Pyrrole Reduction: The Zinc/Acid Reduction of Octahydrocarbazoles

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The stereo- and regiochemical course of the zinc/acid reduction of 1,2,3,4,5,6,7,8,-octahydrocarbazole is strongly influenced by experimental conditions and by the nature of the *N*-substituent.

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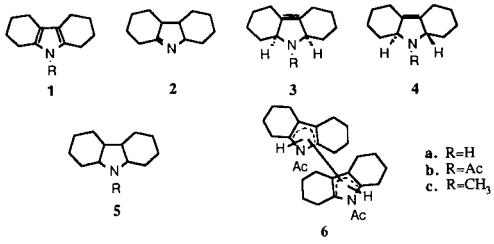
Principal reviews of pyrrole chemistry [2-4] report that *trans*-3-pyrrolines are the major products from metal/acid reduction of 2,5-dimethyl- [5] and 1,2,5-trimethylpyrrole [6] and this might be regarded as general. In the course of some synthetic work involving the 1,2,3,4,5,6,7,8- octahydrocarbazoles **1a**, **1b** and **1c** [7], we found that both the regio- and stereoselectivity of the pyrrole reduction by zinc and acid were highly dependent upon the reaction conditions, especially the acidity of the medium, and the nature of the *N*-substituent. Any of the *cis*- or *trans*-3-pyrrolines **3** or **4** [8] or the 1-pyrroline **2** [8] (from **1a**) could be made the dominant product.



1 2 3 4 5 6

The standard procedure for the reduction was the controlled addition of acid to a chilled, vigorously stirred mixture of the pyrrole and zinc dust in a suitable solvent. When carboxylic acids were used as the proton source, the zinc could be added gradually to a solution of the pyrrole in the carboxylic acid ("inverse procedure"). The use of zinc-copper couple gave essentially the same product mixture as the zinc dust under the same conditions but did have the advantage of a more efficient use of the zinc dust so that there was less zinc ion to dispose of during isolation of the product amines. 3-Pyrrolines are not further reduced under these conditions, so that all the pyrrolidine derives from 1- or 2-pyrroline.

The reduction products were somewhat unstable and tended to decompose upon chromatography. The product mixtures, therefore, had to be analysed by ^{13}C nmr spectroscopy using long recycle times and nOe suppresion. The 1-pyrroline **2** was isolated by extraction at controlled *p*H from solutions of the more basic 3-pyrrolines **3a** and **4a** and the pyrrolidine **5a** [9]. (The stereochemistry of the 1-pyrroline **2** is not known). One very selective reduction (Table 1, entry 6) afforded a single pure (by nmr) 3-pyrroline which was shown to be the *trans* isomer **4a** by resolution *via* its tartrate salts [10]. (The *cis* isomer **3a** is a *meso* compound). Acetylation and methylation provided authentic **4b** and **4c** which permitted analysis of the spectra of the product mixtures from **1b** and **1c** [11]. A selection of the results is presented in Table 1 [12].

A notable feature of the results was that the *trans*-3-pyrroline was not always the major stereoisomer, and that in the case of the *N*-methyloctahydrocarbazole (**1c**) it was the *cis* stereoisomer that predominated, often markedly so, under all conditions that were tried. This latter result is opposite to the stereoselectivity reported for the zinc/acid reduction of 1,2,5-trimethylpyrrole [6].

An unexpected result was the formation of a hydrodimer **6** in the reduction of **1b** [13]. This product crystallized from ether solutions of the product mixtures from zinc/acetic acid reductions of **1b**, but was a mixture, and preparative chromatography on silica resulted in a less homogeneous product. Once recognized, hydrodimerization was easily minimized by using lower concentrations of **1b**: the problem was not encountered with the pyrroles **1a** and **1c**.

The reductions gave mixtures whose compositions were very sensitive to even small changes in reduction conditions. The variations in product ratios were marked for the pyrroles **1a** and **1b**, from which both *cis*- and *trans*-3-pyrrolines could predominate. The reduction of the free pyrrole **1a** could also be directed towards the 1-pyrroline **2**. Such control is preparatively useful as it makes several pyrrolines accessible in fair yields from a single pyrrole. Thus the 1-pyrroline **2** can be obtained in greater than 50% yield (entries 2 and 6) and the *trans*-3-pyrroline **4a** is available completely free of the *cis* isomer in over 40% yield (entry 6): both without recourse to chromatography.

The general observation was made that reduction of pyrrole **1a** using hydrogen chloride in ethanol could be directed towards the *trans*-3-pyrroline **4a** with increasing regio- and stereoselectivity by decreasing the rate of addition of acid, increasing the volume of solvent, and reducing the temperature. Thus under the conditions of entry 3 a yield of **4a** of over 80% was obtained, although a small amount of the *cis* isomer **3a** was still also formed. Reductions of **1a** using formic acid were always strongly stereoselective towards the *trans* isomer, but the regioselectivity

Table 1

Reduction of Octahydrocarbazoles [a]

