via* Indolylmagnesium Salts: Synthesis of 3*H*-Indoles and Oxidative Rearrangement to Spiro[cycloalkane-1,2'-indolin]-3'-ones

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Alkylation of cycloalkano[*b*]indolylmagnesium iodide with alkyl halides has been analyzed to prepare cycloalkano-3*H*-indoles, methyl and *N*,*N*-dimethylpropyl derivatives. Spiro[cycloalkane-1,2'-indolin-3'-one] derivatives appear as secondary products in this reaction. Selectivity and optimization of the reaction has been determined and a mechanism for the formation of the spiro derivative is proposed.

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Introduction.

The synthesis of tryptamines have been carried out utilizing Grignard reagents by coupling an indolylmagnesium halide with α-haloacetonitriles, α-chloroacetamides, and acyl chlorides, generally resulting in low yields. The coupling reaction has been intensively investigated because the products serve for the preparation of tryptamines and alkaloids [1-3].

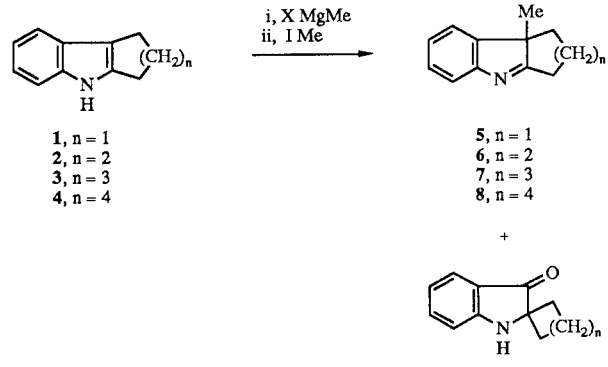
Reaction of the 1*H*-indole with Grignard reagents gives the indolylmagnesium halide in quantitative yield [4] which reacts further with an alkylating agent giving substituted indoles in position 3, in variable yields [5,6]. The alkylating reagent may react with the indolylmagnesium derivative giving a *N*- or *C*-alkylation product. The regioselectivity in this reaction seems dependent on the solvent: ethereal solvents favour alkylation in position 3, while in hexamethylenephosphorotriamide as solvent, *N*-alkylation is the main product [7].

On the other hand, 2,3-disubstituted indolylmagnesium iodide affords 3*H*-indole derivatives, albeit in low yields [8]. We are interested in the study of the *C*-alkylation of cycloalkano[*b*]indoles through organomagnesium reagents and alkyl halides in order to prepare 3*H*-indole derivatives of tricyclic compounds.

Alkylation of Cycloalkano[*b*]indolylmagnesium Iodide.

Preparation of the starting cycloalkano[*b*]indoles, namely cyclopentano-, cyclohexano-, cycloheptano-, and cyclooctano- **1-4**, was carried out by a thermal reaction of the phenylhydrazone of the appropriate cycloalkanone in ethylene glycol as the solvent in 76% to 84% yield. Preparation of the indolylmagnesium derivatives was carried out "*in situ*" by means of methylmagnesium iodide with the cycloalkano[*b*]indoles **1-4** in quantitative yield. Thus, the reaction between 1,2,3,4-tetrahydrocyclopentano[*b*]indolylmagnesium and methyl iodide, was carried out in diethyl ether (or THF) as the solvent in variable concentrations of the Grignard reagent and an excess of methyl iodide; in low concentrations of the indolylmagnesium salt the starting indole was recovered untransformed; the increment of the concentration to 0.41 mol·l^{-1} and degassification of the solvent, gave only the 3*H*-indole **5** in 44% yield, recovering the starting indole product in large amounts.

However, it is noteworthy that the yield in the alkylation product was considerably lower than that found for the remaining cycloalkano[*b*]indoles, Table 1, although the indolylmagnesium derivative was formed in practically quantitative yield. Thus, the tension or planarity of the cyclopentane ring in the cyclopentano[*b*]indolylmagnesium salt, partially inhibits the reaction with methyl iodide through the nucleophilic 8b position. The *N*-alkylation product at gc/ms detection limits, was never observed.



1, n = 1
2, n = 2
3, n = 3
4, n = 4

5, n = 1
6, n = 2
7, n = 3
8, n = 4

+

9, n = 1
10, n = 2
11, n = 3
12, n = 4

The reaction between 1,2,3,4-tetrahydrocarbazolylmagnesium iodide (n = 2) and methyl iodide gave two products detected by gc/ms: i) The expected 4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole **6**, and ii) the spiro[cyclopentane-1,2'-indolin-3'-one] **10**. On the basis of our experimental results it can be deduced that the yield in the alkylation and the spiro derivative products was dependent on the concentration in indolylmagnesium reagent. In this sense it was also observed that the 3*H*-indole/-

pseudoindoxyl (**6**/**10**) ratio, decreases with the dilution of the reagents, while in high concentrations and using an argon saturated ethereal solvent this ratio strongly increases, Table 2.

It is convenient to understand the origin of the incorporation of the oxygen to the indolic system, to avoid the spiro derivative and thus to improve the alkylation product.

