ON THE CONFIGURATION AND THE CONFORMATION OF 2-ACYLINDAZOLE ARYLHYDRAZONES

Giuseppe Cusmano*, Gabriella Macaluso*, Werner Hinz**, and Silvestre Buscemi*

*Istituto di Chimica Organica - Facoltà di Scienze - Università di Palermo, Via Archirafi, 20, 90123, Palermo, Italy

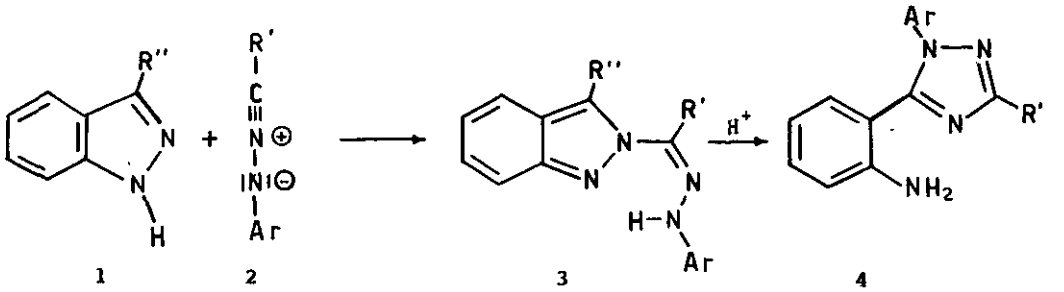
**Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, PQ, Canada, H3A 2K6

Abstract —— The Z configuration of 2-acylindazole arylhydrazones 3 was assigned on the basis of solvent effects on their ^{1}H-nmr spectra. Due to free rotation around the N-C bond, the title compounds exist in a solvent dependent equilibrium between the intramolecular N-H bonded conformer 6 and its rotamers.

In a previous paper, we described the 1,3-addition reaction of indazole 1 with nitrilimines 2a, 2b and 2d to give 2-acylindazole phenylhydrazones 3, and the further transformation of hydrazones 3 into 1-phenyl-5-(o-aminophenyl)-1,2,4-triazole derivatives 4 and into 1,2,4-triazolo[1,5-f]phenanthridines 5.[1] The hydrazone structure of compounds 3a, 3b and 3d had been confirmed by analytical and spectral data as well as by the structures of products 4 and 5 obtained.

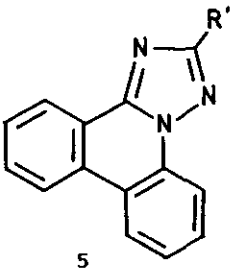
However, since the Z configuration of hydrazones 3 plays an important role in the postulated acid catalysed rearrangement of 3 to give 4[1], an investigation of the structure of intermediates 3, involving ^{1}H-nmr spectroscopy and infrared spectroscopy was warranted.

For the purpose of this study, additional hydrazones 3c and 3e-h were prepared following the established procedure.[1] The ^{1}H-nmr data in $CDCl_3$ confirm the 2-substituted indazole structure for 3a-h : H-4 and H-7 are distinct and display the expected chemical shifts, for 3b-g H-3 was found downfield from H-3 for the parent compound indazole and the characteristic $^5J_{H3-H7}$ was determined to be ca 1 Hz in all cases, as required[2] (see Experimental).



1 2 3 4

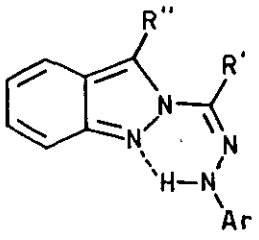
1) $NaNO_2$/HCl
2) H_3PO_2



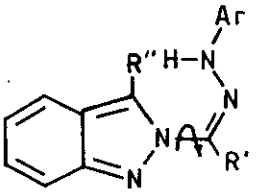
5

	Ar	R'	R"
a	Ph	Ph	H
b	Ph	CO_2Et	H
c	Ph	CO_2Me	H
d	Ph	COMe	H
e	4-Cl-C_6H_4	COMe	H
f	4-Me-C_6H_4	COMe	H
g	4-MeO-C_6H_4	COMe	H
h	Ph	COMe	Me

