2'-Substituted 1'-(2-Dimethylcarbamoylethyl)-3'-spirocycloalkanoindolines: Synthesis and Conformational Analysis of the Propanamide Fragment

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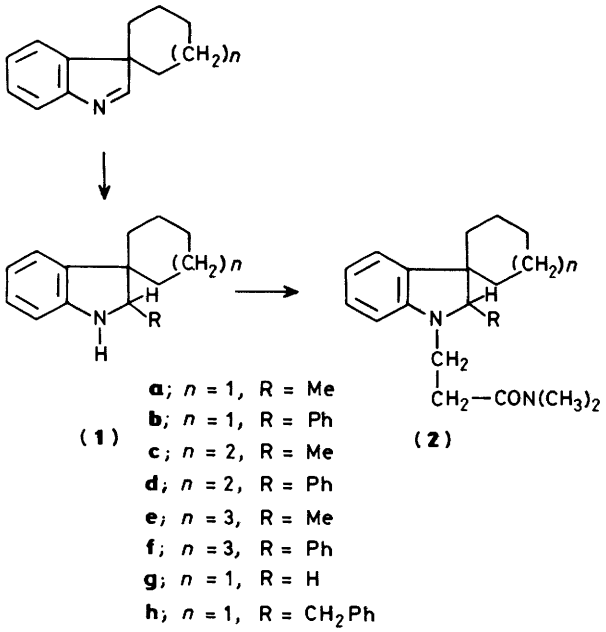
2'-Substituted 1'-(2-dimethylcarbamoylethyl)-3'-spirocycloalkanoindolines (**2a**—**f**) have been obtained by a phase-transfer attack of 3-chloro-*NN*-dimethylpropanamide on the indolines (**1a**—**f**). ^{1}H N.m.r. spectra of the nitrogen side chain in compounds (**2a**—**f**) show an ABCD proton system for the CH_2–CH_2–CON fragment. Conformational analyses of this fragment for (**2a**—**f**) are given and the conformer populations discussed in terms of the bulky ring and the 2'-substituent. Conformational analysis of the CH–CH_2–Ph fragment in the indoline (**1h**) is also given.

The 3'-spirocycloalkanoindolines (**2a**—**f**) have been synthesized as an annular indole-type system with strong steric hindrance at the 3'-position. This effect may be necessary for their potential antidepressant action. In relation to this, we have examined (a) nucleophilic attack on the N=C bond of the spiro[cycloalkane-1,3'-3*H*-indole] to form the 2'-substituted indolines[1] and (b) alkylation of the N–H position of these indolines by 3-chloro-*NN*-dimethylpropanamide (Scheme).



Scheme.

With reference to the structure–biological activity relation of compounds (**2a**—**f**), we are interested in the behaviour of the *NN*-dimethylpropanamide side-chain. In this paper, we present the conformational analysis of the side chain and the influence on the conformational equilibrium of the spirocycloalkane and also the substituent on the 2'-position.

Results and Discussion

The CH_2–CH_2–CON chain in the indolines (**2a**—**f**) shows an ABCD proton system in each one of ^{1}H n.m.r. spectra which were analysed using the iterative computer program LAOCOON III.[2] The frequencies, coupling constants, and root mean square values (differences between observed and calculated line positions) are given in Table 1. The correctness of these analyses is shown by the agreement between the experimental and computer-simulated spectra.

Table 1. Frequencies (Hz), coupling constants (Hz), and root mean squares for the ABCD proton system of the CH_2–CH_2–CON fragment in the indoline derivatives (**2a**—**f**)

