Synthesis of 1'-(3-Dimethylaminopropyl)-2'-Substituted Spiro[cycloalkane-1,3'-indolines]

José-Gonzalo Rodriguez* and Fernando Temprano
Departamento de Quimica Organica, Facultad de Ciencias, Universidad Autonoma de Madrid, Canto Blanco, 28049-Madrid, Spain

Reactivity of the C=N bond in spiro[cycloalkane-1,3'-3*H*-indoles] has been analysed. Indolines were obtained in practically quantitative yield using organomagnesium reagents in the presence of copper(I) chloride in toluene at 120 °C. On the basis of an analysis of the reaction products and the e.s.r. spectra, a mechanistic pattern could be proposed. *N*-Alkylation of 2'-substituted spiro[cycloalkane-1,3'-indolines] has been carried out using as alkylating agent 3-chloro-*N*,*N*-dimethylpropionamide, which gave the 1'-(3-dimethylaminopropyl)-2'-substituted spiro[cycloalkane-1,3'-indolines] in good yield on reduction with $LiAlH_4$.

Synthesis of 1'-(3-dimethylaminopropyl)spiro[cycloalkane-1,3'-indolines] as their 2'-substituted derivatives was carried out because of their potential antidepressant activity. Steric hindrance above the spiro carbon atoms seem to be a relevant factor in drug activity for these compounds.[1]

A synthetic scheme was previously outlined for the preparation of spiro-3*H*-indoles (**1**), which were obtained by cyclization of the phenylhydrazone of the cycloalkane carbaldehydes under careful acid catalysis.[2]

In this paper we describe the reaction of the C=N bond of compounds (**1**) with Grignard reagents to obtain 2'-substituted indolines (**2**) in good yield. Moreover, we also describe the *N*-alkylation of spiroindolines (**2**) with 3-chloro-*N*,*N*-dimethylpropionamide to give the carbamoyl derivatives (**4**), which can be reduced to the required dimethylaminopropyl derivatives (**5**), Scheme 1.

The 2'-substituted indoline derivatives (**2**) can be obtained from the 3*H*-indoles (**1**) by nucleophilic attack on the C=N bond. In this way, Grignard addition reaction on the C=N bond of several 3,3-disubstituted 3*H*-indoles afforded the 2,3,3-trisubstituted indolines in poor yields.[3] However, when the organomagnesium reagents were treated with the spiro-3*H*-indoles (**1**) in attempts to give products (**2**) in ethereal solvents, only the starting materials (**1**) were recovered.† Organolithium reagents exhibit the same behaviour with compounds (**1**) in the same ethereal solvents. When the solvent was changed, *e.g.* toluene instead of diethyl ether, and a small amount of copper(I) chloride was added to the mixture of 3*H*-indole (**1**) and RMgX, the respective indoline (**2**) was obtained in practically quantitative yield.

Results and Discussion

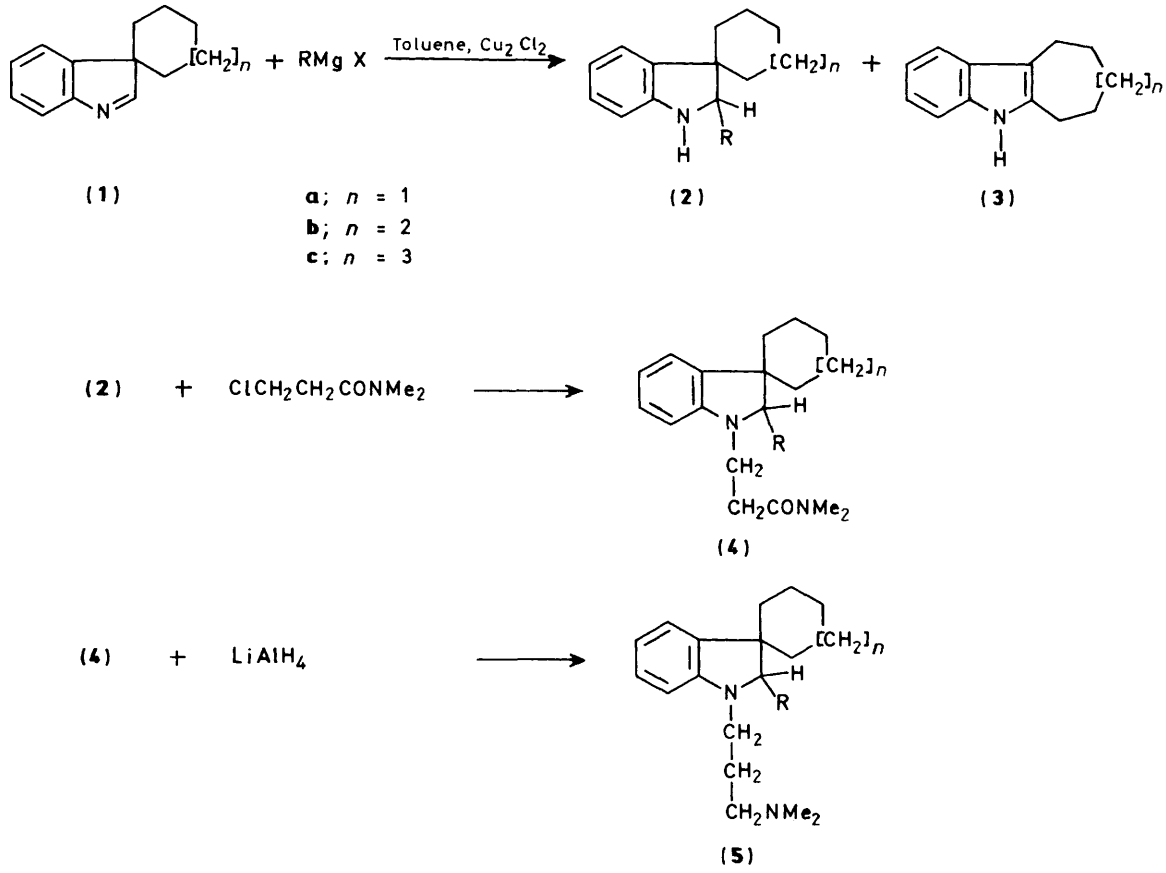
Synthesis of 2'-Substituted Spiro[cycloalkane-1,3'-indolines].—In a previous paper,[4] we described the reaction of the C=N bond of spiro[cyclohexane-1,3'-3*H*-indole] (**1a**) with organometallic reagents. Attack of MeMgI or PhMgBr on the C=N bond of compound (**1a**), in the presence of copper(I) chloride, in toluene as solvent at 120 °C, afforded the indoline derivatives (**2a**; R = Me) and (**2a**; R = Ph), respectively, in practically quantitative yield. Moreover, this reaction was affected by the molar ratio of (**1a**) to the Grignard reagent. In effect, a molar ratio of (**1a**) to the Grignard reagent of 1:5 was used to guarantee a quantitative yield of the indoline derivatives. Under identical conditions, attack of MeMgI or PhMgBr to compound (**1b**) afforded the indoline derivatives (**2b**; R = Me) and (**2b**; R = Ph) respectively, in quantitative yield.

