CONFIGURATIONAL ASSIGNMENT OF ARYL HETEROARYL KETOXIMES BY MEANS OF HOMONUCLEAR NOE DIFFERENCE SPECTROSCOPY

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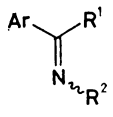
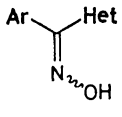
Dedicated with best wishes to Dr Miroslav Protiva on the occasion of his 70th anniversary.

The utility of homonuclear NOE difference spectroscopy as a simple and rapid method for the configurational assignment of aryl heteroaryl ketoximes is demonstrated employing oximes derived from 4-methoxyphenyl 2-pyrazinyl ketones, (substituted phenyl) 4-pyridazinyl ketones, and benzimidazolyl phenyl ketones.

Previously, we have demonstrated that homonuclear NOE (Nuclear Overhauser Enhancement) difference spectroscopy represents a powerful tool for the rapid determination of the configuration in compounds with a –C=N– bond as outlined in formula *A* (refs[1-3]). In extension of these investigations we now became interested in the applicability of this method to configurational assignment with compounds of type *B*, i.e. ketoximes derived from aryl heteroaryl ketones.



A

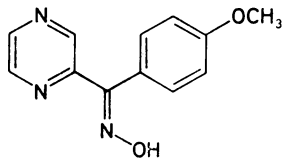


B

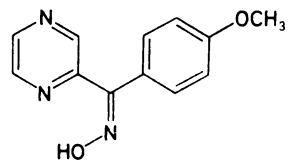
R^1 = H, CH_3
R^2 = OH, OCH_3, NRR', Ar

With such compounds the determination of stereochemistry is more complicated than with compounds of type *A*, since standard methods (e.g. differences in ^1H chemical shifts, determination of the $^2J(^{15}N, ^1H)$ coupling constants) in most of these cases are not appropriate. Two recently published examples indicating the utility of homonuclear NOE difference spectroscopy also in the aryl heteroaryl ketoxime series[4,5] now prompt us to report on our studies with aryl 2-pyrazinyl

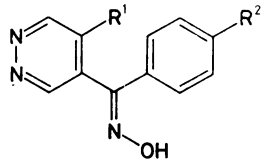
ketoximes (*I*), aryl 4-pyridazinyl ketoximes (*II*–*IV*), and of the antiviral aryl benzimidazolyl ketoximes *V*.



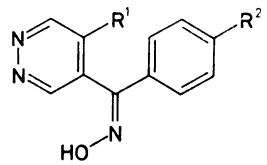
E - *I*



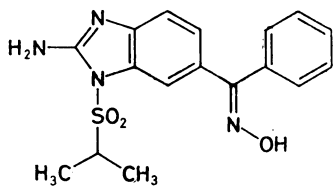
Z - *I*



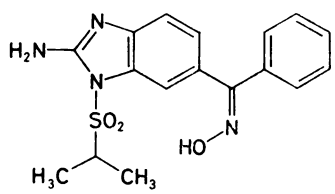
E - *II*, R^1= $COOCH_3$; R^2= H
E - *III*, R^1= H ; R^2= OCH_3
E - *IV*, R^1= H ; R^2= Cl



Z - *II*, R^1= $COOCH_3$; R^2= H
Z - *III*, R^1= H ; R^2= OCH_3
Z - *IV*, R^1= H ; R^2= Cl



E - *V*



Z - *V*

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. The IR spectra (KBr) were recorded on a Jasco IRA-1 spectrophotometer (wavenumbers in cm^{-1}). Mass spectra were obtained on a Varian MAT 311A (70 eV) or on a Hewlett–Packard 5890A/5970B-GC/MSD (70 eV) instrument. The NMR spectra were recorded from CD_3SOCD_3 solutions in 5 mm sample tubes at 30°C on a Bruker AC 80 (operating frequency for ^1H: 80·13 MHz, for ^{13}C: 20·15 MHz) or on a Bruker AM 400 WB spectrometer (operating frequency for ^1H: 400·14 MHz), both equipped with Aspect 3000 computers and standard software. Chemical shifts are reported in ppm (δ-scale), coupling constants (J) in Hz. Acquisition parameters for the homonuclear NOE difference experiments at 80 MHz: 8 K data points, spectral width: 1 362 Hz, acquisition time: 3 s, pulse width: 2 μs (51°), relaxation delay: 1—3 s,