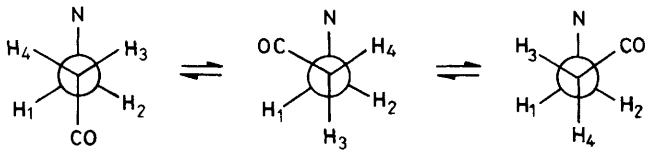
	(2a)	(2c)	(2e)
W_1	705.23	710.48	708.10
W_2	694.15	689.28	690.01
W_3	520.61	504.87	510.71
W_4	506.05	503.86	502.48
J_{12}	−14.54	−14.88	−14.85
J_{13}	8.86	9.32	9.03
J_{14}	5.24	5.43	5.53
J_{23}	6.32	5.60	6.14
J_{24}	8.77	9.32	8.97
J_{34}	−14.96	−15.20	−15.18
R.m.s.	0.07	0.04	0.07
	(2b)	**(2d)**	**(2f)**
W_1	698.31	707.18	700.57
W_2	646.05	651.94	643.22
W_3	505.41	498.58	503.42
W_4	483.21	488.02	485.25
J_{12}	−14.71	−14.80	−14.69
J_{13}	9.69	10.37	9.65
J_{14}	4.94	4.60	4.90
J_{23}	6.07	5.59	6.15
J_{24}	9.45	10.15	9.44
J_{34}	−15.29	−15.42	−15.19
R.m.s.	0.06	0.06	0.06

However, in compound (**2g**),† the above mentioned complex proton system for the CH_2–CH_2–CON fragment now appears as an A_2B_2 type. Thus, we think that the protons of each methylene of the CH_2–CH_2–CON side chain of the indoline derivatives (**2a**—**f**) are diastereotopic due to the presence of a chiral centre on the 2'-position of the indoline ring. Evidence for this effect was obtained by analysis of the influence of the chiral centre on a chain at the 2'-position. Thus, the ^{1}H n.m.r. spectrum of the (**1h**) was analysed and CH_2 and 2'-H appear as an ABX proton system.

Conformational analyses of the CH_2–CH_2–CON side chain in the indolines (**2a**—**f**) were performed by use of the following system of equations:

† The 2'-H indoline derivative (**1g**) has been obtained as the reduction product in the reaction between the spiro[cyclohexane-1,3'-3*H*-indole] and phenethylmagnesium bromide (see ref. 1).

Table 2. Conformational populations of the propionamide side chain the indolines (**2a—f**)



1 2 3

	(2a)	(2c)	(2e)
% 1	51	55	51
% 2	19	21	21
% 3	29	23	27
	(2b)	**(2d)**	**(2f)**
% 1	57	63	56
% 2	16	14	16
% 3	27	23	27

Table 3. Differences of the frequencies (Hz) for each of the pairs of diastereotopic protons

	(2a)	(2c)	(2e)
$W_1 - W_2$	11.08	21.20	18.09
$W_3 - W_4$	14.56	1.01	8.23
	(2b)	**(2d)**	**(2f)**
$W_1 - W_2$	52.26	55.23	57.35
$W_3 - W_4$	22.20	10.56	18.17

$$J_{13} = n_1 J^1{}_{13} + n_2 J^2{}_{13} + n_3 J^3{}_{13}$$
$$J_{14} = n_1 J^1{}_{14} + n_2 J^2{}_{14} + n_3 J^3{}_{14}$$
$$J_{23} = n_1 J^1{}_{23} + n_2 J^2{}_{23} + n_3 J^3{}_{23}$$
$$J_{24} = n_1 J^1{}_{24} + n_2 J^2{}_{24} + n_3 J^3{}_{24}$$
$$1 = n_1 + n_2 + n_3$$

J_{13}, J_{14}, J_{23}, and J_{24} are the experimental values of the vicinal coupling constants, n_1—n_3 the molar ratios of the conformations 1—3, and $J^n{}_{13}$, $J^n{}_{14}$, $J^n{}_{23}$, and $J^n{}_{24}$ (n = 1—3) the theoretical values of the vicinal coupling constants in conformations 1—3, resulting from Altona's equation,[3] using the optimized parameters for the fragment with two non-hydrogen substituents. The resolution of the above system of the equations was carried out by means of a least squares program. Two solutions can be considered, that shown in Table 2 and that which interchanges H-4 and H-3 in the *anti* conformer. The last was rejected when standard deviations were considered.