However, when the reaction of the 3*H*-indole (**1c**) with MeMgI or PhMgBr was carried out with a molar ratio of (**1c**): Grignard reagent of 1:5, in the presence of copper(I) chloride in toluene as solvent, only the cycloalka[*b*]indole (**3c**), as the rearrangement product,‡ was obtained. The rearrangement reaction seems to be dependent on the molar ratio of the Grignard reagent to 3*H*-indole (**1c**) and can be avoided. Thus, indoline derivatives (**2c**) were obtained in quantitative yield when a 1:20 molar ratio of (**1c**) to organomagnesium reagents, MeMgI or PhMgBr, was used. On the other hand, when reaction of the 3*H*-indole (**1a**) with benzylmagnesium bromide, in toluene at 120 °C, in the presence of copper(I) chloride was carried out in a molar ratio of (**1a**) to $PhCH_2MgBr$ of 1:5, the expected indoline (**2a**; R = CH_2Ph) was isolated in quantitative yield. The reaction of the 3*H*-indole (**1a**) with phenethylmagnesium bromide was investigated in the presence of copper(I) chloride in toluene at 120 °C. With a molar ratio of (**1a**) to $PhCH_2CH_2MgBr$ of 1:5, several products were isolated:

† Investigations into the nature of the Grignard reagents have been numerous: B. J. Wakefield, *Organomet. Chem. Rev.*, 1966, **1**, 131; E. C. Ashby, *Q. Rev., Chem. Soc.*, 1967, **21**, 259. Ethylmagnesium bromide has been analysed in the solid state and the packing consists of discrete monomer units with two molecules of the ether solvated to the magnesium. The ethyl group, bromine atom, and the two ether groups form a slightly distorted tetrahedral array about a single magnesium atom: L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, 1968, **90**, 5375. There was evidence in the phenyl Grignard structure for tetrahedral co-ordination of the two oxygens of the ether solvated to the magnesium; the molecule exists as monomer units in the crystallographic packing: G. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, 1963, **85**, 1002; 1964, **86**, 4825. Thus, both Grignard reagents seem to show an important steric hindrance about the magnesium atom in their reaction with the C=N group in the 3*H*-indoles.

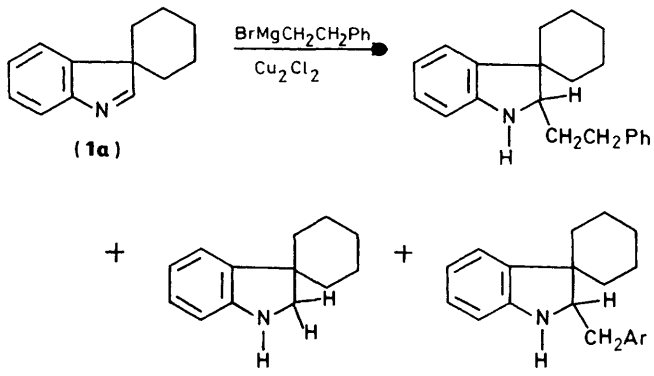
‡ 3*H*-Indoles are known to isomerize in the presence of acids, probably by a Wagner–Meerwein rearrangement: M. Nakazaki and K. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 466; F. J. Evans, G. B. Lyle, J. Watkins, and R. E. Lyle, *J. Org. Chem.*, 1962, **27**, 1553; F. Evans and R. E. Lyle, *Chem. Ind. (London)*, 1963, 968. In this way the spiro-[cycloalkane-1,3'-3*H*-indoles] were converted by sulphuric acid into cycloalka[*b*]indole derivatives (see ref. 2).

The rearrangement of the 3*H*-indoles (**2**) under the reaction conditions; RMgX; toluene as solvent; 120 °C; in the presence of copper(I) chloride, can be explained by a radical mechanism.



Scheme 1.

