Cyclization of *N*-Alkenyl-*o*-chloroanilides with Organonickel(0) Complexes: Conformational Analysis of 3-Substituted Oxindoles

J. Gonzalo Rodriguez,* Laureano Canoira, and Fernando Temprano
Departamento de Quimica Organica, Universidad Autonoma de Madrid, Canto Blanco, Madrid 28049, Spain

3-Substituted oxindoles (**1**)—(**6**) have been obtained as the main products of the cyclization reaction of *N*-alkenyl-*o*-chloroanilides with the zerovalent complex tetrakis(triphenylphosphine)nickel(0). ^{1}H N.m.r. spectra of the oxindoles (**2**)—(**6**) show an AMX proton system for the CH–CH_2R^2 fragment. Conformational analyses of this fragment for (**2**)—(**6**) are given. Moreover, conformational analysis of the *N*-β-cyanoethyl chain in oxindole (**6**) is also given.

Oxindole derivatives (**1**)—(**6**) were obtained as the main products of the cyclization reaction of *N*-alkenyl-*o*-chloroanilides with the zerovalent complex tetrakis(triphenylphosphine)nickel(0), in toluene as solvent.[1] Synthesis of the oxindole derivatives has been undertaken as potentially antidepressant drugs. However, oxindole derivatives (**2**)—(**6**) show a complex ^{1}H n.m.r. spectrum for the $CHCH_2R^2$ fragment and (**6**) also shows a complex ^{1}H n.m.r. spectrum for the CH_2CH_2 fragment of the side chain. Some structural requirements related to the activity of these compounds have been outlined[2] and thus, conformational analysis of the side chains has been carried out.

Results and Discussion

The $CHCH_2R^2$ fragment in oxindoles (**2**)—(**6**) shows an AMX proton system in each ^{1}H n.m.r. spectrum analysed using the iterative computer program LAOCOON III.[3] The frequencies, coupling constants, and r.m.s. 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. Figure 1 shows the experimental (a) and the computer-simulated (b) spectrum of the $CHCH_2R^2$ fragment for (**2**). Moreover, in these compounds the H_X proton shows a long-range coupling constant of 0.5 Hz with the 4-H proton of the aromatic ring, which produces broadness in the lines of the absorption signal.

We think that this CH–CH_2R^2 fragment of the oxindole derivatives (**2**)—(**6**) is freely rotating, but due to the presence of a chiral centre, the two protons of the methylene group are diastereotopic. In contrast, for (**1**), the AMX system was not observed. Moreover, the nature of the R^2 in (**2**)—(**6**) seems to have some influence on the conformational equilibrium showed in Figure 2.

Conformational analysis of the $CHCH_2R^2$ fragment in the oxindole derivatives (**2**)—(**6**) was performed by use of the system of equations (1)—(3) where J_{AX} and J_{MX} are the

$$J_{AX} = X_A J^1_{AX} + X_B J^2_{AX} + X_C J^3_{AX} \quad (1)$$

$$J_{MX} = X_A J^1_{MX} + X_B J^2_{MX} + X_C J^3_{MX} \quad (2)$$

$$X_A + X_B + X_C = 1 \quad (3)$$

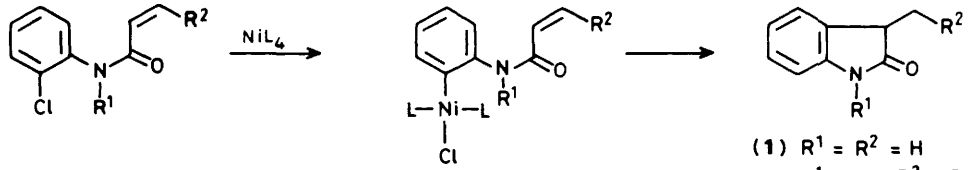
experimental values of the vicinal coupling constants, X_A, X_B and X_C are the molar ratios of conformations (*A*)—(*C*), and J^n_{AX} and J^n_{MX} (n = 1—3) are the theoretical values of the vicinal coupling constants in conformations (*A*)—(*C*), resulting from Altona's equation,[4] using the optimized parameters for the fragment with three non-hydrogen substituents.