The affinity of the indolylmagnesium intermediates to the residual amounts of air dissolved in the ethereal solvent was proved in the following two assays with the 1,2,3,4-tetrahydrocarbazolylmagnesium iodide: i) A suspension of the cycloalkano[*b*]indolylmagnesium derivative and methyl iodide in diethyl ether was treated with a saturated solution of oxygen in diethyl ether and the pseudoindoxyl derivative **10** was obtained as the only product. ii). The suspension of indolylmagnesium salt and methyl iodide was carried out in ethereal solvents previously degassified and then bubbled continuously with a stream of argon and the pseudoindoxyl product extremely decreased. Thus, to improve the yield in the 3*H*-indole derivative, a high concentration of the reagents in argon saturated solvents is required, Table 1. Optimal concentration of the indolylmagnesium iodide to obtain good yields in the alkylation product was that between 0.4-0.5 mol·l^{-1}.

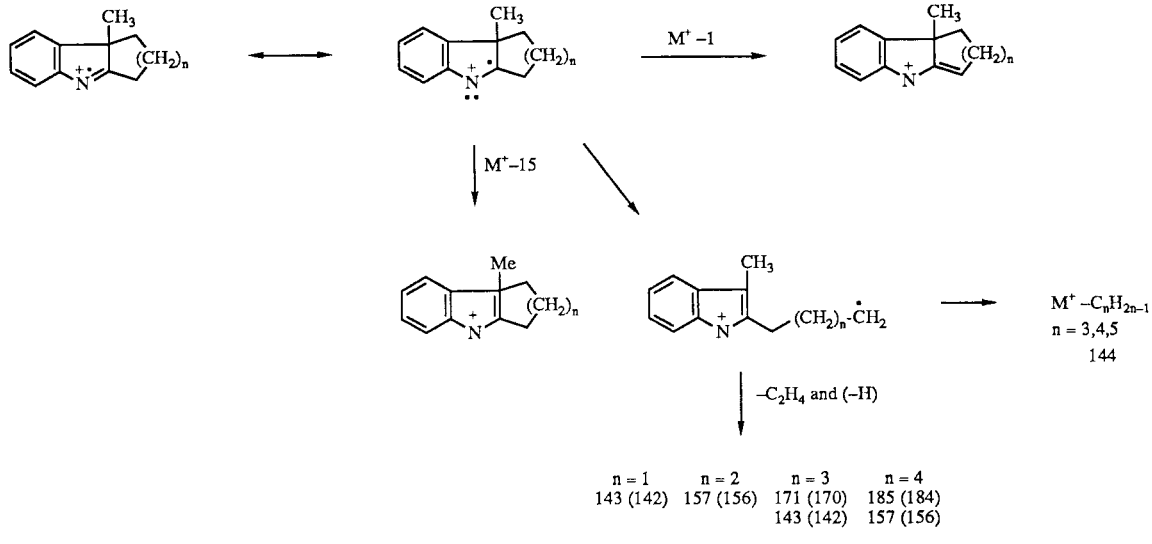
The reaction between the 5,6,7,8,9,10-hexahydrocycloheptano[*b*]indolylmagnesium in diethyl ether (argon saturated, 0.50 mol·l^{-1}) and methyl iodide affords the 10a-methyl-6,7,8,9,10,10a-hexahydrocycloheptano[*b*]indole, **7**, in 65% yield and the pseudoindoxyl **11** in 9% yield (after 72 hours, Table 1). The alkylation reaction between cycloctano[*b*]indolylmagnesium (0.45 mol·l^{-1}) in diethyl ether (argon saturated) and methyl iodide gives the 11a-methyl-6,7,8,9,10,11-hexahydro-11a*H*-cyclooctano[*b*]-indole, **8**, in 75% yield and the spiro[cycloheptane-1,2'-indolin-3'-one] **12** in 12% yield. An alternative way for the preparation of methyl-3*H*-indole derivatives was the Fischer reaction of phenylhydrazones of 2-methylcycloalkanones. 2-Methylcyclopentanone and 2-methylcycloheptanone were prepared by methylation of the enamines of the corresponding cycloalkanones [9]. The Fischer reaction of these phenylhydrazones was carried out by acid catalysis or a thermal reaction giving, in general, two main products; the methylcycloalkan-3*H*-indoles and the methylcycloalkano[*b*]indoles in variable ratio depending on the reaction conditions (See Experimental). It is interesting to note the linkage of the 3-dimethylaminopropyl radical on the 3*H*-indole structures to prepare potentially antidepressant drugs. The synthesis of 4a-(3-dimethylaminopropyl)-1,2,3,4-tetrahydro-4a*H*-carbazole **13** was carried out by means of the alkylation reaction of the 1,2,3,4-tetrahydrocarbazolylmagnesium iodide in diethyl ether (argon saturated, 0.4 mol·l^{-1}) with 3-chloro-*N*,*N*-dimethylpropylamine. Compound **13** was obtained after column chromatography separation in 50% yield and pseudoindoxyl **10** in 10% yield.

On the other hand, the synthesis of 5a-(3-dimethylaminopropyl)-6,7,8,9,10,10a-hexahydrocycloheptano[*b*]indole **14** was carried out by the reaction of the 5,6,7,8,9,10-hexahydrocycloheptano[*b*]indolylmagnesium iodide in diethyl ether (saturated in argon, 0.4 mol·l^{-1}) with 3-chloro-*N*,*N*-dimethylpropylamine. Compound **14** was isolated in 53% yield and pseudoindoxyl **11** in 12% yield respectively after column chromatography.

Analysis of the Methyl-3*H*-indoles.