Table. Reaction of spiro[cyclohexane-1,3′-3*H*-indole] with phenethylmagnesium bromide[a]



Solvent	M.r.[b]	$Ph[CH_2]_2$-MgBr[c]	Yield (%) of (2a) R = CH_2-CH_2Ph	R = H	R = CH_2Ar
Toluene	1/5	0.14	40	37	20 (Ar = Ph)
Toluene	1/5	0.50	45	51	4 (Ar = Ph)
p-Xylene	1/5	0.14	43	36	19 (Ar = *p*-Tolyl)

[a] Toluene or *p*-xylene as solvent. *T* 120 °C. [b] Molar ratio of the spiro[cyclohexane-1,3′-3*H*-indole] to $PhCH_2CH_2MgBr$. [c] Concentration (mol l^{-1}) of $PhCH_2CH_2MgBr$.

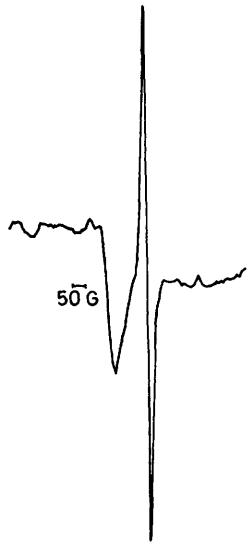


Figure. E.s.r. spectrum of the reaction mixture from methylmagnesium iodide and spiro[cyclohexane-1,3′-3*H*-indole] (**1a**) in the presence of copper(I) chloride, in toluene at 100 °C

the 2′-phenethyl-, the 2′-H-, and the 2′-benzyl-indoline derivatives. The relative proportions of the products of the reaction were affected by the concentration of the Grignard reagent; see the Table.

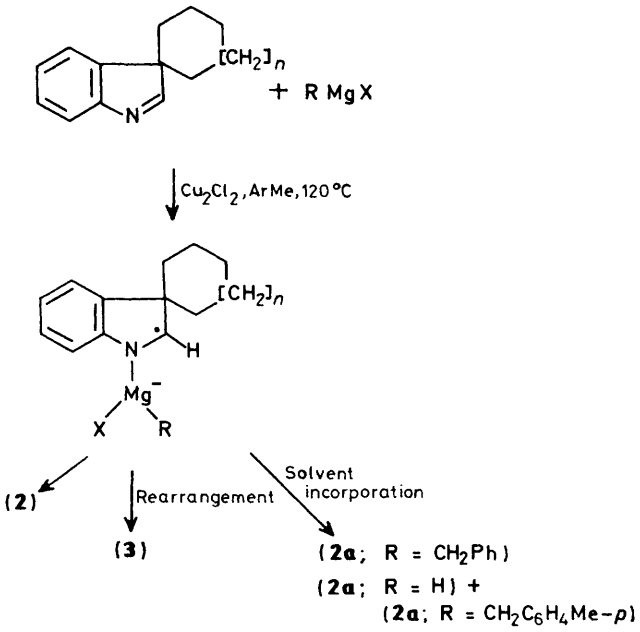
In effect, when the concentration of the Grignard reagent is increased the relative proportion of the 2′-phenethyl and

especially of the 2′-H derivative increases,* whilst that of the 2′-benzyl derivative decreases. The presence of the last product seems to arise by incorporation of a molecule of toluene used as solvent to the 2′-position of the indoline. This fact was unequivocally confirmed when the reaction was carried out in *p*-xylene as solvent. In this case, the 2′-*p*-xylyl indoline (**2a**; R = $CH_2C_6H_4Me$-*p*) was obtained; see the Table.

The formation of the 2′-benzyl and 2′-*p*-xylyl derivatives (**2a**; R = CH_2Ph; $CH_2C_6H_4Me$-*p*) in the above reaction suggests that the attack of the Grignard reagent on the C=N bond of the 3*H*-indoles (**1**) occurs through a radical mechanism, under the conditions of the reaction. A study of the reaction of methylmagnesium iodide with spiro[cyclohexane-1,3′-3*H*-indole] (**1a**), in the presence of copper(I) chloride, in toluene as solvent at several temperatures, was carried out by electron spin resonance.

The e.s.r. spectrum of the above mixture at 20 °C shows only a broad signal (113 G) which was reproduced only when MeMgI and Cu_2Cl_2 were mixed in toluene as solvent.† However, the e.s.r. spectrum of the mixture of reaction at 100 °C shows two signals, the broad one (113 G) mentioned above and another intense signal (34 G) (Figure);‡ when this last signal is missing all the starting 3*H*-indole (**1a**) is consumed to afford the indoline derivative (**2a**).

The e.s.r. evidence of a radical intermediate, together with the aforementioned formation of the 2′-benzyl (or 2′-*p*-xylyl) derivatives (**2a**; R = CH_2Ph or R = $CH_2C_6H_4Me$-*p*), in the reaction of compound (**1a**) with $PhCH_2CH_2MgBr$, suggest an intermediate for the reaction between the Grignard and the 3*H*-indole reagents as shown in Scheme 2. This radical intermediate is consistent with all the above products of the reaction: (a) the formation of the indoline derivatives (**2**); (b) the incorporation of the solvent radical to the 2′-position in structure (**2**); and (c) the formation of the indole derivative (**3**) by means of a rearrangement process.



Scheme 2.

Alkylation of the 2′-Substituted Spirocycloalkane-1,3′-indolines.—On the other hand, the steric hindrance affecting the N-atom in the indolines due to the bulky spirocycloalkane ring and also to the 2′-substituent renders the attempted alkylation unsuccessful with several reagent systems: (a) *N*-acylation with acyl chlorides, and (b) *N*-acylation with the carboxylic acid and ethyl chloroformate.