	Substrate	Solvent (initial [pyrrole])	Acid [b]	Products (%) 2	3	4	5	Other
1	**1a**	MeOH [0.40]	A	25	25	49	0	
2	"	EtOH [0.67]	A [c]	50	26	17	4	
3	"	EtOH [0.40]	B	7	10	83	0	
4	"	Et_2O [c] [0.2]	B	6.5	51	33	2	
5	"	EtOH [0.40]	C in EtOH (2:1)	20	3.5	76	0.5	
6	"	HCO_2H [d] [1.0]	"inverse"	42	0	35	0	
7	**1b**	MeOH [0.25]	A	– –	10	85	trace	5 [e]
8	"	EtOH [0.50]	C	– –	13	70	14	2 [e]
9	"	HOAc/H_2O [f] (20:1) [0.95]	"inverse" [g]	– –	54	13	16	12 [e]
10	**1c**	MeOH [0.80]	A	– –	64	11	3.5	0 [h]
11	"	EtOH [0.80]	B	– –	59	31	1	8.5 [h]
12	"	EtOH [0.40]	C [i]	– –	26	4	0	68 [h]

[a] Except where noted otherwise, all reductions were conducted at 0-10°, and the additions of acid or zinc were spread over 100 to 300 minutes. [b] A. Concentrated aqueous hydrochloric acid; B. Saturated ethanolic hydrogen chloride; C. 98% formic acid. [c] Acid added over 8 minutes. [d] At room temperature. [e] **6**: Accurate M. [f] At reflux. [g] Zinc added over 45 minutes. [h] Recovered **1c**. [i] Zinc added over 90 minutes.

was much reduced. Reductions of **1a** using hydrogen chloride in ether, on the other hand, favoured the *cis*-3-pyrroline **3a** over the *trans* isomer.

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REFERENCES AND NOTES

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[2] R. A. Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977; R. A. Jones, in "Comprehensive Heterocyclic Chemistry", A. R. Katritzky and C. W. Rees, series eds, Vol **4**, C. W. Bird and G. W. H. Cheeseman, eds, Pergamon Press, Oxford, 1984, pp 201-312.

[3] A. Gossauer, "Die Chemie der Pyrrole", Springer-Verlag, Berlin, 1974.

[4] K. Schofield, "Heteroaromatic Nitrogen Compounds", Butterworths, London, 1967.

[5a] G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951); [b] D. M. Lemal and S. D. McGregor, *ibid.*, **88**, 1335 (1966).

[6] R. L. Hinman and S. Theodoropulos, *J. Org. Chem.*, **28**, 3052 (1963).

[7] Compounds **1b** and **1c** were made from cyclohexylketazine by modified Piloty syntheses [14]. Heating of **1b** with aqueous ethanolic potassium hydroxide afforded **1a** [15].

[8] Systematic names are: 1,2,3,4,4b,5,6,7,8,8a-decahydro-4a*H*-carbazole (**2**); and *cis*- and *trans*-1,2,3,4,5,6,7,8,8a,9a-decahydrocarbazole (**3a**) and (**4a**) respectively.

[9] The imine **2** was extracted (*n*-pentane) from an aqueous solution of the reduction residue and EDTA (50 mmol/3.1 g Zn) at *p*H 7.5-8.0. Further basification (to *p*H 12) of the aqueous phase liberated the amines **3a**, **4a** and **5a**.

[10] The *d*-**4a** $[\alpha]_D^{21.7}$ +61.6 (c 9.61, CH_2Cl_2), was isolated *via* the *d*-hydrogen tartrate. The *l*-**4a**, $[\alpha]_D^{23.0}$ −61.8 (c 10.3, CH_2Cl_2), was isolated *via* the *l*-hydrogen tartrate.

[11] Pure *cis*-9-acetyl-1,2,3,4,5,6,7,8,8a,9a-decahydrocarbazole (**3b**) fortuitously crystallized from a zinc/acetic acid reduction product.

[12] Satisfactory spectral and/or analytical data were obtained for all new compounds (or their derivatives). Selected ^{13}C nmr (25 MHz) spectral data δ (deuteriochloroform, TMS) are the following. **2**: 180.0 (C=N), 74.0 (C13), 55.1, 51.2, 32.2, 31.9, 31.2, 27.9, 26.4, 25.9, 25.7, 24.6. **3a**: 132.2 (C11,12), 64.9 (C10,13), 38.3 (C4,5), 26.7 (C1,8), 24.9, 24.6. **4a**: 131.7 (C11,12), 65.8 (C10,13), 36.8 (C4,5), 26.7 (C1,8), 25.2, 24.9. **3b**: 169.6 (C=O), 131.0, 129.1 (C11,12), 66.2, 65.5 (C10,13), 36.7, 35.3 (C4,5), 27.5, 27.2 (C1,8), 25.0, 24.3, 22.3 (CH_3). **4b**: 169.1 (C=O), 130.2, 128.6 (C11,12), 66.1, 65.4 (C10,13), 35.2, 33.0 (C4,5), 27.0, 26.8 (C1,8), 25.2, 24.5, 24.3, 22.8 (CH_3). **3c**: 130.5 (C11,12), 72.4 (C10,13), 39.7 (CH_3), 35.1 (C4,5), 26.0 (C1,8), 24.7, 24.2. **4c**: 131.0 (C11,12), 70.5 (C10,13), 34.3 (CH_3), 31.3 (C4,5), 26.8 (C1,8), 25.1, 24.5.

[13] For **6**, Found $M^{+\cdot}$, 436.306; $M^{+\cdot}/2$, 218.153. $C_{28}H_{40}N_2O_2$ requires 436.309; $C_{14}H_{20}NO$ requires 218.154.

[14] H. Posvic, R. Dombro, H. Ito and T. Telinski, *J. Org. Chem.*, **39**, 2575 (1974).

[15] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **125**, 1503 (1924).