Table 1. Frequencies, coupling constants, and r.m.s. for the AMX system of the oxindole derivatives (**2**)—(**6**)

	(2)	(3)	(4)	(5)	(6)
δH_X	3.76	3.81	3.92	3.95	3.87
δH_M	3.50	3.08	3.10	3.13	3.13
δH_A	2.96	2.82	2.72	2.66	2.85
J_{MX}	4.60	4.52	3.17	3.16	3.28
J_{AX}	9.28	8.01	8.94	9.34	8.18
J_{AM}	−13.74	−16.84	−16.51	−16.31	−16.67
R.m.s.	0.04	0.04	0.05	0.05	0.03

Table 2. Conformational populations of the $CHCH_2$ fragment in the oxindole derivatives (**2**)—(**6**)

Compound	%(*A*)	%(*B*)	%(*C*)
(**2**)	66.8	17.0	16.2
(**3**)	53.0	15.8	31.2
(**4**)	62.7	1.3	36.0
(**5**)	67.1	1.3	31.5
(**6**)	55.4	2.2	43.3



L = PPh_3

(**1**) $R^1 = R^2 = H$
(**2**) $R^1 = H$, $R^2 = Ph$
(**3**) $R^1 = H$, $R^2 = CO_2Me$
(**4**) $R^1 = H$, $R^2 = CONMe_2$
(**5**) $R^1 = Me$, $R^2 = CONMe_2$
(**6**) $R^1 = CH_2CH_2CN$, $R^2 = CONMe_2$

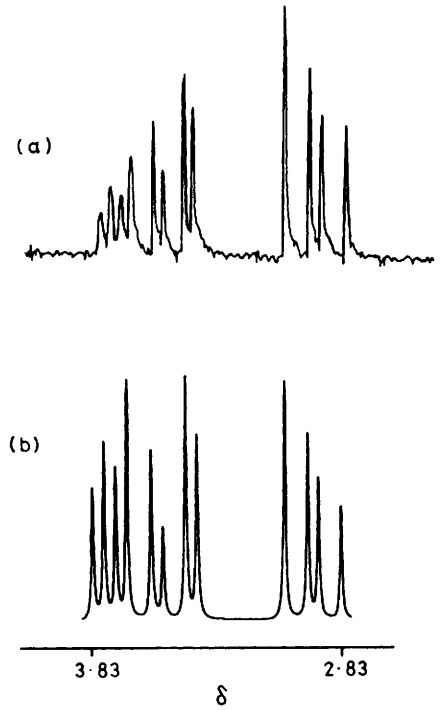


Figure 1. ^{1}H N.m.r. spectra: experimental (a) and simulated (b) for the AMX fragment of the compound (**2**)

Table 3. Frequencies, coupling constants, and r.m.s. for the ABCD system of the oxindole (**6**)

δH_A 4.11; δH_B 4.01; δH_C 2.78; δH_D 2.78
J_{AB} − 13.96; J_{AC}, 7.39; J_{AD}, 7.03; J_{BC}, 8.86; J_{BD}, 5.57; J_{CD}, − 16.15
R.m.s. 0.04

Table 4. Dihedral angles (φ) and conformational populations of the $^3J_{HH}$ values from Table 3

	Solution 1	Solution 2
φ_{AC}	37.5	139.5
φ_{AD}	137.7	39.7
φ_{BC}	23.0	23.0
φ_{BD}	43.0	42.5
$\%n_A$	29.8	37.0
$\%n_B$	25.1	42.0
$\%n_C$	45.0	20.9

Table 2 gives the results of the conformational analysis of the $CHCH_2R^2$ fragment of the oxindole derivatives (**2**)—(**6**). From Table 2 can be deduced a preference in all the cases for the *anti* conformation (*A*) over the *gauche* ones (*B*) and (*C*). The *anti* conformation (*A*) avoids the steric hindrance between R^2 and the carbonyl group. Moreover, both *gauche* (*B*) and (*C*) have different populations, except for (**2**), showing the former to have