The alkylation of the N-atom of the indolines (**2**) was undertaken by reaction with 3-chloro-*N*,*N*-dimethylpropylamine in an ethanol–water mixture (8:2) as solvent containing Na_2CO_3, according to a previously described procedure for the monoalkylation of aniline derivatives.[5] Intramolecular and intermolecular reaction of the alkylating reagent was observed whilst the expected *N*-alkylation product was not detected. However, when the alkylating agent 3-chloro-*N*,*N*-dimethylpropionamide was used in the above ethanol–water (8:2) mixture as solvent containing Na_2CO_3, the 1′-(2-dimethylcarbamoylethyl) derivative of the indolines (**2**) was isolated. The yield of the product increases with increasing time of the reaction.

Finally, reduction of the carbamoyl derivatives (**4**) to the 1′-(3-dimethylaminopropyl)-2′-phenylspiro[cycloalkane-1,3′-indolines] (**5**) was carried out with $LiAlH_4$ in tetrahydrofuran (THF) at room temperature in good yields.

Experimental

M.p.s were determined on a Reichert stage microscope and are uncorrected. ^1H N.m.r. spectra were obtained on a Bruker WM-200-SY with [^2H]chloroform as solvent and tetramethylsilane as internal standard. Mass spectral data were obtained on a Hewlett Packard 5985A GC/MS System. Elemental analyses were performed with a Model 240 Perkin-Elmer analyser. E.s.r. spectra were obtained on a Varian E-12 instrument. All reactions involving organometallic reagents were carried out under dry nitrogen using standard techniques for the manipulation of air-sensitive compounds.

Preparation of the 2′-Substituted Spiro[cycloalkane-1,3′-indolines]: General Procedure.—To magnesium turnings (1.31 g, 0.05 mol) in dry diethyl ether was added a solution of an alkyl (or aryl) halide (0.05 mol) in diethyl ether. When the alkyl- (or aryl-)magnesium halide was completely generated, dry toluene (30 ml) was added to the mixture and the diethyl ether was distilled off. A solution of a spiro[cycloalkane-1,3′-3*H*-indole] (**1**) (0.01 mol) in dry toluene (30 ml) was added. The mixture was heated at 120 °C in the presence of copper(I) chloride (12 mg) during 2 h, under nitrogen. After cooling, the mixture was hydrolysed with aqueous ammonium chloride and extracted with dichloromethane. The solvent was removed to give an oil,§ which was chromatographed on a silica gel column, with chloroform–hexane (5:1) as eluant, to provide the indoline (**2**), with the following yields and spectral data.

2′-Methylspiro[cyclohexane-1,3′-indoline] (**2a**; R = Me) was a yellow oil, 97% yield, picrate m.p. 151—152 °C (recrystallized from ethanol–water) (Found C, 55.7; H, 5.25; N, 13.2. $C_{20}H_{22}$-

* The formation of the 2′-H derivative can be explained by capture of H from the solvent, as well as by a reduction reaction from $PhCH_2CH_2MgBr$: M. Mori, S. Kudo, and Y. Ban, *J. Chem. Soc., Perkin Trans. 1*, 1979, 771.

† Methylmagnesium iodide and copper(I) chloride, in toluene as solvent, yielded a black solid, which was isolated and analysed. This analysis indicated the presence of magnesium and copper in variable molar ratios. These bimetallic aggregates gave the broad signal (113 G) referred to above.

‡ Both radical products show different solubility in toluene. Thus, the first radical (113 G) can be separated from the second radical product, which was soluble in toluene. This last radical generated (34 G) is quite persistent in toluene, even in the presence of oxygen (half-life > 24 h at room temperature).

§ By g.l.c. the indoline (**2**) is the only product of the reaction.

N_4O_7 requires C, 55.81; H, 5.15; N, 13.02%); the free base showed *m/z* (70 eV) 201 (M^+, 18%), 186 (16), 144 (100), and 130 (33); δ_H 7.1—6.5 (4 H, m, ArH), 3.4 (1 H br s, NH), 3.61 (1 H, q, *J* 6.42 Hz, 2'-H), 1.7 (10 H, m, $[CH_2]_n$), and 1.02 (3 H, d, *J* 6.42 Hz, Me).

2'-Phenylspiro[cyclohexane-1,3'-indoline] (**2a**; R = Ph) was a yellow oil 96% yield, picrate, m.p. 180—181 °C (from ethanol–water) (Found: C, 60.7; H, 4.6; N, 11.25. $C_{25}H_{24}N_4O_7$ requires C, 60.97; H, 4.87; N, 11.38%); the free base showed *m/z* (70 eV) 263 (M^+, 44%), 206 (100), 172 (52), and 130 (21); δ_H 7.3—6.6 (9 H, m, ArH), 4.58 (1 H, s, 2'-H), 3.9 (1 H, br s, NH),and 1.6 (10 H, m, $[CH_2]_n$).

2'-Methylspiro[cycloheptane-1,3'-indoline] (**2b**; R = Me) was a yellow oil, 98% yield, picrate m.p. 120—122 °C (Found: C, 56.4; H, 5.2; N, 12.3. $C_{21}H_{24}N_4O_7$ requires C, 56.75; H, 5.40; N, 12.61%); the free base showed *m/z* (70 eV) 215 (M^+, 24%), 200 (10), 144 (100), and 130 (28); δ_H 7.2—6.6 (4 H, m, ArH), 3.54 (1 H, q, *J* 6.55 Hz, 2'-H), 3.0 (1 H, br s, NH), 1.7 (12 H, m, $[CH_2]_n$), and 1.18 (3 H, d, *J* 6.55 Hz, Me).

