STEREOCHEMICAL ASPECTS OF PYRROLE FORMATION FROM SUBSTITUTED PIPERIDIN-4-ONE OXIMES AND ACETYLENE

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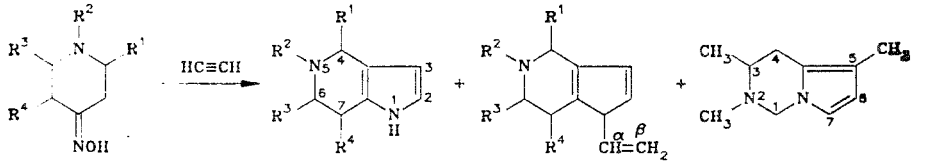
Oxime derivatives of 1,2,5-trimethylpiperidin-4-one, 2-methyl-, and 2-(2-furyl)-4-ketodecahydroquinoline react with acetylene to form substituted pyrrolo[3,2-c]piperidines and their N-vinyl derivatives. During the course of pyrrolization the configuration at the 7-position is partially changed, resulting in the formation of two stereoisomeric pyrroles.

The application or utilization of substituted piperidin-4-one oximes I and their bicyclic derivatives, decahydroquinolin-4-ones II-V, in pyrrole synthesis reactions [1] is a promising area of research, both for the search for new physiologically active substances as well as for studying the stereochemical aspects of the reaction, which have remained unexplored until now. Both of these factors underlie the purpose of the present paper. Since the pyrrolization of 1,2,5-trimethylpiperidin-4-one oxime (I) with acetylene has been studied previously [2, 3], this oxime was used as a model substrate to facilitate the understanding and interpretation of the present results.

Reactions of oximes I-V with acetylene were carried out in KOH–DMSO at 85-95°C for 3-7 h (Table 1).



I-V VIa, b, VIIa-c VIIIa, b, IXa, b, X XI

I, VIa,b, VIIIa,b $R^1=R^2=R^4=CH_3$, $R^3=H$; II, IXa,b $R^1=a$-CH_3; III $R^1=e$-CH_3; IV, VIIa,b $R^1=2a$-Fur; V, VIIc, X $R^1=2e$-Fur; II–V, VIIa-c, IXa,b X $R^2=H$, $R^3-R^4(CH_2)_4$

The preparative yield of 4,5,7-trimethylpyrrolo[3,2-c]piperidine (VIa) could be increased to 62% (versus 22% reported in [3]) based on oxime used by reducing the reaction temperature by 10-15°C compared to the literature procedure [2] (95-100°C), in accord with the results of a kinetic study of cycloalka[b]pyrrole synthesis [4] conducted by constant monitoring of the composition dynamic of the reaction mixture; lowering the temperature also avoided the formation of 2,3,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-c]pyrimidine (XI) side product. The latter material is formed in 16% yield under harsher reaction conditions (Table 1).

It is logical to assume or expect that the initially formed pyrrolopiperidine VIa (Table 1, experiment 1) should undergo further vinylation to give only the corresponding 1-vinyl-4,5,7-trimethylpyrrolo[3,2-c]piperidine (VIIIa), with similar PMR spectral characteristics for the unchanged portion of the molecule. This has been confirmed experimentally. Thus, the PMR spectra of both pyrrolopiperidines VIa and VIIIa (Table 2) exhibit larger gem- and trans-SSCC (spin-spin coupling constants) for the 6a-H protons, and larger (gem-) and smaller (cis-) SSCC for the 6e-H proton, which suggest and are consistent with an equatorial orientation of the methyl group in the 7-position. Comparison of the chemical shift values for the C(6) atom in the ^{13}C-NMR spectra of compounds VI and VIb (Table 3) (especially in light of recent literature data [5] showing that the larger chemical shift value corresponds to an equatorial methyl substituent for the adjacent carbon atom), leads to and supports a similar conclusion. In the case of isomers VIb and VIIIb the methyl group in the 7-position is located in an axial orientation, although this fact cannot be determined unequivocally from their PMR spectra (Table 2) due to the complexity of the signal multiplets and the overlapping positions of the 6-H and 7-H proton signals in the spectra of pyrrolopiperidine VIb and the vinylpyrrolopiperidine derivative VIIIb.

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TABLE 1. Pyrrolization Products of Oximes I-V*

Experiment	Oxime	Reaction products** NH-pyrrole	yield, %	N-vinylpyrrole	yield, %	Experiment	Oxime	Reaction products** NH-pyrrole	yield, %	N-vinylpyrrole	yield, %
1	I	VIa	69	VIIIa	6	4	III	—***		—***	
		VIb	18			5	IV	VIIa	18	X	31
2	I	VIa	4	VIIIa	28			VIIb	14		
		VIb	4	VIIIb	22	6	V	VIIc	3	—***	
3	II	—***		IXa	55						
				IXb	45						

*Experiment 1 was carried out in a flask at atmospheric acetylene pressure, T 85°C, 1.4% water in DMSO; experiments 2-6 were carried out in an autoclave at an acetylene pressure of 12 atm, T 85-95°C, 0.2% water in DMSO. Yields were calculated based on GLC data.