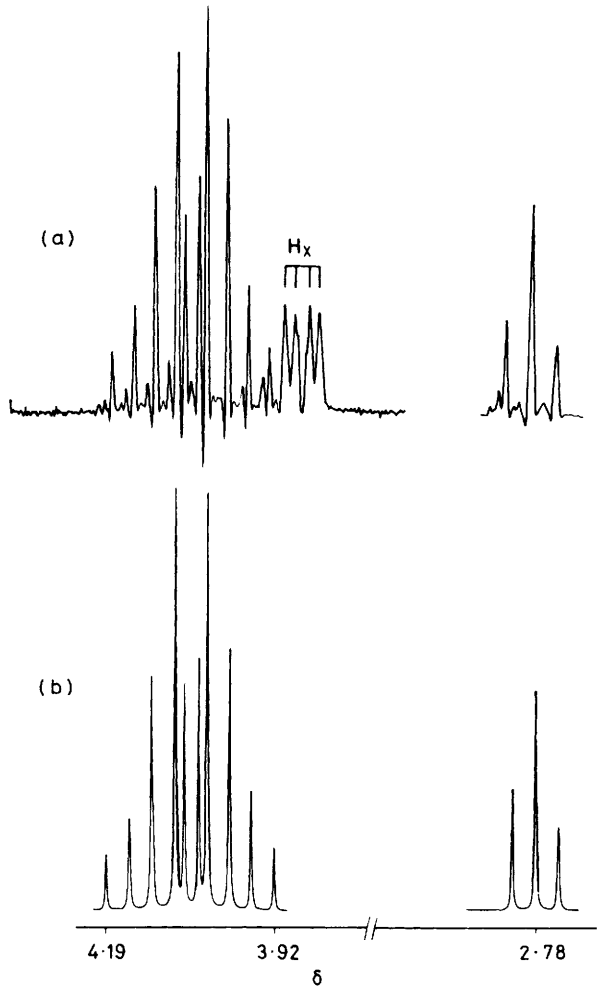


Figure 3. ^{1}H N.m.r. spectra: experimental (a) and simulated (b) for the ABCD fragment of oxindole (**6**). The CH_2 groups are of different intensities.

the highest energy due to the mentioned steric effect. In the same manner, (**2**), which has a bulky phenyl substituent, also shows a preference for the *anti* conformation (*A*), but both *gauche* ones (*B*) and (*C*) have almost the same population (or the same energy). In contrast, the *gauche* conformations in (**3**)—(**6**) have different populations (or different energies) and thus, with a carbonyl derivative as substituent instead of phenyl, there is some electrical repulsion between it and the carbonyl group of the ring. Moreover, there is differing behaviour by the *NN*-dimethylamide and ester groups on the conformational equilibrium. The former decreases the *gauche* (*B*) *versus gauche* (*C*) population. When *N*-oxindole substitution is considered [(**5**) and (**6**)] (*A*) decreases and (*C*) increases as can be expected from the size of the side chain on nitrogen. These steric effects can be analysed using mechanical models. The *NN*-

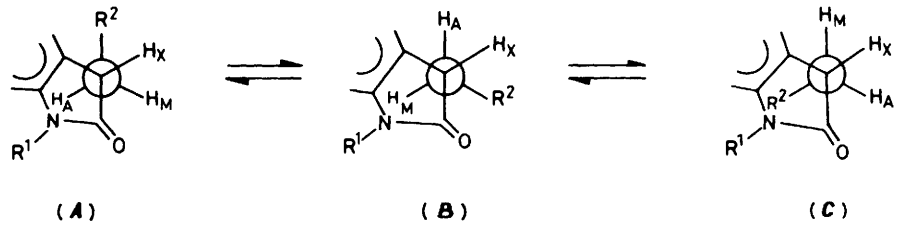


Figure 2. Conformational equilibrium for the AMX proton system of compounds (**2**)—(**6**)