2'-Phenylspiro[cycloheptane-1,3'-indoline] (**2b**; R = Ph) was a yellow oil, 96% yield, picrate, m.p. 101—102 °C (Found: C, 61.4; H, 5.0; N, 11.1. $C_{26}H_{26}N_4O_7$ requires C, 61.66; H, 5.13; N, 11.06%); the free base showed *m/z* (70 eV) 277 (M^+, 32%), 206 (100), 193 (28), 186 (41), and 130 (27); δ_H 7.3—6.7 (9 H, m, ArH), 4.53 (1 H, s, 2'-H), 3.9 (1 H, br s, NH), and 1.6 (12 H, m, $[CH_2]_n$).

2'-Methylspiro[cyclo-octane-1,3'-indoline] (**2c**; R = Me). Treatment of compound (**1c**) (2 mmol) with methylmagnesium iodide (10 mmol) in toluene, in the presence of Cu_2Cl_2, according to the General Procedure, give only the 5,6,7,8,9,10,11,12-octahydrocyclonona[*b*]indole (**3c**) in practically quantitative yield. However, treatment of compound (**1c**) (1 mmol) with methylmagnesium iodide (20 mmol) in toluene, under the same conditions, give only the indoline (**2c**; R = Me) as yellow crystals, m.p. 49—50 °C, in practically quantitative yield (Found: C, 83.9; H, 10.25; N, 6.0. $C_{16}H_{23}N$ requires C, 83.78; H, 10.11; N, 6.11%); *m/z* (70 eV) 229 (M^+, 12%), 144 (100), and 130 (24); δ_H 7.1—6.7 (4 H, m, ArH), 3.58 (1 H, q, *J* 6.59 Hz, 2'-H), 3.2 (1 H, br s, NH), 1.7 (14 H, m, $[CH_2]_n$), and 0.98 (3 H, d, *J* 6.59 Hz, Me).

2'-Phenylspiro[cyclo-octane-1,3'-indoline] (**2c**; R = Ph). Treatment of compound (**1c**) (2 mmol) with phenylmagnesium bromide (10 mmol) in toluene, in the presence of Cu_2Cl_2, according to the General Procedure, give the indole (**3c**) in practically quantitative yield. However, treatment of compound (**1c**) (1 mmol) with phenylmagnesium bromide (20 mmol) in toluene, under the same conditions, give the indoline (**2c**; R = Ph) as white crystals, m.p. 139—140 °C, in practically quantitative yield (Found: C, 86.3; H, 8.5; N, 4.6. $C_{21}H_{25}N$ requires C, 86.54; H, 8.65; N, 4.81%); *m/z* (70 ev) 291 (M^+, 48%), 206 (100), 193 (28), 186 (10), and 130 (37); δ_H 7.3—6.7 (9 H, m, ArH), 4.54 (1 H, s, 2'-H), 4.0 (1 H, br s, NH), and 1.5 (14 H, m, $[CH_2]_n$).

2'-Benzylspiro[cyclohexane-1,3'-indoline] (**2a**; R = CH_2Ph). Treatment of compound (**1a**) (0.01 mol) with benzylmagnesium bromide (0.05 mol) in toluene, in the presence of Cu_2Cl_2 at 120 °C during 2 h, give the indoline (**2a**; R = CH_2Ph) as a white solid, m.p. 94—95 °C, in practically quantitative yield (Found: C, 82.6; H, 8.3; N, 4.9. $C_{20}H_{23}N$ requires C, 86.58; H, 8.36; N, 5.05%); *m/z* (70 eV) 277 (M^+, 5%), 186 (100), 130 (38), and 91 (12); δ_H 7.2—6.6 (9 H, m, ArH), 3.62 (1 H, m, 2'-H), 3.58 (1 H, br s, NH), 2.79 (1 H, m, *H*CPh), 2.43 (1 H, m, HCPh), and 1.7 (10 H, m, $[CH_2]_n$).

2'-Phenethylspiro[cyclohexane-1,3'-indoline] (**2a**; R = CH_2CH_2Ph). Treatment of compound (**1a**) (2 mmol) with phenethylmagnesium bromide (10 mmol) in toluene, in the presence of Cu_2Cl_2 at 120 °C during 2 h, according to the General Procedure, give an oil, which was chromatographed on a silica gel column with chloroform–hexane (5:1) as eluant to provide the indolines (**2a**; R = CH_2CH_2Ph), (**2a**; R = H), and (**2a**; R = CH_2Ph). Relative proportions of the products depend on the concentration of the Grignard reagent; see the Table.

When *p*-xylene was used instead of toluene as the solvent, the indolines (**2a**; R = CH_2CH_2Ph), (**2a**; R = H), and (**2a**; R = $CH_2C_6H_4Me$-*p*) were obtained; see the Table.

2'-Phenethylspiro[cyclohexane-1,3'-indoline] (**2a**; R = CH_2CH_2Ph) hydrochloride had m.p. 114—116 °C (EtOH) (Found: C, 76.7; H, 8.1; N, 4.4. $C_{21}H_{26}ClN$ requires C, 76.91; H, 7.99; N, 4.27%); *m/z* (70 eV) 291 (M^+, 22%), 186 (100), 144 (25), and 130 (43); δ_H 7.2—6.5 (9 H, m, ArH), 3.7 (1 H, br s, NH), 3.39 (1 H, m, 2'-H), 2.71 (2 H, m, H_2CPh, 2 H), 1.80 (2 H, m, 2'-CH_2), and 1.6 (10 H, m, $[CH_2]_n$).