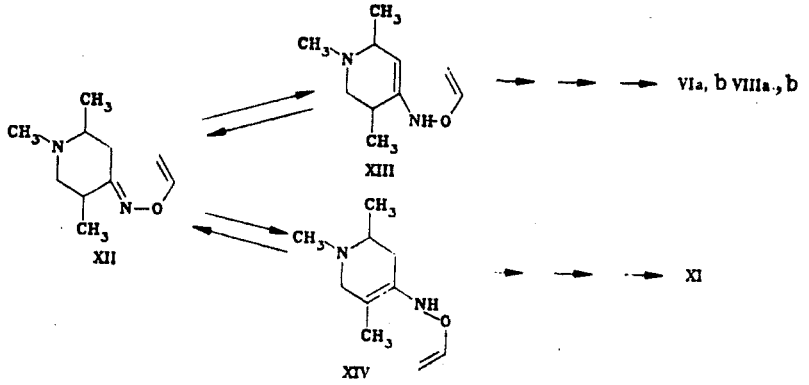
**Pyrrolopyrimidine XI was detected only in experiment 2, in 16% yield.

***Not observed.

Isomers VIa and VIb, VIIIa and VIIIb are stable in an inert atmosphere, and are not interconverted. It is most likely that the ratio of these isomers (Table 1, experiments 1 and 2) is determined at the reaction stage involving prototropic isomerization of the intermediate O-vinyloxime [1], and that the ratio remains unchanged further in the reaction sequence, excluding the possibility of various side reactions occurring.

According to the established mechanism for this reaction [1], the O-vinyloxime intermediate XII should undergo reversible prototropic isomerization to give hydroxylamines XIII and XIV. In the latter case the double bond is immediately adjacent to the substituent R^4 (which becomes position 7 in the product), i.e., this portion of the molecule is the factor responsible for the change in configuration during the course of the reversible reaction leading to the formation of O-vinyloxime XII (Scheme 1).

Scheme 1



Even a very slight change in reaction conditions toward harsher or more rigorous conditions, as in experiment 2 relative to experiment 1 (Table 1), leads to a sharp decrease in both the stereo- and regioselectivity of the reaction (in particular, the formation of the regioisomeric pyrrolopyrimidine XI); these results are consistent with the proposed reaction scheme. A change in regioselectivity with increasing temperature has also been noted in the literature [6] in the case of nonsymmetric dialkylketoximes: increasing the temperature by 20°C led to complete loss of regioselectivity (at 120°C an isomer ratio of 0:100 was obtained, at 140°C 50:50%).

With respect to the pyrrolization of 2-methyl- and 2-(2-furyl)-4-ketodecahydroquinoline oximes II-V, we noted first of all that each of these substrates can exist in the form of only two stereoisomers with an axial or equatorial orientation of the substituent [7-9]; these stereoisomers exhibit trans-coupled or annelated rings and cannot be interconverted (6a-H–7a-H). Each isomer, however, can be composed of two structures with an axial or equatorial orientation of the hydrogen atom attached to nitrogen, although these two structures are mobile (in dynamic equilibrium). Under our pyrrolization reaction conditions oxime II, with an axial orientation for the methyl group, is converted quantitatively to a mixture of 1-vinyl-4-metyl-6,7-tetramethylenepyrrolo[3,2-c]-piperidine isomers (IXa, b). Unfortunately, however, due to the complexity of their PMR spectra we are unable to determine unambiguously why these isomers are formed: whether via stabilization of the active (mobile) structures by the pyrrole ring,

TABLE 2. PMR Spectra of the Condensation Products of Piperidin-4-one Oximes with Acetylene