^{1}H-nmr spectra of these compounds exhibit the aromatic protons as a multiplet centered on 7.3 ppm while

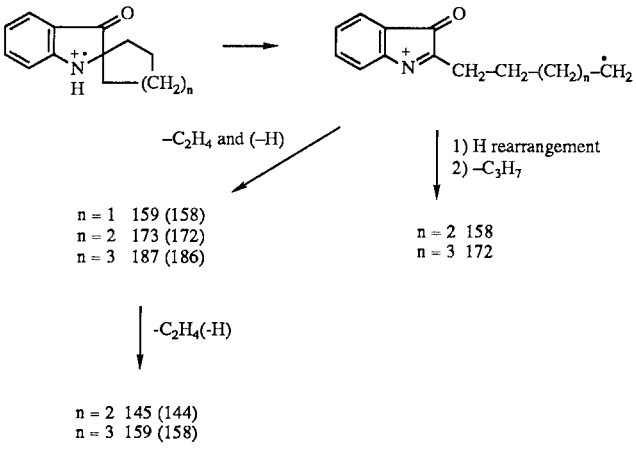
Scheme I



the methyl, on position 3 of the indole ring, shows congested frequencies which are only mildly shielded by the bulk of the cycloalkane ring. Moreover, the generation of the chiral centre on this position 3 produces a diastereotopic effect on the methylene groups of the cycloalkane.

In the ir spectra the intense absorption band is remarkable at 1630 cm^{-1} corresponding to C = N bond stretching.

Scheme II



Mass spectra show important analogies related to the fragmentation pattern. The electronic impact occurs on the nitrogen atom which produces the fragmentation of the cycloalkane ring by a benzylic type position giving a mass loss fragment of C_nH_{2n-1} or successively a mass loss due to ethylene molecules, Scheme I.

Preparation of Spiro[cycloalkane-1,2'-indolin-3'-one].

The spiro[cyclopentane-1,2'-indolin-3'-one] has been isolated in low yield in the reaction of the tetrahydrocarbazole with oxidative reagents such as hydrogen peroxide (or peroxy acids), manganese dioxide, or catalytic Pt oxygenation [10].

The reaction of the indolylmagnesium derivatives with oxygen was analyzed to obtain the pseudoindoxyl derivatives in preparative amounts.

All the attempts carried out for the synthesis of the spiro[cyclobutane-1,2'-indolin-3'-one] **9** were unsuccessful.

The synthesis of spiro[cyclopentane-1,2'-indolin-3'-one] **10** was carried out in the same way, by treatment of 1,2,3,4-tetrahydrocarbazolylmagnesium iodide with diethyl ether saturated with oxygen. Compound **10** was the only reaction product in 70% yield after chromatography.

Under the same conditions, the synthesis of spiro[cyclohexane-1,2'-indolin-3'-one] **11** and spiro[cycloheptane-1,2'-indolin-3'-one] **12** were obtained in 78% and 75% yield respectively after chromatography.

Analysis of the Spiro[cycloalkane-1,2'-indolin-3'-ones] **10**, **11** and **12**.

In the ^{1}H-nmr spectra of these compounds, the aromatic protons appear as a multiplet at 7.5-6.8 ppm. The protons of the cycloalkane ring appear as a broad multiplet at 1.8-1.5 ppm.

In the ir spectrum the strong absorption band at 1670-1680 is remarkable corresponding to the stretching of C = O group and at 3300 cm^{-1} due to the NH group.

Mass spectra show the same route of fragmentation for the pseudoindoxyl derivatives. The electronic impact occurs on the nitrogen atom which produces the fragmentation of the spirocycloalkane ring followed by successive of hydrogen and ethylene loss mass fragments, Scheme II. On the basis of our results, and by analogy with the oxygen incorporation in alkyl and arylmagnesium halides,

Table 1

Reaction of 1-4-MgX with Methyl Iodide. Formation of 3*H*-Indoles

Conc. [a]	t (h)	3*H*-Indole	%Yield [b]	Mp (°C)	m/z	Spiro	% Yield
0.41	48	5	44	152-154 [c]	171	9	–
0.47	24	6	72	66-67	185	10	9
0.50	72	7	65	164-166 [c]	199	11	9
0.45	24	8	75	169-171 [c]	213	12	12

[a] Concentration (in mol • l^{-1}) of starting methylmagnesium iodide. [b] In argon saturated diethyl ether; similar values obtained in THF. [c] As picrate.

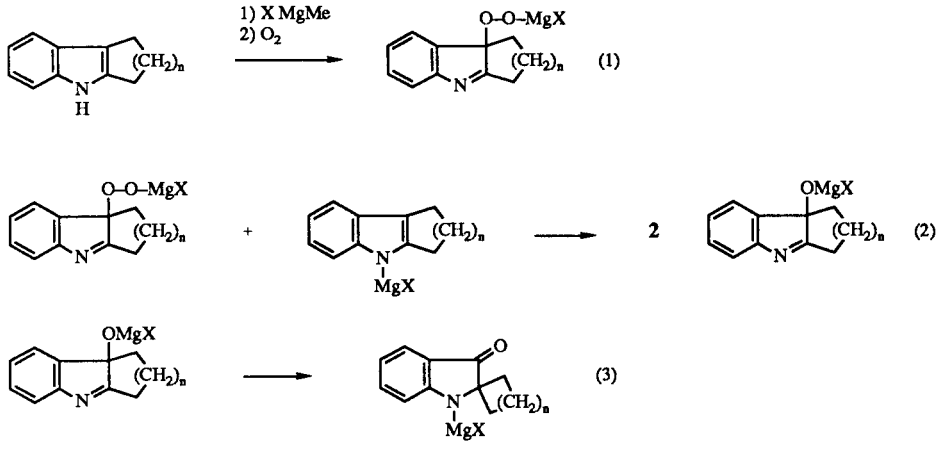
Table 2

Reaction of 2-4-MgX at Variable Concentrations with Methyl Iodide Yield of 3-*H*-Indoles and Pseudoindoxyl Derivatives