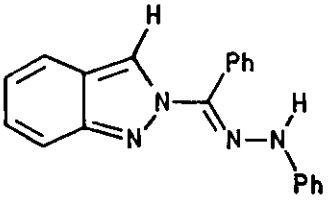
The following tautomeric structures are conceivable for adducts **3** : hydrazones **6-8** and the diazo tautomer **9**, for **3b-h** also the enolic tautomer **10**.



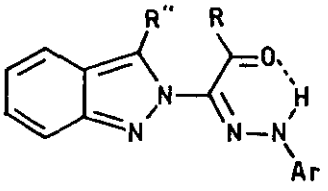
6 (Z N-H bonded)



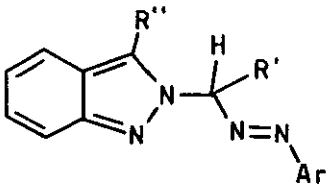
7 (Z N-H free)



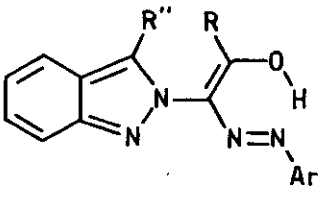
8a (E)



8b-h (E)



9



10

Structure **9** is immediately ruled out by the presence of a low field signal in the ^{1}H-nmr spectrum (N-H or O-H), while infrared data exclude the enolic structure **10**.[3] Carbonyl stretching frequencies in $CHCl_3$ at ca 1710 cm^{-1} (**3b,c**) and ca 1680 cm^{-1} (**3d-h**) (see Table) represent conjugated, non-hydrogen bonded ester and ketone carbonyl absorptions, respectively. This also presents first evidence against structure **8**, in which the E - configuration of the hydrazone should, in the case of **3b-h**, lead to a strong intramolecular N-H---O hydrogen bond.[4]

The ^{1}H-nmr chemical shift values for the N-H and H-3 protons for hydrazones **3a-h** in solvents of increasing polarity (benzene, chloroform, acetone, dimethyl sulfoxide) are given in the **Table.**

Table : Chemical Shift Values for N-H and H-3 Protons and Carbonyl Stretching Frequencies for Hydrazones **3a-h**

	Ar	R'	R"	δ N-H				δ H-3				υ C=O
				C_6D_6	$CDCl_3$	C_3D_6O	DMSO	C_6D_6	$CDCl_3$	C_3D_6O	DMSO	cm^{-1}
3a	Ph	Ph	H	11.17	10.65	10.37	10.01	7.30	8.09	8.44	8.68	--
3b	Ph	CO_2Et	H	13.07	12.66	12.07	11.02	8.84	8.86	8.84	8.70	1710
3c	Ph	CO_2Me	H	13.09	12.73	12.08	11.04	8.79	8.88	8.84	8.70	1712
3d	Ph	COMe	H	13.36	13.08	12.54	11.36	9.09	8.99	8.87	8.61	1680
3e	4-Cl-C_6H_4	COMe	H	13.24	13.18	12.61	11.36	9.08	9.00	8.87	8.60	1680
3f	4-Me-C_6H_4	COMe	H	13.39	13.02	12.52	11.33	9.11	8.98	8.87	8.60	1680
3g	4-MeO-C_6H_4	COMe	H	13.37	13.03	12.49	11.28	9.16	8.98	8.86	8.59	1675
3h	Ph	COMe	Me	10.58	9.96	10.41	10.76	--	--	--	--	1680