irradiation time: 3 s, irradiation power: 45—50 L, number of scans: 160—320; at 400 MHz: 32 K data points, spectral width: 8 064 Hz, acquisition time: 2 s, pulse width: 3 μs (23°), relaxation delay: 1 s, irradiation time: 4 s, irradiation power: 45 L, number of scans: 800. All NOE difference spectra were carried out in CD_3SOCD_3 solutions (non degassed) to obtain narrow OH lines as well as a sharp and intense lock signal[6] facilitating these experiments. ^{13}C chemical shift assignments were performed on basis of multiplicity selection by the *J*-modulated spin-echo technique[7], selective heteronuclear decoupling experiments irradiating unambiguously assigned proton resonances, and ^{13}C, ^{1}H coupling constants derived from fuly coupled ^{13}C spectra obtained with the gated decoupling mode. Compounds *E-II* and *Z-II* were obtained according to ref.[8]. For the synthesis of compounds *E*—*V* (LY 122772, enviroxime) and *Z*—*V* (LY 122771) see ref.[9].

4-Methoxyphenyl 2-Pyrazinyl Ketoxime (*I*)

A mixture of 1·00 g (4·67 mmol) of 4-methoxyphenyl 2-pyrazinyl ketone[10], 650 mg (9·35 mmol) of hydroxylamine hydrochloride, 2 ml of pyridine, 4 ml of ethanol, and 2 ml of water was heated to reflux for 4 h. After cooling, 50 ml of water were added and the mixture was extracted exhaustively with dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The remaining brown solid (1·07 g) was digested several times with ether and the residue (620 mg) was subjected to column chromatography (silica gel, eluent: dichloromethane–ethyl acetate, 1 : 1) to afford 174 mg (16%) of *Z*—*I* (faster eluting component), 190 mg (18%) of *E*/*Z*-mixtures, and 215 mg (20%) of *E*—*I*.

Oxime Z—*I*: colorless crystals, m.p. 151—155°C. IR: 3 160, 3 000, 2 840 (OH), 1 595 (C=N). MS, *m*/*z*: 229 (M^+, 100%), 199 (61%), 184 (22%), 168 (40%), 156 (33%), 108 (30%), 52 (35%). ^{1}H NMR spectrum (80 MHz): 11·52 (OH); 8·77 (d, J = 1·42, 1 H, pyrazine H-3); 8·75 (m, 1 H, pyrazine H-5); 8·66 (d, J = 2·15, pyrazine H-6), 7·41—7·23 (AA'-part of an AA'BB'-system, 2 H, benzene H-2, 6); 7·00—6·82 (BB'-part of an AA'BB'-system, 2 H, benzene H-3, 5); 3·76 (s, 3 H, OCH_3). ^{13}C NMR spectrum (20 MHz): 160·03 (benzene C-4), 152·12 (C=N), 148·62 (pyrazine, C-2), 145·92 (pyrazine C-3), 144·51 (pyrazine C-6), 143·93 (pyrazine C-5), 128·13 (benzene C-2, 6), 127·49 (benzene C-1), 113·82 (benzene C-3, 5), 55·09 (OCH_3). For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 63·10% C, 4·57% H, 18·07% N.