Conc. [a]	t (h)	%6	%10	%7	%11	%8	%12
0.06	2	6	16	–	5	4	9
0.12	2	17	40	1	10	10	33
0.12	24	25	37	3	26	27	30
0.36	24	57	14	5	30	62	18
0.45 [a]	24	70	10	45	10	75	12

[a] In diethyl ether saturated in argon.

Scheme III



we propose the mechanism of the rearrangement reaction shown in Scheme III: Stage 1 refers to the oxygen incorporation in the indolylmagnesium moiety presumably through a radical intermediate [11]. Stage 2, consists of a nucleophilic attack of an indolylmagnesium iodide on the intermediate magnesium peroxidate bond in an analogous manner to that described for the reaction between the Grignard reagents and peroxides [12]. Finally, stage 3 shows a Wagner-Meerwein pathway for the rearrangement to the spiro[cycloalkane-1,2′-indolin]-3′-one as has also been proposed by Witkop to explain analogous rearrangements in indolic systems [13]. The mechanism justifies the difficulty found for the synthesis of the spiro derivative **9** because of the Wagner-Meerwein type rearrangement necessary to give the spiro-cyclobutane derivative, stage 3 or Scheme III. Furthermore, as indicated above, the cyclopentano[*b*]indolylmagnesium iodide exhibits some steric hindrance to the reaction with methyl iodide and probably with the oxygen molecule and hence, the magnesium hydroperoxidate could be formed in low yield. The fact that pseudoindoxyl **11** was always obtained in higher yield for the same reaction time than the remaining pseudoindoxyles **10** and **12**, seems related to the stability of the spiro[cycloalkane-1,2′-indoline-3′-one].

Table 3

Reaction of 1-4-MgX with Methyl Iodide. Formation of Psuedoindoxyl Derivatives

Conc.	Pseudoindoxyl	% Yield [b]	Mp (°C) [c]	m/z
0.41	9	–	–	–
0.47	10	70	76-77	187
0.50	11	78	136-137	201
0.45	12	75	126-127	215

[a] Concentration (in mol • l^{-1}) of starting methylmagnesium iodide. [b] In oxygen saturated diethyl ether. Yield after chromatography. [c] Yellow crystals.

That the six-membered cycloalkane ring in **11** is more stable in good agreement with the effect found in Plancher's rearrangement occurring in spiro[cycloalkane-1,3′-3*H*-indole] [14].

EXPERIMENTAL

Melting points were determined by using a Reichert stage microscope and are uncorrected. Infrared spectra were recorded using a Nicolet 5 DX, as nujol suspension or potassium bromide pellets. Nuclear magnetic resonance spectra were recorded on a Bruker WM-200-SY spectrometer. Chemical shifts (δ), are given relative to internal tetramethylsilane. Elemental analyses were performed with a Perkin-Elmer 240 analyzer. Mass spectra were recorded on a Hewlett-Packard 5985 GC/MS system.

A. Preparation of 3-*H*-indoles.

1. a) Preparation of 8b-Methyl-1,2,3,8b-tetrahydrocyclopentano-[*b*]indole, (**5**).

To a solution of methylmagnesium iodide prepared with magnesium (0.16 g, 7.04 mg-atom) and methyl iodide, 1.0 g (7.33 mmoles) dissolved in 7 ml of anhydrous diethyl ether (previously saturated with argon), was added dropwise a solution of indole **1**, 0.94 g (6 mmoles) in 8 ml of anhydrous diethyl ether, (previously saturated with argon). After 20 minutes of the addition gas evolution ceased and **1** transformed quantitatively into its indolylmagnesium derivative (0.41 mol·l^{-1}). Then, methyl iodide, 10 g (73.3 mmoles) was added and stirred for 24 hours under an argon atmosphere. The mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride, extracted with methylene chloride and dried over sodium sulfate. The solvent was evaporated to provide a residual purple solid which was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. The 3*H*-indole **5** was isolated as a yellow oil in 44% yield; picrate, mp 152-154°. ^{1}H-nmr (deuteriochloroform): 7.2 (4H, m, Ar-H), 2.85 (1H, m) and 2.50 (1H, m) for CH_2-C=N, 2.10 (1H, m) and 1.80 (1H, m) for $(CH_2)_n$, 1.40 (1H, m) and 0.90 (1H, m) for CH_2-C-Me, 1.32 (3H, s, CH_3); ir (film): ν max 1630 cm^{-1}; ms: (70 eV): 171 (M^+, 59%), 170 (68), 156 (32), 144 (25), 143 (100), 142 (27), 130 (22), 128 (45), 116 (51), 115 (88), 102 (30),

91 (32), 77 (91); picrate, mp 152-154°.

Anal. Calcd. for (picrate) $C_{18}H_{16}N_4O_7$: C, 53.99; H, 4.03; N, 14.00. Found: C, 53.74; H, 4.12; N, 14.12.

b) Preparation of 8b-Methyl Derivative: Fischer Reaction of the phenylhydrazone of 2-Methylcyclopentanone.

i. 2-Methylcyclopentanone.