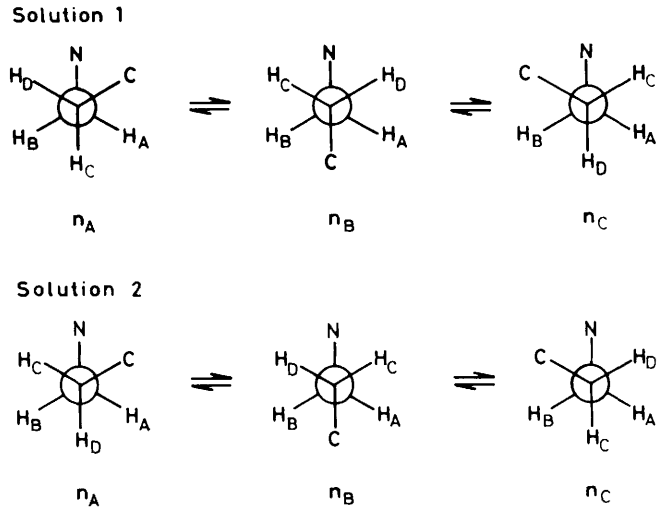


Figure 4. Conformational equilibrium for the ABCD proton system of the oxindole (**6**) (solutions 1 and 2)

dimethylamide and ester groups can be considered planar and parallel to the mean plane of the oxindole ring, and thus these substituents show minor steric hindrance for the *gauche* (*C*) and (*B*) conformations, while electrical repulsion between both carbonyl groups is present in the *gauche* (*B*) conformer.

The ABCD proton system for the NCH_2CH_2 fragment present in the oxindole (**6**) is generally shown by open-chain compounds bearing the *N*-β-cyanoethyl chain, a CON amide group, and an *ortho* substituted aromatic ring, and it has been observed in *o*-chloro-*N*-alkenyl-*N*-β-cyanoethylanilide which is the open-chain precursor of (**6**) in the cyclization reaction. This ABCD proton system in (**6**) has been analysed using the iterative computer program LAOCOON III.[3] The frequencies, coupling constants, and r.m.s. error values are given in Table 3. The correctness of this analysis is showed by the agreement between the experimental and computer-simulated spectrum (Figure 3).

The conformational analyses of the NCH_2CH_2 chain has been carried out using Altona's equation[4] and in Table 4 are given the best values of the φ dihedral angles and the conformational populations, estimated from the experimental values of the vicinal coupling constants. A similar system of equations to that outlined for the conformational analysis of the $CHCH_2R^2$ fragment was carried out to calculate the conformational populations and two solutions were found: (*a*) the *gauche* conformation (n_C) was preferred over the *anti* conformation, and (b) the *anti* conformation (n_B) was preferred over the *gauche* (n_C), Figure 4.

The presence of this complex ABCD proton system has been analysed by ^1H n.m.r. and *X*-ray techniques for *o*-chloro-*N*-alkenylanilides[5] and hence, in a similar manner, the diastereotopic effect showed in the NCH_2CH_2 fragment for oxindole (**6**) can be due to the rigid anchorage of H_A of the α-methylene group to the oxygen atom of the oxindole carbonyl group, forming a five-membered ring. The β-methylene protons show a freely rotating equilibrium between the *gauche* n_A and n_C and the *anti* n_B conformations. The *gauche* ones are stabilized by a dipolar effect, which refers to the dipolar moments of the C≡N group and the N-C_α bond.

Experimental

M.p.s were measured in a hot-stage microscope and are uncorrected. The i.r. spectra were registered on a Pye–Unicam SP1100 spectrophotometer and the ^1H n.m.r. spectra were obtained with a Varian XL-100 spectrometer, except for (**6**) which was obtained with a Brucker WH-200-SY instrument. Mass spectra were obtained in a Hewlett–Packard 5985 g.c.–m.s. system. Elemental analysis were performed with Perkin-Elmer 240 elemental analyser. The solvents and reagents were purified in the usual way. Yields are given from h.p.l.c. analysis.

The *N*-alkenyl-*o*-chloroanilides, used as the starting products for the cyclization reaction, were obtained according to previously reported methods,[1]

The oxindole derivatives (**1**)—(**6**) were obtained as follows. To a solution of bis(acetylacetonato)nickel(II) (0.256 g, 1 mmol) and triphenylphosphine (1.05 g, 4 mmol) in anhydrous toluene, was added triethylaluminium (0.64 g, 6 mmol; 1.62 ml of a solution 50% in toluene), with external cooling at −15 °C under nitrogen. The mixture, after a vigorous initial reaction, was stirred at room temperature for 30 min to acquire the characteristic dark red colour of tetrakis(triphenylphosphine)-nickel(0). A solution of *N*-alkenyl-*o*-chloroanilide derivative (1 mmol) in anhydrous toluene was then added and the mixture warmed at 60—100 °C for 4—5 h. Finally, it was hydrolysed with an aqueous, saturated ammonium chloride solution. The organic layer was extracted with ethyl acetate, dried ($MgSO_4$), and chromatographed on a silica gel column, providing the oxindoles (**1**)—(**6**).