Oxime E—*I*: colorless crystals, m.p. 160—165°C, which decompose at room temperature. IR: 3 140, 3 000, 2 820 (OH), 1 600 (C=N). MS, *m*/*z*: 229 (M^+, 100%), 199 (63%), 184 (23%), 168 (45%), 156 (37%), 108 (31%), 90 (23%), 64 (24%), 63 (25%), 52 (53%), 43 (25%). ^{1}H NMR spectrum (80 MHz): 11·91 (OH); 9·02 (d, J = 1·43, 1 H, pyrazine H-3); 8·62—8·52 (m, 2 H, pyrazine H-5, 6); 7·45—7·27 (AA'-part of an AA'BB'-system, 2 H, benzene H-2, 6); 7·04—6·86 (BB'-part of an AA'BB'-system, 2 H, benzene H-3, 5); 3·78 (s, 3 H, OCH_3). ^{13}C NMR spectrum (20 MHz): 159·41 (benzene C-4), 153·09 (C=N), 151·13 (pyrazine C-2), 143·84 and 143·42 (pyrazine C-5, C-6), 143·29 (pyrazine C-3), 131·32 (benzene C-2, 6), 123·67 (benzene C-1), 113·13 (benzene C-3, 5), 55·09 (OCH_3). For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 63·13% C, 4·61% H, 18·03% N.

4-Methoxyphenyl 4-Pyridazinyl Ketoxime (*E*—*III*)

A mixture of 214 mg (1 mmol) of 4-methoxyphenyl 4-pyridazinyl ketone[11], 139 mg (2 mmol) of hydroxylamine hydrochloride, and 328 mg (4 mmol) of dry sodium acetate in 3 ml of ethanol was stirred at room temperature for 24 h. After filtration, the remaining solution was evaporated under reduced pressure. Recrystallisation of the residue from ethanol afforded 202 mg (88%)

of *E*—*III* as colorless crystals, m.p. 155—160°C. MS, *m/z*: 229 (M^+, 100%), 213 (20%), 134 (24%), 108 (28%). ^{1}H NMR spectrum (80 MHz): 11·70 (OH); 9·35 (dd, J = 1·28 and 5·24, 1 H, pyridazine H-6); 9·16 (dd, J = 1·28 and 2·24, 1 H, pyridazine H-3); 7·63 (dd, J = 2·24 and 5·24, 1 H, pyridazine H-5); 7·38—7·24 (AA'-part of an AA'BB'-system, 2 H, benzene H-2, 6); 7·03—6·90 (BB'-part of an AA'BB'-system, 2 H, benzene H-3, 5); 3·77 (s, 3 H, OCH_3). For $C_{12}H_{11}N_3O_2$ (229·2) calculated: 62·87% C, 4·84% H, 18·33% N; found: 62·87% C, 4·67% H, 18·07% N.

4-Chlorophenyl 4-Pyridazinyl Ketoxime (*E*—*IV*)

Compound *E*—*IV* was obtained in a similar manner as described for the synthesis of *E*—*III* starting from 219 mg (1 mmol) of 4-chlorophenyl 4-pyridazinyl ketone[11] and 139 mg (2 mmol) of hydroxylamine hydrochloride. Yield: 199 mg (85%) of straw yellow crystals, m.p. 182—185°C (ethanol). MS, *m/z*: 233, 235 (M^+, 100%, 32%), 202 (26%), 182 (32%), 168 (41%), 138 (24%), 111 (25%), 75 (31%), 51 (40%). ^{1}H NMR spectrum (80 MHz): 12·12 (OH); 9·37 (dd, J = 1·29 and 5·26, 1 H, pyridazine H-6); 9·20 (dd, J = 1·29 and 2·24, 1 H, pyridazine H-3); 7·66 (dd, J = 2·24 and 5·26, 1 H, pyridazine H-4); 7·44 (m, 4 H, benzene H). For $C_{11}H_8ClN_3O$ (233·7) calculated: 56·54% C, 3·45% H, 17·98% N; found: 56·48% C, 3·70% H, 17·94% N.

RESULTS AND DISCUSSION

Both isomeric 4-methoxyphenyl 2-pyrazinyl ketoximes (*E*—*I* and *Z*—*I*) were obtained conveniently by reaction of the corresponding ketone with hydroxylamine hydrochloride and subsequent column chromatographic separation. In Fig. 1 the NOE difference spectra of *E*—*I* and *Z*—*I*, resulting from irradiation of the hydroxyl proton, are displayed. In the case of the faster eluting isomer a significant enhancement of the pyrazine H-3 signal is observed (Fig. 1*b*), whereas the signals of H-2 and H-6 of the benzene ring remain nearly unaffected, thus clearly indicating *Z*-configuration*.