In a Dean-Stark system were placed cyclopentanone, 12.6 g (0.15 mole), pyrrolidine, 10.65 g (0.15 mole) and a small amount of *p*-toluensulfonic acid, in 50 ml of benzene. The mixture was warmed at 110° until water evolution ceased (3 hours). The solvent was removed at reduced pressure and the enamine was obtained as a transparent oil. Anhydrous tetrahydrofuran, 40 ml, was added and then methyl iodide, (22.0 g, 0.15 mole) was added dropwise and the mixture was warmed under argon atmosphere overnight. The yellow solid which formed, was filtered under pressure and washed several times with diethyl ether. Hydrolysis was accomplished with 50 ml of an aqueous solution of 5% acetic acid at 100° for 4 hours. The mixture, after cooling, was neutralized with a saturated solution of sodium bicarbonate and extracted with dichloromethane. The solvent was removed and the residual red oil of 2-methylcyclopentanone was distilled as a transparent oil, bp 40-42°/16 mm Hg, in 45% yield based on the starting cyclopentanone.

ii. Phenylhydrazone of 2-Methylcyclopentanone.

A mixture of 2-methylcyclopentanone, 4.9 g (0.05 mole) and recently distilled phenylhydrazine, 5.6 g (0.05 mole) in 60 ml of benzene under an argon atmosphere was placed in a Dean-Stark system at 110° until water evolution ceased (3 hours). The solvent was removed at reduced pressure and the phenylhydrazone was obtained as an orange oil in almost quantitative yield.

iii. Fischer Reaction of the Phenylhydrazone of 2-Methylcyclopentanone.

The phenylhydrazone of 2-methylcyclopentanone, (3.05 g, 16 mmoles) and glacial acetic acid (20 ml) were warmed at 110° under an argon atmosphere for 6 hours. The mixture was neutralized with 25% sodium hydroxide and extracted with dichloromethane. The solvent was removed and the residual oil was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent giving a main product identified as 4-acetyl-8b-methyl-1,2,3,3a-tetrahydro-8b*H*-cyclopentano[*b*]indole in 30% yield while **5** apears in only 5% yield.

Thermal Reaction of Phenylhydrazone of 2-Methylcyclopentanone.

The phenylhydrazone of 2-methylcyclopentanone, (1 g, 5.3 mmoles) in ethylene glycol, 10 ml, was warmed at 180° under an argon atmosphere for 24 hours. The mixture was poured on a water-ice bath, extracted with dichloromethane and dried over magnesium sulfate The solvent was removed and the residual brown oil was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. The main product, 8b-methyl-1,2,3,8b-tetrahydrocyclopentano[*b*]indole, **5**, was obtained as a yellow oil in 22% yield and 3-methyl-1,2,3,4-tetrahydrocyclopentano[*b*]indole as a slightly yellow oil in 6% yield.

2. a) Preparation of 4a-Methyl-1,2,3,4-tetrahydro-4a*H*-carbazole, **6**.

To 12 mmoles of methylmagnesium iodide in 10 ml of diethyl ether (saturated with argon), a solution of the 1,2,3,4-tetrahydrocarbazole **2** (2 g, 11 mmoles) in 15 ml of diethyl ether (saturated with argon) was added dropwise until gas evolution ceased (0.47 mol·l^{-1} in carbazolylmagnesium derivative). Then methyl iodide (10 g, 6 mmoles), was added at room temperature. The mixture was stirred for 24 hours and then treated as indicated in A1.a). Two products of the reaction were isolated, the 3*H*-indole **6** as an orange oil which was recrystallized from diethyl ether as yellow crystals, mp 66-67° in 72% yield, and the spiro[cyclopentane-1,2'-indolin-3'-one] **10** in 9% yield. When this reaction was carried out with different indolylmagnesium concentrations, the yield of both products varies Table 2.

b) Fischer Reaction of the Phenylhydrazone of 2-Methylcyclohexanone.

i. Phenylhydrazone of 2-Methylcyclohexanone.

A mixture of 2-methylcyclohexanone, (4.9 g, 43.75 mmoles) and recently distillated phenylhydrazine, (4.9 g, 44.5 mmoles) in 70 ml of benzene, under an argon atmosphere, was placed in a Dean-Stark system at 110° until water evolution ceased (3 hours). The solvent was removed under reduced pressure and the phenylhydrazone was obtained as an orange oil in nearly quantitative yield. The phenylhydrazone of 2-methylcyclohexanone, (4.06 g, 0.02 mole) and 20 ml of glacial acetic acid were warmed at 110° under an argon atmosphere for 24 hours. The mixture was neutralized with 25% sodium hydroxide, extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed and the residual dark oil was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. The 4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole **6** was isolated as yellow crystals, mp 67-68° in 70% yield and the 1-methyl-1,2,3,4-tetrahydrocarbazole as colorless crystals, mp 68-69° [15] in 25% yield.

Thermal Reaction of the Phenylhydrazone of 2-Methylcyclohexanone.

Phenylhydrazone of 2-methylcyclohexanone (4.06 g, 0.02 mole) in 100 ml of ethylene glycol, was warmed at 180° under an argon atmosphere for 48 hours and then poured on a water-ice bath, extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed and the residual dark oil was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. Two products were isolated, the 3*H*-indole **6** and 1-methyl-1,2,3,4-tetrahydrocarbazole in 54 and 46% yield, respectively.