Figure 1 shows the dependence of the chemical shift values of the N-H protons of compounds **3a-h** upon the solvent used. For compounds **3a-g** a marked upfield shift is observed in the series benzene - dimethyl sulfoxide, characteristic for the presence of an intramolecular hydrogen bond[5] (structure **6**). For the 3-methyl derivative **3h**, the bulky substituent in the 3-position does not permit the near coplanar arrangement required by conformer **6** and thus does not allow the formation of a strong intramolecular hydrogen bond. This was confirmed by the chemical shift value for the N-H resonance of **3h** being concentration dependent while this was not the case for derivatives **3a-g** (see Experimental). Evidently, if configuration **8** were correct, a 3-substituent should not affect the then present N-H---O hydrogen bond (as in structure **8b-h**). Furthermore, the chemical

shift values for the N-H resonance for compound **3a** follow the general pattern, in the absence of either ester or ketone functionality.

Figure 2 depicts the dependence of the chemical shift values for protons H-3 upon the solvent used. Again, for compounds **3b-g** an intramolecular hydrogen bond is indicated, as present in structure **6**, where H-3 protons experience the deshielding effect of the coplanar carbonyl group. For the phenyl derivative **3a** an at first sight surprising pattern is observed.

FIGURE 1

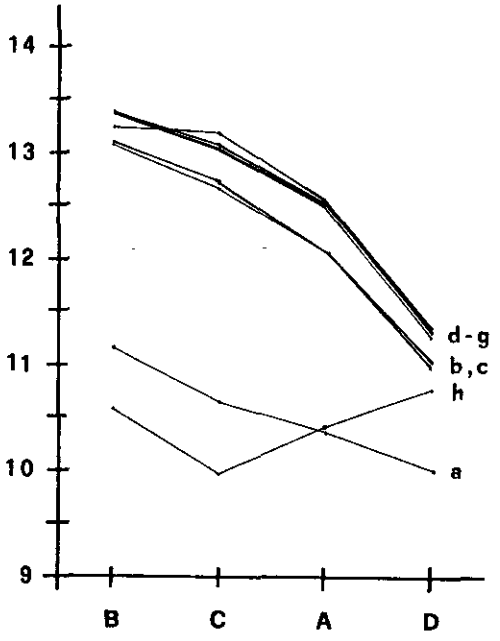
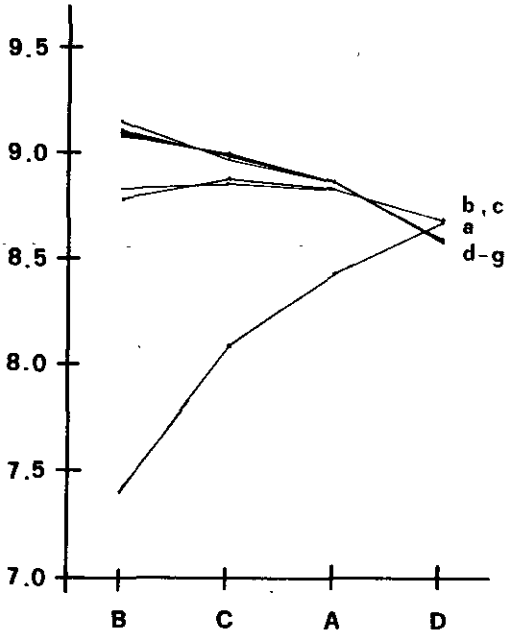


FIGURE 2



Figures 1 + 2: Graph of chemical shift values as a function of the solvent : Benzene (B), Chloroform (C), Acetone (A), Dimethyl sulfoxide (D). **Figure 1** : N-H resonances. **Figure 2** : H-3 resonances.

In nonpolar solvents, with the predominant conformer being **6**, H-3 is ideally located within the shielding cone of the benzene ring, which, sterically, will be forced into a position perpendicular to the plane of the molecule. With increasing solvent polarity, the intramolecular N-H---N hydrogen bond is broken and the coplanarity is destroyed, leading to a downfield shift of the H-3 resonance also as a function of the interaction between H-3 and the solvent.[2] Electronwithdrawing and electrondonating substituents on the phenylhydrazone moiety (**3d-g**) proved to have only a minor effect on the strength of the hydrogen bond.

