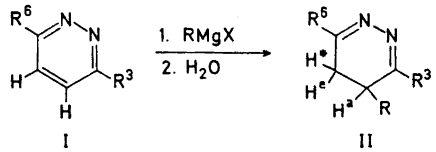
Dihydropyridazines

Part XII. Stereochemical Course of Protonation of Pyridazine Grignard Adducts

INGOLF CROSSLAND

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

In order to gain insight into the stereochemical course of protonation of addition products formed between Grignard reagents and pyridazines, the three dihydropyridazines (IIa, IIb, and IIc; see Chart and Table 1) have been prepared in a conventional way from the appropriate pyridazines and Grignard reagents.[1,2] The coupling constants of the three protons (Table 1), denoted H^a, H^e, and H*, signify their relative positions as being *anti* ($J = 8-10$ cps), *gauche* ($J = 1-4$ cps), and *geminal* ($J = -17$ cps) (H^aH^*, H^aH^e, and H^eH^*, respectively; see the Chart). The chemical shifts of the three protons were computed from the spectra and compared with shifts measured on specifically deuterated compounds (Table 1). The shifts of H* were obtained from the spectra of dideuterated (IIa) and (IIc), prepared



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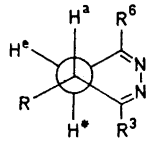

II

from (I) ($R^3 = R^6 = CH_3O$; or $R^3 = CH_3O$, $R^6 = N(CH_3)_2$), deuterated at positions 4 and 5.[3] The corresponding data for H^a and H^e were obtained by using D_2O for the decomposition of the adducts of (I) and the appropriate Grignard reagents.[3] NMR data for compounds (IId) and (IIe)[4] are included in the table for comparison.

The experimental data demonstrate that the proton introduced from water takes up a pseudoaxial position, marked H* in the Chart, and is thus situated identically with the proton introduced by base-catalyzed exchange of two similar 4,5-dihydropyridazines (II, $R^3 = R^6 = N(CH_3)_2$, R = *t*-butyl or phenyl).[5]

Table 1. NMR data for compounds IIa to IIe.

	Compounds, see Chart			Chemical shifts			Coupling constants		
	R^3	R^6	R	H^a	H^e	H*	J^{ae}	J^{a*}	J^{e*}
IIa[a]	OCH_3	OCH_3	*t*-C_4H_9	2.17	2.42	2.50	1.1	10.1	−17.4
IIb[a]	OCH_3	OCH_3	C_6H_5	3.69	2.55	2.82	4.3	8.5	−16.6
IIc[a]	OCH_3	$N(CH_3)_2$	*t*-C_4H_9	2.10	2.70	2.30	1.6	9.3	−16.7
IIa[b]				2.18	2.41	2.45			
IIb[b]				3.64	2.46				
IIc[b]				2.11	2.70	2.28			
IId[c]	Cl	$N(CH_3)_2$	*t*-C_4H_9	2.27	2.76	2.35	1.1	9.2	−16.5
IIe[c]	$N(CH_3)_2$	Cl	C_6H_5	3.99	2.69	3.11	1.1	8.4	−17.3

[a] NMR spectra were recorded on a Varian A 100 spectrometer. The solvent was deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts (in ppm from TMS) and coupling constants were computed using a modified Laocoon 3 program. [b] NMR spectra were recorded on a Varian A 60 spectrometer. The compounds were specifically deuterated (see text) and dissolved in deuteriochloroform. The centre of the observed multiplets are tabulated. The broadest of the two multiplets in the spectrum, where H* is D, was assigned to H^e. H^a in (IIb) gave a broad doublet. [c] Data from Ref. 4.

Experimental. 3-Methoxy-6-dimethylaminopyridazine (I, $R^3=CH_3O$, $R^6=(CH_3)_2N$). 3-Chloro-6-dimethylaminopyridazine [6] (15.8 g) was refluxed with sodium methoxide (from 10 g of sodium) in methanol (120 ml) for two days. The conversion was 94 % after reflux for 20 h. Addition of water, extraction with chloroform, and distillation gave a colourless, hygroscopic oil (10.1 g, b.p. 88°/0.4 mm, m.p. *ca.* 25°), redistilled for analysis. (Found: C 54.22; H 7.41; N 27.32. Calc. for $C_7H_{11}N_3O$: C 54.89; H 7.24; N 27.43.)

3-Methoxy-4-t-butyl-6-dimethylamino-4,5-dihydropyridazine (IIc). A mixture of 3-methoxy-6-dimethylaminopyridazine (1.5 g), *t*-butylmagnesium chloride (*ca.* 30 mmol) and ether (40 ml) was stirred for 1 h at 25°. The product was poured onto ice, the ether decanted, and the aqueous layer extracted twice with chloroform. The emulsion was broken by adding hydrochlorid acid (pH ~ 9). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a semicrystalline residue (1.73 g). Recrystallisation from petroleum ether gave yellow crystals (1.33 g, m.p. 65–74°). Two additional recrystallisations gave light yellow crystals, m.p. 77–79°. (Found: C 62.70; H 9.95; N 19.77. Calc. for $C_{11}H_{21}N_3O$: C 62.53; H 10.02; N 19.89.)

3-Methoxy-4-t-butyl-6-dimethylaminopyridazine. Bromine (1.5 ml) was added dropwise to a stirred solution of the dihydropyridazine (IIc, crude, from 5.1 g of (I)) in water (30 ml). Sodium hydroxide was added to pH 6 and the product was extracted with ether. The solvent was evaporated and the residue refluxed with a solution of sodium methoxide (from 2.0 g of sodium) in methanol (20 ml) for 10 min. Addition of ice, extraction with chloroform, and distillation gave (according to NMR, see below) crude 3-methoxy-4-*t*-butyl-6-dimethylaminopyridazine (3.3 g, b.p. 96°/0.15 mm). The same product was obtained by treating 3-chloro-4-*t*-butyl-6-dimethylaminopyridazine [7] (500 mg) with sodium methoxide (from 200 mg of sodium) in methanol (4 ml) for 8 days at 100°. The crude reaction product consisted of a 1:3 mixture of the methoxylated pyridazine and the starting material; the identity of the former and the 3-methoxy-4-*t*-butyl-6-dimethylaminopyridazine prepared above was confirmed by the coincidence of peaks in their NMR-spectra.

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Models of Copper-Protein Interaction: The Crystal Structure of (Glycyl-L-histidylglycinato)-copper(II) Sodium Perchlorate Hydrate

R. ÖSTERBERG,[a] B. SJÖBERG[a] and R. SÖDERQUIST[b](†)

[a] *Department of Medical Chemistry, University of Göteborg, Fack, S-400 33 Göteborg 33, Sweden and* [b] *Research Institute of National Defence (FOA), S-172 04 Sundbyberg 4, Sweden*

It is indicated from recent studies on copper proteins that nitrogen ligand atoms are important for binding copper.[1,2] Thus, attention is focused on histidine and lysine side chains as well as α-amino and amide groups. Of these, the histidine side chain is known to be involved in the labile copper(II) interaction of both myoglobin [3] and serum albumin.[4] Therefore, in order to construct proper models for the co-ordination structures in copper proteins, it seems important to ask what copper ion complexes will form with imidazole groups when they are present within a peptide chain. The smallest possible molecule of this kind, glycylhistidylglycine (HA), was chosen as a model in this study.

Violet crystals, $CuH_{-1}A(NaClO_4)H_2O$, were prepared from solutions of copper(II), glycylhistidylglycine (HA) and sodium perchlorate in the pH range 4.5 to 10. At pH