4a-Methyl-1,2,3,4-tetrahydro-4a*H*-carbazole, **6**.

This compound had ^{1}H-nmr (deuteriochloroform): 7.3 (4H, m, Ar-H), 2.85 (1H, m) and 2.60 (1H, m) for CH_2-C=N, 2.25 (2H, m) and 1.75 (2H, m) for $(CH_2)_n$, 1.42 (1H, m) and 1.15 (1H, m) for CH_2-C-Me, 1.31 (3H, s, CH_3); ir (film): ν max 1630 cm^{-1}; ms: (70 eV) 185 (M^+, 82%), 184 (100), 171 (8), 170 (70), 157 (32), 156 (53), 144 (20), 143 (28), 142 (19), 130 (19), 128 (28), 116 (15), 115 (41), 102 (8), 91 (5), 77 (10).

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.32; H, 8.10; N, 7.56. Found: C, 84.18; H, 7.96; N, 7.61.

3. a) Preparation of 10a-Methyl-6,7,8,9,10,10a-hexahydrocycloheptano[b]indole **7**.

To 17 mmoles of methyl magnesium iodide in 15 ml of dry diethyl ether (saturated with argon), was added dropwise a solu-

tion of the indole derivative **3**, (2.3 g, 16 mmoles) in diethyl ether (18 ml) until gas evolution ceased (indolylmagnesium derivative 0.50 mol·l^{-1}). Then, methyl iodide (15.6 g, 0.11 mole) was added with stirring under an argon atmosphere for 48 hours. The mixture was treated as indicated in A1.a) and the 3*H*-indole **7** was isolated as an orange oil in 65% yield. The picrate was obtained as yellow crystals, mp 164-166°. In this reaction was also isolated the spiro[cyclohexane-1,2'-indolin-3'-one] **11** in 10% yield. When different indolylmagnesium concentrations were used in the reaction, the ratio of both products **7**/**11** varies, Table 2.

b) Preparation of 10a-Methyl-6,7,8,9,10,10a-hexahydrocycloheptano[*b*]indole **7**. Fischer Reaction of the Phenylhydrazone of 2-Methylcycloheptanone.

i). 2-Methylcycloheptanone.

In a Dean-Stark system, were placed 2.8 g (25 mmoles) of cycloheptanone and 1.8 g (25 mmoles) of pyrrolidine in 30 ml of benzene and a small amount of *p*-toluensulfonic acid. The mixture was stirred under an argon atmosphere at 120° until water evolution ceased (3 hours). Benzene was removed and then methyl iodide (4 g, 28 mmoles) in 40 ml of THF was added and the mixture warmed at 60° for 24 hours. The yellow solid obtained was filtered off under vacuum, washed several times withdiethyl ether, and hydrolyzed with an aqueous solution of acetic acid at 100° for 3 hours. The mixture was neutralized with sodium bicarbonate, extracted with dichloromethane, and dried over magnesium sulfate. The solvent was removed and the orange residual oil was distilled under reduced pressure at 90°/20mm Hg to give 2-methylcycloheptanone in 45% yield.

ii. Phenylhydrazone of 2-Methylcycloheptanone.

In a Dean-Stark system were placed 2-methylcycloheptanone, (0.7 g, 5.5 mmoles) and phenylhydrazine, (0.6 g, 5.5 mmoles) in 35 ml of benzene. The mixture was warmed at 110° under an argon atmosphere until water evolution ceased. The solvent was removed and phenylhydrazone was obtained as an orange oil in nearly quantitative yield.

iii. Fischer Reaction of the Phenylhydrazone of 2-Methylcycloheptanone.

The phenylhydrazone of 2-methylcycloheptanone (0.5 g, 2.3 mmoles) in 20 ml of 85% acetic acid, under an argon atmosphere, was warmed at 95° for 24 hours. The mixture was neutralized with sodium hydroxyde (25%) and extracted with dichloromethane. The solvent was removed and the residual dark-brown oil was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. Two reaction products were isolated, **7** as an orange oil in 61% yield (picrate as yellow crystals, mp 166-168°), and 6-methyl-5,6,7,8,9,10-hexahydrocycloheptano[*b*]indole, as a yellow oil in 20% yield (picrate as orange crystals, mp 164-166°); ^{1}H-nmr (deuteriochloroform) 7.4 (4H, m, Ar-H), 2.95 (1H, m) and 2.65 (1H, m) for CH_2-C=N), 2.05 (2H, m) and 1.65 (4H, m) for $(CH_2)_n$, 1.35 (1H, m) and 0.85 (1H, m) for CH_2-C-Me, 1.31 (3H, s, CH_3); ir (film): max 1630 cm^{-1} ms: (70 eV): 199 (M^+, 83%), 198 (42), 184 (57), 171 (23), 170 (35), 157 (21), 156 (63), 144 (100), 143 (63), 142 (21), 130 (53), 128 (43), 116 (34), 115 (93), 102 (32), 91 (31), 77 (75).

Anal. Calcd. for the picrate $C_{20}H_{20}N_4O_7$: C, 56.07; H, 4.67; N, 13.08%. Found: C, 55.92; H, 4.43; N, 12.89.

4. a) Preparation of 11a-Methyl-6,7,8,9,10,11-hexahydro-11a*H*-cyclooctano[*b*]indole **8**.