3-Methyloxindole (**1**) was a solid (24%), m.p. 124 °C[6] (Found: C, 73.2; H, 6.1; N, 9.3. Calc. for C_9H_9NO: C, 73.4; H, 6.2; N, 9.5%); ν(KBr) 3 240 (br, NH) and 1 720 cm^{-1} (CON oxindole); $\delta_H(CDCl_3)$ 8.70 (br s, NH, 1 H), 7.35—6.82 (m, ArH, 4 H), 3.38 (br q, CH, 1 H, *J* 7.6 Hz), and 1.48 (d, Me, 3 H, *J* 7.6 Hz); *m/z* (70 eV) 147 (M^+, 60%), 132 ($M^+ - 15$, 19), 118 ($M^+ - 29$, 100), 104 (28), and 91 (42).

3-Benzyloxindole (**2**) was a solid (35%), m.p. 131 °C[7] (Found: C, 81.1; H, 5.6; N, 6.3. Calc. for $C_{15}H_{13}NO$: C, 80.7; H, 5.9; N, 6.3%); ν (KBr) 3 220 (NH) and 1 720 cm^{-1} (CON oxindole); $\delta_H(CDCl_3)$ 8.25 (br s, NH, 1 H), 7.27—6.70 (m, ArH, 9 H), 3.76 (dd, 3-H, 1 H, *J* 4.60 and 9.28 Hz), 3.50 (dd, CH_MPh, 1 H, *J* −13.74 and 4.60 Hz), and 2.96 (dd, CH_APh, 1 H, *J* −13.74 and 9.28 Hz); *m/z* (70 eV) 223 (M^+, 29%), 205 ($M^+ - 18$, 2), 159 (5), 146 ($M^+ - 77$, 5), 132 ($M^+ - 91$, 21), 117 (2), 104 (4), and 91 (100).

3-Oxindolylmethyl acetate (**3**) was a solid (73%), m.p. 185—186 °C[8] (Found: C, 64.15; H, 5.2; N, 6.6. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%); ν(KBr) 3 200 (NH), 1 735 (CO_2Me), 1 720 (CON oxindole), and 1 200 cm^{-1} (C–O–C); $\delta_H(CDCl_3)$ 9.20 (br s, NH, 1 H), 7.68—6.84 (m, ArH, 4 H), 3.81 (dd, 3-H, 1 H, *J* 4.52 and 8.01 Hz), 3.69 (s, OMe, 3 H), 3.08 (dd, CH_MCO_2Me, 1 H, *J* −16.84 and 4.52 Hz), and 2.82 (dd, CH_ACO_2Me, 1 H, *J* −16.84 and 8.01 Hz); *m/z* (70eV) 205 (M^+, 18%), 173 ($M^+ - 32$, 14), 162 ($M^+ - 43$, 21), 145 ($M^+ - 60$, 100), 132 (13), 117 (18), and 104 (4).

NN-*Dimethyl*-3-*oxindolylacetamide* (**4**) was an oil (94%) (Found: C, 65.8; H, 6.2; N, 12.6. $C_{12}H_{14}N_2O_2$ requires C, 66.0; H, 6.5; N, 12.8%); ν(KBr) 3 440 (sharp, free NH), 3 230 (br, associated NH), 1 725 (CON oxindole), and 1 650 cm^{-1} (CON amide); $\delta_H(CDCl_3)$ 9.02 (br s, NH, 1 H), 7.29—6.29 (m, ArH, 4 H), 3.92 (dd, 3-H, 1 H, *J* 3.17 and 8.94 Hz), 3.10 (dd, CH_MCON, 1 H, *J* −16.51 and 3.17 Hz), 2.97 (s, NMe, 3 H), 2.95 (s, NMe, 3 H), and 2.72 (dd, CH_ACON, 1 H, *J* −16.51 and 8.94 Hz); *m/z* (70eV) 218 (M^+, 29%), 173 ($M^+ - 45$, 8), 146 ($M^+ - 72$, 74), 145 (100), 128 (41), 117 (70), 104 (11), 90 (28), 72 (57), and 46 (96).