The observed solvent effects can be well interpreted considering the hydrazones **3a-g** existing as their Z - isomers. Due to free rotation around the N-C bond, the hydrazones exist in a solvent dependent equilibrium between the intramolecular N-H bonded rotamer **6** and the N-H free **7**, whereby the N-H and the H-3 chemical shift values represent a weighted time average for the rapid exchange between **6** and its rotamers.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus; ir spectra were recorded on a Perkin-Elmer infrared spectrometer (model 297), solutions being prepared by dissolving 0.03 mmol of the corresponding hydrazone in 1 ml of chloroform; uv spectra (ethanol) were determined with a Varian Superscan 3 spectrophotometer; ^{1}H-nmr spectra were recorded on a Varian XL 200 FT NMR spectrometer (operating at 200.057 MHz; TMS as internal standard), acquisition time 3,072 s, spectral window 3000.3 Hz, number of points 18,432 , pulse width 4s, solutions being prepared by dissolving 0.03 mmol of the corresponding hydrazone in 1 ml of benzene-d_6, chloroform-d, acetone-d_6 or dimethyl sulfoxide-d_6.

General Method for the Preparation of the 2-Acylindazole Arylhydrazones **3.** Compounds **3** were prepared according to the procedure described previously[1] for **3a,b,d**, by treatment of **1** with equimolar amounts of suitable hydrazidoyl chloride[1,6] and threefold excess of triethylamine in anhydrous THF, and were crystalized from ethanol.

Compound **3a** (Ar = Ph, R' = Ph, R" = H) (yield 50%), mp 104°C; ^{1}H-nmr ($CDCl_3$) δ : 6.91-7.42 (m,10H,ArH), 7.62 (m,2H,ArH), 7.71 and 7.86 (2m,2H,H-4 and H-7), 8.09 (d,1H,H-3,^{5}J=1.9 Hz), 10.65 (s,1H,NH); uv nm λ_{max} (log ε) : 232sh(4.38), 296(4.20),350(4.29).

Compound **3b** (Ar = Ph, R' = CO_2Et, R" = H) (yield 77%), mp 128°C; ^{1}H-nmr ($CDCl_3$) δ : 1.47 (t,3H,OCH_2CH_3), 4.45 (q,2H,OCH_2CH_3), 7.04-7.35 (m,7H,ArH), 7.72-7.77 (m,2H,H-4 and H-7), 8.86 (d,1H,H-3,^{5}J=0.9 Hz), 12.66 (s,1H,NH); uv nm λ_{max} (log ε) : 229(4.21),286(4.10),356(4.32).

Compound 3c (Ar = Ph, R' = CO_2Me, R" = H) (yield 90%), mp 142°C; ^{1}H-nmr ($CDCl_3$) δ : 3.99 (s,3H,OCH_3), 7.05-7.41 (m,7H,ArH), 7.73-7.76 (m,2H,H-4 and H-7), 8.88 (d,1H,H-3,^{5}J=1.9 Hz), 12.73 (s,1H,NH); uv nm λ_{max} (log ε) : 230(4.21), 285(4.11),357(4.34). Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found : C, 65.35; H, 4.82; N, 18.95.

Compound 3d (Ar = Ph, R' = COMe, R" = H) (yield 93%), mp 140°C; ^{1}H-nmr ($CDCl_3$) δ : 2.72 (s,3H,$COCH_3$), 7.07-7.36 (m,7H,ArH), 7.71-7.75 (m,2H,H-4 and H-7), 8.99 (d,1H,H-3,^{5}J=0.9 Hz), 13.08 (s,1H,NH); uv nm λ_{max} (log ε) : 234(4.16), 291(4.10),367(4.36).