To 11 mmoles of methylmagnesium iodide in 12 ml of anhydrous diethyl ether, previously purged with argon, was added dropwise a solution of indole **4**, (2 g, 10 mmoles) in 12 ml of diethyl ether (previously saturated with argon), until gas evolution ceased (0.41 mol·l^{-1} in indolylmagnesium iodide). Then, methyl iodide, (10 g, 7 mmoles) was added with stirring under argon atmosphere for 48 hours. The mixture was treated as indicated in A1.a) and the 3*H*-indole **8** was obtained as a viscous orange oil in 75% yield. The picrate of **8** was obtained as yellow crystals, mp 169-171°. In this reaction the spiro derivative **11** was also isolated in 12% yield. The reaction was carried out at variable indolylmagnesium concentrations, Table 2.

Compound **8** had ^{1}H-nmr (deuteriochloroform): 7.3 (4H, m, Ar-H), 2.85 (1H, m) and 2.65 (1H, m) for CH_2-C=N, 2.25 (2H, m), 2.10 (2H, m), 1.50 (2H, m) and 1.30 (2H, m) for $(CH_2)_n$, 0.90 (2H, m, CH_2-C-Me), 1.25 (3H, s, CH_3); ir (film): ν 1630 cm^{-1}; ms: (70 eV) 213 (M^+, 47%), 212 (10, 199 (7), 198 (42), 185 (30), 184 (26), 171 (13), 170 (71), 157 (35), 156 (31), 144 (100), 143 (36), 142 (16), 130 (36), 128 (32), 116 (19), 115 (51), 102 (13), 91 (16), 77 (30).

Anal. Calcd. for the picrate of **8**, $C_{21}H_{22}N_4O_7$: C, 57.01; H, 4.97; N, 12.66. Found: C, 56.88; H, 4.69; N, 12.44.

5. a) Preparation of 4a-(3-Dimethylaminopropyl)-1,2,3,4-tetrahydro-4a*H*-carbazole **13**.

To 6 mmoles of methylmagnesium iodide in 7 ml of anhydrous diethyl ether (previously purged with argon), was added dropwise a solution of the indole **2** (1.0 g, 5.8 mmoles), in 6 ml of diethyl ether, stirring under argon atmosphere, until gas evolution ceased (0.40 mol·l^{-1} in indolylmagnesium iodide). Then a solution of 3-chloro-*N*,*N*-dimethylpropylamine (0.72 g, 6 mmoles), in diethyl ether (5 ml) was added dropwise. The mixture was stirred for 24 hours and after treated as indicated in A1.a). Two reaction products were isolated, the 3*H*-indole **13** as colorless crystals, mp 98-100° in 50% yield and the spiro derivative **10** in 10% yield.

Compound **13** had ^{1}H-nmr (deuteriochloroform): 7.2 (4H, m, Ar-H), 2.65 (2H, m, CH_2-C=N), 2.25 (2H, m), 2.00 (2H, m) and 1.25 (2H, m) for $(CH_2)_3NMe_2$, 2.14 (6H, s, $CH_3)_2$N, 2.15 (2H, m) and 1.65 (2H, m) for $(CH_2)_n$, 1.10 (2H, m, CH_2-C-.

Anal. Calcd. for $C_{17}H_{24}N_2$: C, 79.68; H, 9.37; N, 10.93. Found: C, 79.45; H, 9.48; N, 10.80.

6. a) Preparation of 10a-(3-Dimethylaminopropyl)-6,7,8,9,10,10a-hexahydrocycloheptano[*b*]indole **14**.

To 6 mmoles of methylmagnesium iodide in 8 ml of diethyl ether (previously saturated with argon), was added dropwise a solution of the indole **3** (1.0 g, 5.4 mmoles) in 7 ml of diethyl ether (saturated with argon), stirring under an argon atmosphere, until gas evolution ceased (0.40 mol·l^{-1} in indolylmagnesium iodide). Then a solution of 3-chloro-*N*,*N*-dimethylpropylamine, (0.72 g, 6 mmoles), in 5 ml of diethyl ether was added. The mixture was stirred under argon atmosphere for 40 hours and treated as indicated in A1.a). Two reaction products were isolated, the 3*H* indole **14**, as colorless crystals, mp 96-98° in 53% yield and the spiro[cyclohexane-1,2'-indolin-3'-one], **11** in 12% yield.

Compound **14** had ^{1}H-nmr (deuteriochloroform): 7.2 (4H, m, Ar-H), 2.50 (2H, m, CH_2-C=N), 2.25 (2H, m), 1.90 (2H, m), and 1.25 (2H, m) for $(CH_2)_3NMe_2$, 2.28 (6H, s, $(CH_3)_2$N), 2.00 (2H, m) and 1.70 (4H, m) for $(CH_2)_n$, 1.15 (2H, m, CH_2-C-).

Anal. Calcd. for $C_{18}H_{26}N_2$: C, 80.00; H, 9.62; N, 10.37. Found: C, 79.82; H, 9.80; N, 10.25%.

B. Preparation of the Spiro[cycloalkane-1,2′-indolin-3′-ones] **9**, **10**, **11**, and **12**.

1. Synthesis of Spiro[cyclobutane-1,2′-indolin-3′-one] **9**.

To 6.6 mmoles of methylmagnesium iodide in 10 ml of anhydrous diethyl ether was added dropwise a solution of the indole **1**, (1 g, 6.6 mmoles) in 10 ml of anhydrous diethyl ether until gas evolution ceased. Then diethyl ether saturated with oxygen (15 ml) was added with stirring in an oxygen atmosphere for 24 hours. The mixture was hydrolyzed with 40 ml of a saturated aqueous solution of ammonium chloride and extracted with dichloromethane. The solvent was removed and only the starting product **5** was isolated. Compound **9** was not detected by gc/ms analysis of the solid.