In accordance, irradiation of the OH-resonance in the second isomer leads to a significant NOE on the benzene H-2, H-6 signals (Fig. 1*d*). Additionally, the pyrazine H-3 signal is enhanced, albeit only to a minor degree, which may be attributed to steric reasons (see below).

Similar observations were made with the ketoximes *II* derived from methyl 5-benzoyl-4-pyridazinecarboxylate, the stereochemistry of which previously had been assigned based on UV arguments[8]. With the *E*-isomer a marked through-space connection is detectable between the hydroxyl-H and H-2, H-6 of the phenyl group, whereas the signal of the pyridazine H-3 is only slightly affected upon irradiation

* This assignment is in full agreement with the ^{13}C NMR data: the resonance of the pyrazine C-2 atom in *Z*—*I* is shifted 2·51 ppm upfield compared to that in *E*—*I*, whereas there is a 3·82 ppm downfield shift of the benzene C-1 signal in *Z*—*I* compared to the corresponding line in *E*—*I* (see Experimental). This has to be attributed to the gamma-effect of the oxime oxygen, leading to an upfield shift of the resonance of the *syn*-alpha-carbon atom[12].

of the OH resonance. On the other hand, with *Z—II* the following observations were made: *a*) stronger enhancement of the pyridazine H-3 signal than that of the phenyl H-2, H-6 resonances upon iradiation of the OH-transition; *b*) marked enhancement of the OH signal upon irradiation of the pyridazine H-3 line; *c*) practically no enhancement of the OH line upon irradiation of the phenyl H-2, H-6 resonance.

In case of the (4-substituted phenyl) 4-pyridazinyl ketoximes *III* and *IV*, prepared by standard methods from the corresponding ketones, the NMR spectra revealed only one isomeric form to be present. Based on the finding that with both compounds the through-space connection between the hydroxyl proton and the pyridazine protons H-3 and H-5 is markedly larger than that between OH and benzene H-2, H-6, *Z*-configuration has to be assigned to these oximes.

It is well known that the biological activity of compounds with a –C=N– substructure strongly depends on their configuration. As a typical example the antiviral agent enviroxime (*E—V*) may serve: the corresponding *Z*-compound is less active with regard to inhibition of rhinovirus multiplication[9]. In this series, the isomers have been distinguished by X-ray analysis and on basis of ^{13}C chemical shift considerations (shielding effect of the oxime oxygen atom to one of the alpha carbon

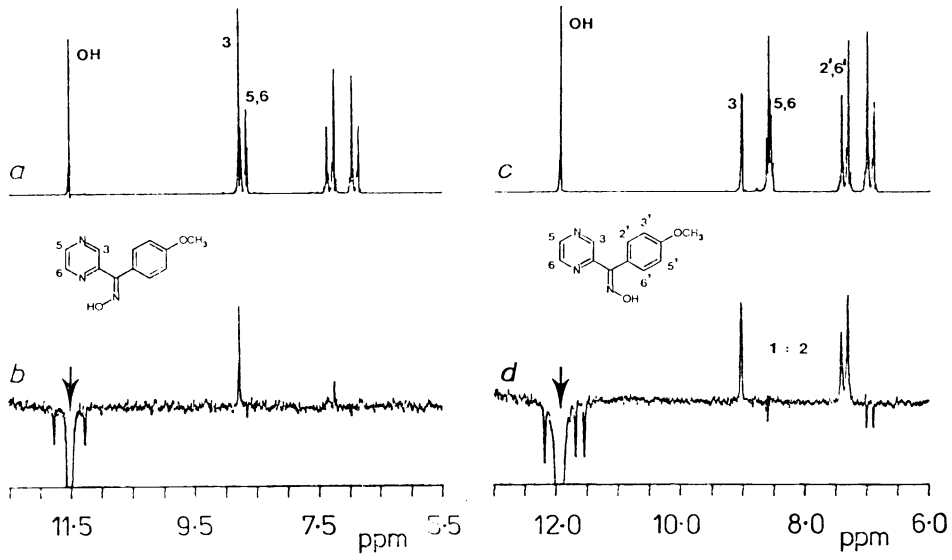


FIG. 1

Spectra of oximes: *a* ^1H NMR spectrum of *Z—I* (80 MHz, CD_3SOCD_3); *b* NOE difference spectrum of *Z—I* resulting from irradiation of OH; *c* ^1H NMR spectrum of *E—I* (80 MHz, CD_3SOCD_3); *d* NOE difference spectrum of *E—I* resulting from irradiation of OH