Compound 3e (Ar = 4-Cl-C_6H_4, R' = COMe, R" = H) (yield 80%), mp 178°C; ^{1}H-nmr ($CDCl_3$) δ : 2.71 (s,3H,$COCH_3$), 7.10-7.32 (m,6H,ArH), 7.68-7.77 (m,2H,H-4 and H-7), 9.00 (d,1H,H-3,^{5}J=0.9 Hz), 13.18 (s,1H,NH); uv nm λ_{max} (log ε) : 236(4.18), 291(4.17),368(4.41). Anal. Calcd. for $C_{16}H_{13}N_4OCl$: C, 61.44; H, 4.19; N, 17.91. Found : C, 61.55; H, 4.21; N, 17.86.

Compound 3f (Ar = 4-Me-C_6H_4, R' = COMe, R" = H) (yield 92%), mp 175°C; ^{1}H-nmr ($CDCl_3$) δ : 2.35 (s,3H,CH_3),2.70 (s,3H,$COCH_3$), 7.09-7.38 (m,6H,ArH), 7.73-7.77 (m,2H,H-4 and H-7), 8.98 (d,1H,H-3,^{5}J=1.0 Hz), 13.02 (s,1H,NH); uv nm λ_{max} (log ε) : 236(4.16),291(4.12),373(4.40). Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.17. Found : C, 70.00; H, 5.53; N, 19.24.

Compound 3g (Ar = 4-MeO-C_6H_4, R' = COMe, R" = H) (yield 70%), mp 134°C; ^{1}H-nmr ($CDCl_3$) δ : 2.69 (s,3H,$COCH_3$), 3.82 (s,3H,OCH_3),6.92-7.41 (m,6H,ArH), 7.69-7.76 (m,2H,H-4 and H-7), 8.98 (d,1H,H-3,^{5}J=0.9 Hz), 13.03 (s,1H,NH); uv nm λ_{max} (log ε) : 234(4.14),296(4.12),383(4.35). Anal. Calcd. for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.23; N, 18.17. Found : C, 66.41; H, 5.19; N, 18.25.

Compound 3h (Ar = Ph, R' = COMe, R" = Me) (yield 72%), mp 188°C; ^{1}H-nmr ($CDCl_3$) δ : 2.52 (s,3H,CH_3),2.69 (s,3H,$COCH_3$), 7.03-7.40 (m,7H,ArH), 7.64-7.68 (m,2H,H-4 and H-7), 9.96 (s,1H,NH); ($CDCl_3$ ca 1 mg / 0.5 ml) δ : 9.93 (s,1H,NH); uv nm λ_{max} (log ε) : 232sh(4.18),285sh(4.00),345(4.36). Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; H, 5.52; N, 19.17. Found : C, 69.97; H, 5.53; N, 19.14.

ACKNOWLEDGEMENT

We thank Ministero P.I. (Rome) for support.

REFERENCES AND NOTES

1. M. Ruccia, N. Vivona, G. Cusmano, and A. M. Almerico, Heterocycles, 1978, **9**, 1577.
2. J. Elguero, A. Fruchier, and R. Jacquier, Bull. Soc. Chim. France, 1966, 2075.
3. A. D. Mitchell and D. C. Nonhebel, Tetrahedron Lett., 1975, 3859; Tetrahedron, 1979, **35**, 2013 and references cited therein.
4. P. Courtot, R. Pichon, and J. Le Sant, Tetrahedron Lett., 1979, 1591.
5. O. L. Chapman, R. W. King, W. J. Welstead, Jr., and T. J. Murphy, J. Am. Chem. Soc., 1964, **86**, 4968; R. N. Butler and S. M. Johnston, J. Chem. Soc. Perkin Trans. I, 1984, 2109.
6. For the general procedure adopted in the synthesis of additional hydrazidoyl chlorides : W. Dieckmann and L. Platz, Chem. Ber., 1905, **38**, 2986.

Received, 6th January, 1987