2. Synthesis of Spiro[cyclopentane-1,2′-indolin-3′-one] **10**.

To 6 mmoles of methylmagnesium iodide in 10 ml of diethyl ether was added dropwise a solution of the indole **2**, (1.03 g, 6 mmoles) in 10 ml of diethyl ether until gas evolution ceased. Then diethyl ether saturated with oxygen (15 ml) with stirring in an argon atmosphere for 24 hours. The mixture was hydrolyzed as indicated in B1. The solvent was removed and the residual orange solid was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. Spiro derivative **10** was isolated as yellow crystals, mp, 76-77° in 70% yield; ^{1}H-nmr (deuteriochloroform): 7.5 (2H, m) and 6.8 (2H, m) for Ar-H, 1.9 (8H, m, $(CH_2)_n$), 4.9 (1H, s, N-H); ^{13}C-nmr (deuteriochloroform): 205.2 (C=O), 160.0 (C-7′a), 136.8 (C-6′), 124.5 (C-4′), 120.6 (C-3′a), 118.6 (C-5′), 112.2 (C-7′), 74.4 (C-2′), 38.0 (C-2), 38.0 (C-5), 25.4 (C-3), 25.4 (C-4); ir (Nujol): ν max 3290 (N-H), 1670 (C=O); ms: (70 eV) 187 (M^+, 28%), 159 (29), 158 (100), 130 (41), 77 (49).

Anal. Calcd. for **10** $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.48. Found: C, 76.68; H, 6.88; N, 7.37.

3. Synthesis of Spiro[cyclohexane-1,2′-indolin-3′-one] **11**.

To a suspension of 6 mmoles of methylmagnesium iodide in 10 ml of anhydrous diethyl ether was added dropwise a solution of the indole **3** (1.16 g, 6 mmoles) in 10 ml of diethyl ether until gas evolution ceased. Then, diethyl ether saturated with oxygen (15 ml) was added dropwise with stirring in an oxygen atmosphere for 24 hours. The mixture was hydrolyzed as indicated in B1. The solvent was removed and the residual orange solid was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. The spiro derivative **11** was isolated as yellow crystals, mp 136-137° in 78% yield; ^{1}H-nmr (deuteriochloroform): 7.5 (2H, m) and 6.8 (2H, m) for Ar-H, 1.85 (4H, m) and 1.45 (6H, m) for $(CH_2)_n$, 5.0 (1H, s, N-H); ^{13}C-nmr (deuteriochloroform): 204.8 (C=O), 159.9 (C-7′a), 136.9 (C-6′), 125.0 (C-4′), 120.5 (C-3′a), 118.8 (C-5′), 112.6 (C-7′), 66.9 (C-2′), 32.8 (C-2), 32.8 (C-6), 24.7 (C-4), 22.6 (C-3), 22.6 (C-5); ir (Nujol): 3324 (N-H), 1670 (C=O); ms: (70 eV) 201 (M^+, 76%), 173 (43), 172 (100), 159 (5), 158 (16), 145 (56), 144 (99), 130 (36), 77 (30).

Anal. Calcd. for **11**, $C_{13}H_{15}NO$: C, 77.61; H, 7.46; N, 6.96. Found: C, 77.40; H, 7.38; N, 6.83.

4. Synthesis of the Spiro[cycloheptane-1,2′-indolin-3′-one] **12**.

To a suspension of 6 mmoles of methylmagnesium iodide in 10 ml of anhydrous diethyl ether, was added dropwise a solution of the indole **4** (1.1 g, (6 mmoles), in 10 ml of diethyl ether until gas evolution ceased. Then diethyl ether saturated with oxygen (15 ml) was added and stirred in an oxygen atmosphere for 24 hours. The mixture was hydrolyzed as indicated in B1. The solvent was removed and the residual brown solid was chromatographed on a silica gel column using ethyl acetate-hexane (1:3) as the eluent. The spiro derivative **12** was isolated as a yellow oil which crystallized from methanol as yellow crystals, mp 126-128° in 75% yield; ^{1}H-nmr (deuteriochloroform): 7.5 (2H, m), 6.8 (2H, m) for Ar-H, 1.85 (4H, m), 1.60 (8H, m) for $(CH_2)_n$, 4.9 (1H, s, N-H); ^{13}C-nmr (deuteriochloroform): 205.7 (C=O), 159.7 (C-7′a), 136.7 (C-6′), 124.8 (C-4′), 121.1 (C-3′a), 118.3 (C-5′), 112.2 (C-7′), 69.4 (C-2′), 36.1 (C-2), 36.1 (C-7), 28.9 (C-4), 28.9 (C-5), 23.1 (C-3), 23.1 (C-6); ir (Nujol): ν max 3361 (N-H), 1680 (C=O); ms: (70 eV) 215 (M^+, 68%), 187 (15), 186 (42), 172 (20), 159 (100), 158 (82), 145 (21), 144 (45), 130 (61), 77 (40).

Anal. Calcd. for **12** $C_{14}H_{17}NO$: C, 78.13; H, 7.90; N, 6.51. Found: C, 77.96; H, 8.01; N, 6.48.

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