atoms)[9]. Figure 2 shows that also in this case, configurational assignment simply can be achieved by NOE difference spectroscopy.

Like discussed with compounds *I*–*IV*, also with the ketoximes *V* not only the expected enhancements of proton signals of the substituent *syn* to the OH group are observed. Again, there is at least a small influence on signals of the *anti*-substituent too. A plausible explanation for this phenomenon consists in decreasing differences of distances (OH – "*syn*"-H versus OH – "*anti*"-H) between the protons involved in the through-space connections due to non-coplanarity of the aromatic rings in such systems (compare, for instance, the geometry of compound *E*–*V* given in ref.[9]).

Although these observations call for careful interpretation of such NOE experiments, the results of this study together with the findings given in refs[4,5] clearly show the utility of this rapid method for configurational assignment also for aryl heteroaryl ketoximes. It should be noted that – as a major advantage – in many cases this technique can be employed even if only one isomer is at hand.

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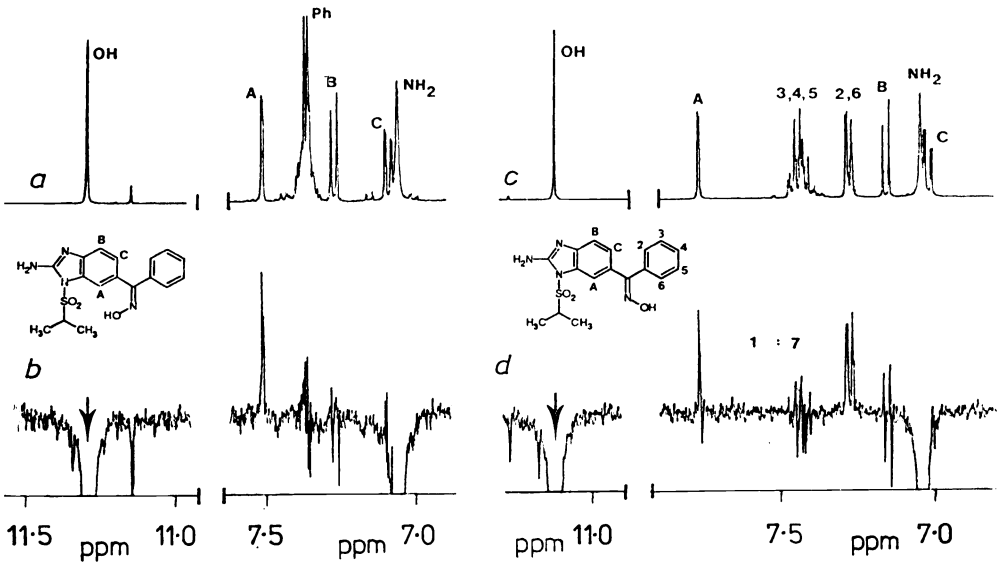

FIG. 2

Spectra of oximes: *a* ^{1}H NMR spectrum of *Z*–*V* (400 MHz, CD_3SOCD_3); *b* NOE difference spectrum of *Z*–*V* resulting from irradiation of OH; *c* ^{1}H NMR spectrum of *E*–*V* (400 MHz, CD_3SOCD_3); *d* NOE difference spectrum of *E*–*V* resulting from irradiation of OH

the 400 MHz spectra (oximes V) and to the Lilly Research Laboratories, Indianapolis, for generously providing samples of compounds V (LY 122771, LY 122772). We also want to thank Dr N. Haider for preparing compounds II—IV.

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