Table 2 gives the best results of the conformational analyses of the CH_2–CH_2–CON side chain of the indoline derivatives (**2a—f**). The preference in all cases for the *anti* (1) *versus* the gauche conformations 2 and 3 can be deduced from Table 2. The *anti* conformation 1 avoids the steric hindrance between carbonyl group and the indoline ring. Moreover, both *gauche* 2 and 3 have different populations. In all the indoline derivatives (**2a—f**) the *gauche* conformation 3 is preferred to 2. The bulk of the cycloalkane ring apparently does not influence the population of the conformers. Moreover, the proportion of the *gauche* conformation 3 in all the indoline derivatives (**2a—f**) is not influenced by the 2′-substituent, Me or Ph, while the *gauche* conformer 2 is affected by this substituent. In effect, when the 2′-substituent is changed from Me to Ph, the population of conformer 2 decreases while the population of the *anti* conformer 1 increases. The population of conformer 3 in all indolines (**2a—f**) remains constant. We therefore think that the 2′-substituent in conformer 2 is near to the *NN*-dimethylcarbamoyl group.

Table 4. Frequencies (Hz), coupling constants (Hz), and root mean squares for the ABX proton system of the CH–CH_2–Ph chain in the indoline derivative (**1h**)

W_1	724.13	J_{13}	11.52
W_2	558.08	J_{23}	−13.13
W_3	486.28	R.m.s.	0.01
J_{12}	2.64		

Table 3 shows differences ($W_i - W_j$) between the frequencies for each of the pairs of diastereotopic protons. Those differences are affected by the substituent at the 2′-position and by the size of the spirocycloalkane ring. The former effect is observed when the substituent group at the 2′-position is changed from Me to Ph. The increases $W_1 - W_2$ and $W_3 - W_4$ are more important for the protons on the *N*-methylene group nearest of the chiral centre. Moreover, the Ph group can anisotropically influence 2-H and hence the difference $W_1 - W_2$ increases by this shielding effect (H-1 shows a minor variation in frequency).

On the other hand, variations of the differences $W_i - W_j$ in relation to the size of the spirocycloalkane ring are not clear. The cycloheptane derivative shows anomalous behaviour, which is probably due to its particular conformation.

Conformational analysis of the CH_2–CH_2–CON chain of the indoline derivative (**2g**) was attemped. The two *gauche* forms of the staggered conformers (**2g**) are mirror images and hence of equal energy. The observed value of J_{AB} (7.35 Hz) is then simply obtained as the weighted average of the values in the *anti* (J_t) and *gauche* (J_g) conformations, according to the method of Abraham and Gatti,[4] with $J_{AB} = n_g J_g + n_t J_t$ and $n_g + n_t = 1$. Here, n_t and n_g are the populations of the *trans* and *gauche* conformers, respectively. J_t (8.68 Hz) and J_g (6.52 Hz) values for the CH_2–CH_2 fragment have been obtained from a previous paper.[5] Thus, n_g = 62% and n_t = 38%. This result agrees with the above mentioned decrease of the *anti* conformer population when the size of the 2′-substituent decreases.

The ABX proton system of the CH–CH_2–Ph fragment in the indoline (**1h**) was analysed using the iterative computer program LAOCOON III.[2] The frequencies, coupling constants, and root mean square values are given in Table 4. The correctness of this analysis is showed by the agreement between the experimental and computer-simulated spectra.

The conformational analysis of the CH–CH_2–Ph fragment in the indoline (**1h**) was performed by use of a system of equations in a similar way to that described above for the indolines (**2a—f**). This analysis shows that the conformer 1 (Figure) is the only one present in solution at room temperature. The dihedral angles, calculated by Altona's equation,[3] between the vicinal protons in this fixed conformation are φ_{12} 64 and φ_{13} 164°.

Experimental

M.p.s were measured on a hot-stage microscope and are uncorrected. I.r. spectra were taken with a Pye–Unicam SP1100 spectrophotometer and ^{1}H n.m.r. spectra were recorded on a Brüker WM-200-SY spectrometer. Simulation was carried out with the PANIC program on an Aspect-2000 computer. Elemental analysis were performed in a Perkin-Elmer 240 elemental analyser. Solvents and reagents were purified in the usual way.