NN-*Dimethyl*-(3-N-*methyloxindolyl*)*acetamide* (**5**) was a solid (98%), m.p. 135—136 °C (diethyl ether) (Found: C, 67.1; H, 6.6; N, 12.15. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%); ν(KBr) 1 725 (CON oxindole) and 1 635 cm^{-1} (CON amide); $\delta_H(CDCl_3)$ 7.42—6.77 (m, ArH, 4 H), 3.95 (dd, 3-H, 1 H, *J* 3.16 and 9.34 Hz), 3.23 (s, NMe, 3 H), 3.13 (dd, CH_MCON, 1 H, *J* −16.31 and 3.16 Hz), 2.99 (s, NMe, 6 H), and 2.66 (dd, CH_ACON, 1 H, *J* −16.31 and 9.34 Hz); *m/z* (70 eV) 232 (M^+,

27%), 160 (M^+ − 72, 96), 146 (M^+ − 86, 22), 130 (100), 117 (64), 103 (22), 91 (50), 72 (76), and 42 (88).

NN-Dimethyl-(3-N-β-cyanoethyloxindolyl)acetamide (**6**) was a solid (98%), m.p. 113—115 °C (Found: C, 66.2; H, 6.35; N, 15.7. $C_{15}H_{17}N_3O_2$ requires C, 66.4; H, 6.3; N, 15.5%); ν(Nujol) 2 270 (C≡N), 1 725 (CON oxindole), and 1 635 cm^{-1} (CON amide); $\delta_H(CDCl_3)$ 7.38—6.45 (m, ArH, 4 H), 4.11 [m, NCH(1), 1 H, J −13.96, 7.39, and 7.03 Hz], 4.01 [m, NCH(2), 1 H, J −13.96, 8.85, and 5.56 Hz], 3.87 (dd, 3-H, 1 H, J 3.28 and 8.17 Hz), 3.13 (dd, CH_MCON, 1 H, J −16.67 and 3.28 Hz), 3.03 (s, NMe, 3 H), 2.93 (s, NMe, 3 H), 2.85 (dd, CH_ACON, 1 H, J −16.67 and 8.17 Hz), 2.78 [m, CH(3)CN, 1 H, J −16.15, 7.39, and 8.85 Hz], and 2.78 [m, CH(4)CN, 1 H, J −16.15, 7.03, and 5.56 Hz]; m/z (70 eV) 271 (M^+, 53%), 225 (M^+ − 46, 15), 199 (M^+ − 72, 21), 198 (51), 158 (100), 146 (17), 130 (26), 117 (11), 103 (7), and 72 (26).

Acknowledgements

We thank CAYCIT by financial support and MEC for a research grant to L. C.

References

1 J. G. Rodriguez and L. Canoira, *J. Heterocycl. Chem.*, 1985, **22**, 1511.
2 (*a*) J. Lopez de Lerma, S. Garcia Blanco, and J. G. Rodriguez, *Acta Crystallogr.*, 1977, **B33**, 2311; (*b*) J. Lopez de Lerma, M. Martinez Ripoll, S. Garcia Blanco, and J. G. Rodriguez, *ibid.*, 1979, **B35**, 1739.
3 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.
4 C. A. G. Haasnoot, F. A. A. H. de Leew, and C. Altona, *Tetrahedron*, 1980, **36**, 2783.
5 J. G. Rodriguez, L. Canoira, S. Garcia Blanco, M. Martinez Ripoll, and C. Esteban Calderon, *J. Chem. Soc., Perkin Trans. 2*, 1986, 199.
6 L. Horner, *Justus Liebigs Ann. Chem.*, 1941, **548**, 117.
7 J. Stanek and D. Rybar, *Chem. Listy*, 1946, **40**, 173.
8 W. C. Sumpter, M. Miller, and L. N. Hendrick, *J. Am. Chem. Soc.*, 1945, **67**, 1037.

Received 17*th June* 1985; *Paper* 5/1016