Spiro[cyclohexane-1,3'-indoline] (**2a**; R = H) was obtained as crystals, m.p. 76—77 °C (Found: C, 83.0; H, 9.2; N, 7.5. $C_{13}H_{17}N$ requires C, 83.36; H, 9.15; N, 7.49%); *m/z* (70 eV) 187 (M^+, 23%), 144 (21), 130 (100), 117 (9), and 77 (7); δ_H 7.2—6.7 (4 H, m, ArH), 4.2 (1 H, br s, NH), 3.43 (2 H, s, 2'-H_2), and 1.6 (10 H, m, $[CH_2]_n$).

2'-p-Xylylspiro[cyclohexane-1,3'-indoline] (**2a**; R = $CH_2C_6H_4Me$-*p*) hydrochloride had m.p. 116—118 °C (Found: C, 76.7; H, 8.1; N, 4.2. $C_{21}H_{26}ClN$ requires C, 76.91; H, 7.99; N, 4.27%); *m/z* (70 eV) 291 (M^+, 5), 186 (100), 143 (7), and 130 (63); δ_H 7.2—6.5 (8 H, m, ArH), 4.6 (1 H, br s, NH), 3.69 (1 H, m, 2'-H), 2.89 (1 H, m, HCC_6H_4Me), 2.47 (1 H, m, HCC_6H_4Me), 2.34 (3 H, s, Me), and 1.7 (10 H, m, $[CH_2]_n$).

Alkylation of 2'-Methyl-(or phenyl)spiro[cycloalkane-1,3'-indolines]. General Procedure.—A mixture of a 2'-methyl(or phenyl)spiro[cycloalkane-1,3'-indoline] (6 mmol), 3-chloro-*N*,*N*-dimethylpropionamide (18 mmol), sodium carbonate (0.95 g), ethanol (16 ml), and water (4 ml) was refluxed for 25 days. The reaction was followed by h.p.l.c. to observe the disappearance of the starting indoline. A further mixture of 3-chloro-*N*,*N*-dimethylpropionamide (6 mmol), sodium carbonate (0.31 g), ethanol (8 ml), and water (2 ml) was added every 6 days to the above mixture until complete absence of the starting indoline. The mixture was then concentrated under reduced pressure, diluted with water, and extracted with dichloromethane. Solvent and the residual acrylamide were removed under reduced pressure to give an oil, which was chromatographed on a silica gel column with ethyl acetate–hexane (2:1) as eluant to provide the corresponding 1'-(2-dimethylcarbamoylethyl)-2'-methyl(or phenyl)spiro[cycloalkane-1,3'-indoline]. The hydrochloride salts of the indoline derivatives (**4**) were precipitated as crystals or amorphous solids in diethyl ether as solvent, and in general quickly decompose under air contact to give dark oils.

1'-(2''-Dimethylcarbamoylethyl)-2'-methylspiro[cyclohexane-1,3'-indoline] (**4a**; R = Me). The indoline derivative (**4a**; R = Me) was obtained as a yellow oil in 69% yield (Found: C, 75.8; H, 9.6; N, 9.7. $C_{19}H_{28}N_2O$ requires C, 75.94; H, 9.40; N, 9.33); *m/z* (70 eV) 300 (M^+, 87%), 285 (59), 243 (43), 214 (100), 200 (81), 198 (56), 144 (39), 100 (40), and 72 (43); δ_H 7.2—6.4 (4 H, m, ArH), 3.53 (1 H, m, 1''-H), 3.47 (1 H, m, 1''-H), 3.41 (1 H, q, *J* 6.46 Hz, 2'-H), 2.96 (3 H, s, MeNCO), 2.94 (3 H, s, MeNCO), 2.56 (2 H, m, CH_2CO), 1.6 (10 H, m, $[CH_2]_n$), and 1.08 (3 H, d, *J* 6.46 Hz, 2'-Me).

1'-(2''-Dimethylcarbamoylethyl)-2'-phenylspiro[cyclohexane-1,3'-indoline] (**4a**; R = Ph). The indoline derivative (**4a**; R = Ph) was obtained as a yellow oil in 64% yield. The hydrochloride had m.p. 120—122 °C (Found: C, 75.65; H, 7.8; N, 7.1. $C_{24}H_{31}ClN_2O$ requires C, 75.25; H, 7.83; N, 7.02%); *m/z* (70 eV) 362 (M^+, 92%), 305 (22), 276 (64), 262 (100), 218 (21), 206 (23), 153 (12), and 100 (18); δ_H 7.3—6.5 (9 H, m, ArH), 4.37 (1 H, s, 2'-H), 3.49 (1 H, m, 1''-H), 3.23 (1 H, m, 1''-H), 2.88 (3 H, s, MeNCO), 2.84 (3 H, s, MeNCO), and 2.47 (10 H, m, $[CH_2]_n$).