The spirocyclohexane indoles and the indoline derivatives

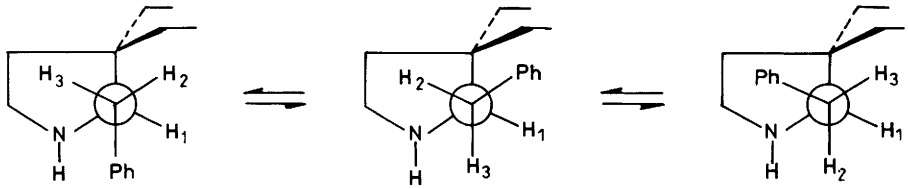


Figure. Conformational equilibrium of the $CH–CH_2–Ph$ chain in the indoline (**1h**)

(**1a**—**g**) used as starting products were obtained according to a previously reported method.[1,5]

The indoline derivatives (**2a**—**g**) were obtained as follows. A mixture of the indoline derivative (**1**) (6 mmol), 3-chloro-*NN*-dimethylpropanamide (18 mmol), sodium carbonate (0.95 g), ethanol (16 ml), and water (4 ml) was refluxed for 25 days. 3-Chloro-*NN*-dimethylpropanamide (6 mmol), sodium carbonate (0.31 g), ethanol (8 ml), and water (2 ml) were incorporated every 6 days into the above mixture. Finally, the mixture was concentrated under reduced pressure, diluted with water, and extracted with dichloromethane. Solvent and the residual acrylamide were removed under vacuum to give an oil, which was chromatographed on a silica gel column eluting with ethyl acetate–hexane (2:1) to provide the indoline derivative (**2**). The hydrochloride salts of the indoline derivatives precipitate as crystals or solid in diethyl ether as solvent, but in general they quickly decompose on air contact to dark oils.

1′-(2-*Dimethylcarbamoylethyl*)-2′-*methyl*-3′-*spirocyclohexanoindoline* (**2a**) was yellow oil (69%) (Found: C, 75.8; H, 9.6; N, 9.5. $C_{19}H_{28}N_2O$ requires C, 75.9; H, 9.4; N, 9.3%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.2—6.4 (m, Ar-H, 4 H), 3.53 (m, 1′-H, 1 H), 3.47 (m, 1′-H, 1 H), 3.41 (q, 2′-H, *J* 6.46 Hz), 2.96 (s, CH_3–NCO), 2.94 (s, CH_3–NCO), 2.56 (m, CH_2–CO), 1.6 [m, $(CH_2)_n$, 10 H], and 1.08 (d, 2′-CH_3, *J* 6.46 Hz).

1′-(2-*Dimethylcarbamoylethyl*)-2′-*phenyl*-3′-*spirocyclohexanoindoline* (**2b**) was a yellow oil (64%), hydrochloride m.p. 120—122 °C (Found: C, 75.65; H, 7.8; N, 7.0. $C_{24}H_{31}ClN_2O$ requires C, 75.25; H, 7.8; N, 7.0%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.3—6.5 (m, Ar-H, 9 H), 3.49 (m, 1′-H, 1 H), 3.23 (m, 1′-H, 1 H), 4.37 (s, 2′-H), 2.88 (s, CH_3–NCO), 2.84 (CH_3–NCO), 2.47 (m, CH_2–CO), and 1.6 [m, $(CH_2)_n$, 10 H].

1′-(2-*Dimethylcarbamoylethyl*)-2′-*methyl*-3′-*spirocycloheptanoindoline* (**2c**) was a yellow oil (71%) (Found: C, 76.2; H, 9.8; N, 8.8. $C_{20}H_{30}N_2O$ requires C, 76.4; H, 9.6; N, 8.9%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.2—6.4 (m, Ar-H, 4 H), 3.55 (m, 1′-H, 1 H), 3.45 (m, 1′-H, 1 H), 3.19 (q, 2′-H, *J* 6.46 Hz), 2.97 (s, CH_3–NCO), 2.96 (s, CH_3–NCO), 2.52 (m, CH_2–CO), 1.7 [m, $(CH_2)_n$, 12 H], and 1.19 (d, 2′-CH_3, *J* 6.46 Hz).

1′-(2-*Dimethylcarbamoylethyl*)-2′-*phenyl*-3′-*spirocycloheptanoindoline* (**2d**) was a yellow oil (58%) (Found: C, 79.5; H, 8.45; N, 7.6. $C_{25}H_{32}N_2O$ requires C, 79.7; H, 8.6; N, 7.4%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.3—6.6 (m, Ar-H, 9 H), 4.25 (s, 2′-H), 3.54 (m, 1′-H, 1 H), 2.87 (s, CH_3–NCO), 2.83 (s, CH_3–NCO), 2.46 (m, CH_2–CO), and 1.6 [m, $(CH_2)_n$, 12 H].

1′-(2-*Dimethylcarbamoylethyl*)-2′-*methyl*-3′-*spirocyclooctanoindoline* (**2e**) was a yellow oil (52%) (Found: C, 76.5; H, 9.9; N, 8.5. $C_{21}H_{32}N_2O$ requires C, 76.8; H, 9.8; N, 8.5%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.1—6.4 (m, Ar-H, 4 H), 3.54 (m, 1′-H, 1 H), 3.45 (m, 1′-H, 1 H), 3.32 (q, 2′-H, *J* 6.62 Hz), 2.96 (s, CH_3–NCO), 2.95 (s, CH_3–NCO), 2.53 (m, CH_2–CO), 1.7 [m, $(CH_2)_n$, 14 H], and 1.18 (d, 2′-CH_3, *J* 6.62 Hz).

1′-(2-*Dimethylcarbamoylethyl*)-2′-*phenyl*-3′-*spirocyclooctanoindoline* (**2f**) was a yellow oil (49%) (Found: C, 79.5; H, 8.6; N, 7.25. $C_{26}H_{34}N_2O$ requires C, 80.0; H, 8.8; N, 7.2%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.3—6.5 (m, Ar-H, 9 H), 4.36 (s, 2′-H), 3.50 (m, 1′-H, 1 H), 3.22 (m, 1′-H, 1 H), 2.88 (s, CH_3–NCO), 2.84 (s, CH_3–NCO), 2.47 (m, CH_2–CO), and 1.5 [m, $(CH_2)_n$, 14 H].

1′-(2-*Dimethylcarbamoylethyl*)-3′-*spirocyclohexanoindoline* (**2g**) was a yellow oil (51%) (Found: C, 75.2; H, 9.3; N, 9.65. $C_{18}H_{26}N_2O$ requires C, 75.5; H, 9.15; N, 9.8%), ν(film) 1 650 cm^{-1} (CON), $\delta_H(Cl_3CD)$ 7.1—6.4 (m, Ar-H, 4 H); 3.49 (t, 1′-H_2, *J* 7.35 Hz), 3.24 (s, 2′-H_2), 2.97 (s, CH_3–NCO), 2.94 (s, CH_3–NCO), 2.57 (t, CH_2–CO, *J* 7.35 Hz), and 1.6 [m, $(CH_2)_n$, 10 H].

The indoline derivative (**1h**) was obtained according to the following procedure. To a solution of benzylmagnesium bromide (0.5 mol) in toluene were added a solution of the spirocyclohexanoindole (0.1 mol) in toluene and a little copper(I) chloride. The mixture was refluxed for 2 h under nitrogen, hydrolysed with saturated ammonium chloride solution, and extracted with dichloromethane to give 2′-*benzyl*-3′-*spirocyclohexanoindoline* (**1h**) (96%), m.p. 94—95 °C (Found: C, 86.2; H, 8.3; N, 4.9. $C_{20}H_{23}N$ requires C, 86.6; H, 8.4; N, 5.05%), ν(KBr) 3 400 cm^{-1} (N–H), $\delta_H(Cl_3CD)$ 7.2—6.6 (m, 9 H, ArH), 3.62 (m, 2′-H, 1 H), 3.58 (br, N–H), 2.79 (m, H–C–Ph, 1 H), 2.43 (m, H–C–Ph, 1 H), and 1.7 [m, $(CH_2)_n$, 10 H].

Acknowledgements

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References

1 J. G. Rodriguez, Y. Benito, and F. Temprano, *Chem. Lett.*, 1985, 427.
2 S. M. Castellano and A. A. Bothner-By, 'Computer Programs in Chemistry,' ed. D. F. de Tar, Benjamin, New York, 1968, vol. 1, p. 10.
3 C. A. G. Haasnoot, F. A. A. H. de Leeuw, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
4 R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 1969, 961.
5 J. G. Rodriguez, Y. Benito, and F. Temprano, *J. Heterocycl. Chem.*, 1985, **22**, 1207.

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