1'-(2''-Dimethylcarbamoylethyl)-2'-methylspiro[cyclo-heptane-1,3'-indoline] (**4b**; R = Me). The indoline derivative

(**4b**; R = Me) was obtained as a yellow oil in 71% yield (Found: C, 76.05; H, 9.8; N, 8.7. $C_{20}H_{30}N_2O$ requires C, 76.39; H, 9.62; N, 8.91%); *m/z* (70 eV) 314 (M^+, 100%), 299 (48), 243 (79), 241 (69), 144 (53), 100 (51), and 72 (53); δ_H 7.2—6.4 (4 H, m, ArH), 3.55 (1 H, m, 1″-H), 3.45 (1 H, m, 1″-H), 3.19 (1 H, q, *J* 6.46 Hz, 2′-H), 2.97 (3 H, s, MeNCO), 2.96 (3 H, s, MeNCO), 2.52 (2 H, m, CH_2CO), 1.7 (12 H, m, $[CH_2]_n$), and 1.19 (3 H, d, *J* 6.46 Hz, 2′-Me).

1′-(2″-Dimethylcarbamoylethyl)-2′-phenylspiro[cycloheptane-1,3′-indoline] (**4b**; R = Ph). The indoline derivative (**4b**; R = Ph) was obtained as a yellow oil in 58% yield (Found: C, 79.6; H, 8.4; N, 7.3. $C_{25}H_{32}N_2O$ requires C, 79.74; H, 8.57; N, 7.44%); *m/z* (70 eV) 376 (M^+, 100%), 305 (50), 290 (52), 276 (76), 218 (30), 206 (43), 153 (29), and 100 (18); δ_H 7.3—6.6 (9 H, m, ArH), 4.25 (1 H, s, 2′-H), 3.54 (1 H, m, 1″-H), 3.26 (1 H, m, 1″-H), 2.87 (3 H, s, MeNCO), 2.83 (3 H, s, MeNCO), 2.46 (2 H, m, CH_2CO), and 1.6 (12 H, m, $[CH_2]_n$).

1′-(2-Dimethylcarbamoylethyl)-2′-methylspiro[cyclo-octane-1,3′-indoline] (**4c**; R = Me). The indoline derivative (**4c**; R = Me) was obtained as a yellow oil in 52% yield (Found: C, 76.4; H, 9.9; N, 8.5. $C_{21}H_{32}N_2O$ requires C, 76.78; H, 9.82; N, 8.53%); *m/z* (70 eV) 328 (M^+, 60%), 313 (19), 243 (100), 228 (27), 144 (59), 100 (30), and 72 (57); δ_H 7.1—6.4 (4 H, m, ArH), 3.54 (1 H, m, 1″-H), 3.45 (1 H, m, 1″-H), 3.32 (1 H, q, *J* 6.62 Hz, 2′-H), 2.96 (3 H, s, MeNCO), 2.95 (3 H, s, MeNCO), 2.53 (2 H, m, CH_2CO), 1.7 (14 H, m, $[CH_2]_n$), and 1.18 (3 H, d, *J* 6.62 Hz, 2′-Me).

1′-(2″-Dimethylcarbamoylethyl)-2′-phenylspiro[cyclo-octane-1,3′-indoline] (**4c**; R = Ph). The indoline derivative (**4c**; R = Ph) was obtained as a yellow oil in 49% yield (Found: C, 79.5; H, 8.5; N, 7.35. $C_{26}H_{34}N_2O$ requires C, 79.96; H, 8.77; N, 7.17%); *m/z* (70 eV) 390 (M^+, 95%) 305 (100), 290 (42), 218 (75), 206 (74), 153 (17), and 100 (44); δ_H 7.3—6.5 (9 H, m, ArH), 4.36 (1 H, s, 2′-H), 3.50 (1 H, m, 1″-H), 3.22 (1 H, m, 1″-H), 2.88 (3 H, s, MeNCO), 2.84 (3 H, s, MeNCO), 2.47 (2 H, m, CH_2CO), and 1.5 (14 H, m, $[CH_2]_n$).

Reduction of 1′-(2-Dimethylcarbamoylethyl)-2′-methyl(or phenyl)spiro[cycloalkane-1,3′-indolines] (**4**). *General Procedure.*—To a stirred suspension of lithium aluminium hydride (1.2 mmol) in dry THF (5 ml) under N_2 was added dropwise a solution of a 1′-(2-dimethylcarbamoylethyl)-2′-methyl(or phenyl)spiro[cycloalkane-1,3′-indoline] (**4**) (0.4 mmol) in THF (15 ml). The mixture was stirred for 3 h at room temperature. The excess of lithium aluminium hydride was destroyed by slow dropwise addition of aqueous THF. The mixture was dried over sodium sulphate, then filtered under reduced pressure, and the solvent was evaporated off to provide the corresponding 1′-(3-dimethylaminopropyl)-2′-methyl(or phenyl)spiro[cycloalkane-1,3′-indoline] (**5**). Hydrochloride salts of the indoline derivatives (**5**) were precipitated as crystals or solids in diethyl ether as solvent, and in general quickly decompose under air contact to give dark oils.

1′-(3″-Dimethylaminopropyl)-2′-methylspiro[cyclohexane-1,3′-indoline] (**5a**; R = Me). The indoline derivative (**5a**; R = Me) was obtained as an oil in 89% yield (Found: C, 79.3; H, 10.2; N, 9.6. $C_{19}H_{30}N_2$ requires C, 79.66; H, 10.56; N, 9.78%); *m/z* (70 eV) 286 (M^+, 91%), 240 (33), 229 (7), 226 (44), 214 (72), 200 (83), 184 (24), 170 (20), 158 (30), 144 (44), and 58 (100); δ_H 7.1—6.3 (4 H, m, ArH), 3.41 (1 H, q, *J* 6.41 Hz, 2′-H), 3.13 (1 H, m, 1″-H), 2.96 (1 H, m, 1″-H), 2.27 (2 H, m, CH_2NMe_2), 2.16 (6 H, s, Me_2N), 1.6 (12 H, m, 2″-H_2 and $[CH_2]_n$), and 0.95 (3 H, d, *J* 6.41 Hz, 2′-Me).

1′-(3″-Dimethylaminopropyl)-2′-phenylspiro[cyclohexane-1,3′-indoline] (**5a**; R = Ph). The indoline derivative (**5a**; R = Ph) was obtained as a yellow oil in 93% yield. The hydrochloride had m.p. 175—177 °C (Found: C, 68.1; H, 8.2; N, 6.8. $C_{24}H_{34}Cl_2N_2$ requires C, 68.38; H, 8.13; N, 6.65%); *m/z* (70 eV) 348 (M^+, 100%), 302 (76), 276 (39), 262 (49), 260 (37), 246 (15), 206 (22), 91 (17), and 53 (54); δ_H 7.2—6.4 (9 H, m, ArH), 4.32 (1 H, s, 2′-H), 3.10 (1 H, m, 1″-H), 2.69 (1 H, m, 1″-H), 2.15 (2 H, m, CH_2NMe_2), 2.08 (6 H, s, Me_2N), and 1.6 (12 H, m, 2″-H_2 and $[CH_2]_n$).

1′-(3″-Dimethylaminopropyl)-2′-methylspiro[cycloheptane-1,3′-indoline] (**5b**; R = Me). The indoline derivative (**5b**; R = Me) was obtained as a yellow oil in 90% yield (Found: C, 79.6; H, 10.5; N, 9.3. $C_{20}H_{32}N_2$ requires C, 79.94; H, 10.73; N, 9.32%); *m/z* (70 eV) 300 (M^+, 42%), 254 (17), 240 (20), 229 (17), 228 (41), 214 (43), 184 (20), 170 (14), 158 (32), 144 (44), and 58 (100); δ_H 7.0—6.3 (4 H, m, ArH), 3.16 (1 H, q, *J* 6.42 Hz, 2′-H), 3.11 (1 H, m, 1″-H), 2.96 (1 H, m, 1″-H), 2.23 (2 H, m, CH_2NMe_2), 2.15 (6 H, s, Me_2N), 1.7 (14 H, m, 2″-H_2 and $[CH_2]_n$), and 1.07 (3 H, d, *J* 6.42 Hz, 2′-Me).

1′-(3″-Dimethylaminopropyl)-2′-phenylspiro[cycloheptane-1,3′-indoline] (**5b**; R = Ph). The indoline derivative (**5b**; R = Ph) was obtained as an oil in 87% yield (Found: C, 82.3; H, 9.2; N, 7.6. $C_{25}H_{34}N_2$ requires C, 82.82; H, 9.45; N, 7.73%); *m/z* (70 eV) 362 (M^+, 100%), 316 (56), 290 (33), 276 (32), 260 (24), 246 (14), 206 (28), 91 (17), and 58 (79); δ_H 7.2—6.4 (9 H, m, ArH), 4.20 (1 H, s, 2′-H), 3.12 (1 H, m, 1″-H), 2.76 (1 H, m, 1″-H), 2.13 (2 H, m, CH_2NMe_2), 2.06 (6 H, s, Me_2N), and 1.5 (14 H, m, 2″-H_2 and $[CH_2]_n$).

1′-(3″-Dimethylaminopropyl)-2′-methylspiro[cyclo-octane-1,3′-indoline] (**5c**; R = Me). The indoline derivative (**5c**; R = Me) was obtained as a yellow oil in 91% yield (Found: C, 79.9; H, 10.7; N, 8.8. $C_{21}H_{34}N_2$ requires C, 80.19; H, 10.89; N, 8.91%); *m/z* (70 eV) 314 (M^+, 47%), 268 (13), 254 (11), 242 (27), 229 (10), 228 (25), 184 (14), 170 (16), 158 (28), 144 (31), and 58 (100); δ_H 7.0—6.3 (4 H, m, ArH), 3.28 (1 H, q, *J* 6.46 Hz 2′-H), 3.12 (1 H, m, 1″-H), 2.96 (1 H, m, 1″-H), 2.26 (2 H, m, CH_2NMe_2), 2.16 (6 H, s, Me_2N), 1.6 (16 H, m, 2″-H_2 and $[CH_2]_n$), and 1.05 (3 H, d, *J* 6.46 Hz, 2′-Me).

1′-(3″-Dimethylaminopropyl)-2′-phenylspiro[cyclo-octane-1,3′-indoline] (**5c**; R = Ph). The indoline derivative (**5c**; R = Ph) was obtained as a yellow oil in 94% yield (Found: C, 82.7; H, 9.5; N, 7.35. $C_{26}H_{36}N_2$ requires C, 82.92; H, 9.63; N, 7.44%); *m/z* (70 eV) 376 (M^+, 100%), 330 (28), 304 (24), 290 (15), 260 (10), 246 (26), 206 (28), 91 (16), and 58 (100); δ_H 7.2—6.4 (9 H, m, ArH), 4.28 (1 H, s, 2′-H), 3.12 (1 H, m, 1″-H), 2.17 (1 H, m, 1″-H), 2.15 (2 H, m, CH_2NMe_2), 2.08 (6 H, s, Me_2N), and 1.5 (16 H, m, 2″-H_2 and $[CH_2]_n$).

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Received 24*th March* 1988; *Paper* 8/01199K