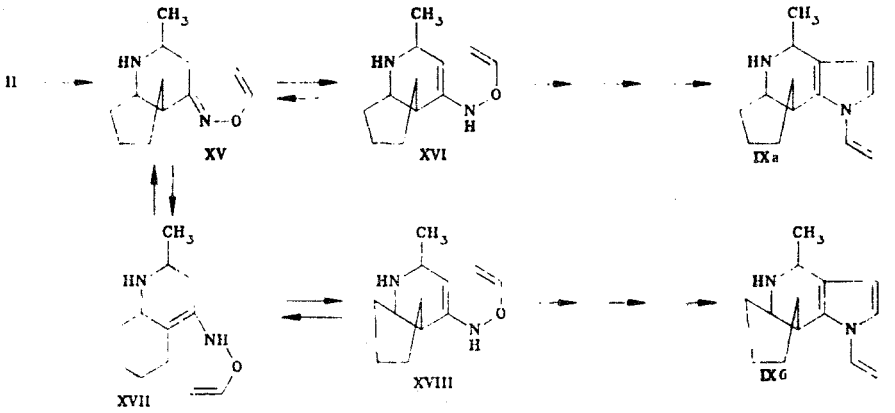
Compound	Solvent	Chemical shift, δ, ppm (J, Hz)							
		NH, N-vinyl	2-H	3-H	4-H	6a-H	6e-H	7-H, M	Other protons
VIa (7e-Me)	$CDCl_3$	7,86 br.s	6,61 (t, J=3,0)	5,95 (t, J=3,0)	3,18 (qd, J=6,5; J=2,3)	2,24 (dd, J=11,5; J=10,5)	2,95 (dd, J=12,0; J=5,0)	3,06	2,41 (s, NCH_3); 1,34 (d, J=6,5, CH_3); 1,13 (d, J=6,5, CH_3)
VIb (7a-Me)	$CDCl_3$	7,90 br.s	6,61 (t, J=3,0)	5,94 (t, J=3,0)	3,42 (qd, J=6,0; J=1,0)	2,67 (dd, J=12,0; J=6,0)	2,66 (dd, J=12,0; J=0,5)	2,87	2,43 (s, NCH_3); 1,29 (d, J=6,5, CH_3); 1,22 (d, J=6,5, CH_3)
VIIa (2a-Fur)	$(CD_3)_2CO$	9,66 br.s	6,59 (t, J=2,6)	5,83 (t, J=2,6)	5,02 br.s	3,13 m		2,58	7,42 (m, 5-Fur); 6,26 (dd, J=3,0; J=1,8; 4-Fur); 5,90 (dt, J=3,0; J=0,5, 3-Fur); 2,7 (br.s, NH); 1,81...1,16 (m, $(CH_2)_4$)
VIIb (2a-Fur)	$(CD_3)_2CO$	9,74 br.s	6,59 (t, J=2,6)	5,86 (t, J=2,6)	4,96 br.s	2,55 m		2,31	7,43 (m 5-Fur); 6,27 (dd, J=3,0; J=1,8, 4-Fur); 5,92 (dt, J=3,0; J=0,5, 3-Fur); 2,6 (br.s, NH); 1,78, 1,38 (m, $(CH_2)_4$)
VIIc (2e-Fur)	$(CD_3)_2CO$	9,72 br.s	6,54 (t, J=2,6)	5,77 (t, J=2,6)	5,13 br.s	2,57 m		2,30	7,43 (m, 5-Fur); 6,32 (dd, J=3,0; J=1,8, 4-Fur); 6,18 (dt, J=3,0; J=0,5; 3-Fur); 2,6 (br.s, NH); 1,80, 1,40 (m, $(CH_2)_4$)
VIIIa (2e-Me)	$CDCl_3$	6,83 dd; 5,01 dd; 4,58 dd (J=16,2; J=9,2; J=1,0)	6,83 (d, J=3,0)	5,97 (d, J=3,0)	3,36 (qd, J=5,5; J=1,2)	2,22 (dd, J=13,8; J=9,0)	3,01 (dd, J=13,8; J=5,5)	3,06	2,39 (s, NMe); 1,22 (d, J=6,5, Me); 1,19 (d, J=6,5, Me)
VIIIb (2a-Me)	$CDCl_3$	6,76 dd; 5,02 dd; 4,60 dd (J=15,8; J=9,2; J=1,2)	6,85 (d, J=3,0)	5,96 (d, J=3,0)	3,20 qd, J=6,0; J=1,6)	2,74 (m, J=12,8; J=3,5)		2,85	2,43 (s, NMe); 1,34 (d, J=6,5, Me); 1,29 (d, J=6,5, Me)
IXa (2a-Me)	$(CD_3)_2CO$	7,09 dd; 5,06 dd; 4,59 dd (J=15,5; J=8,8; J=1,0)	6,95 (d, J=3,0)	5,90 (d, J=3,0)	4,00 (q, J=7,0)	3,21 m		2,25...2,76	1,29 (d, J=7,0, Me); 2,76...2,25, 1,91...1,18 (m, $(CH_2)_4$, NH)
IXb (2e-Me)	$(CD_3)_2CO$	6,95 dd; 5,09 dd; 4,55 dd (J=15,5, J=8,8; J=1,0)	6,84 d	5,92 d	3,88 q	2,25...2,76 m			1,23 (d, J=7,0, Me); 2,76...2,25, 1,91...1,18 (m, $(CH_2)_4$, NH)
X (2a-Fur)	$(CD_3)_2CO$	6,99 dd; 5,15 dd; 4,61 dd (J=15,8; J=9,0; J=1,0)	7,03 d	5,99 d	5,02 s	3,15 m		2,60	7,43 (m, 5-Fur); 6,27 (dd, J=3,0; J=1,8, 4-Fur); 5,91 (dt, J=3,0, J=0,5, 3-Fur); 2,6 (br.s, NH); 1,69, 1,29 (m $(CH_2)_4$)
XI	$(CD_3)_2CO$	Absent							6,41 (d, J=2,6, 7-H), 5,96 (d, J=2,6, 6-H); 4,67 (m, 1a-Hand1e-H), 3,06 (m, 3-H); 2,36 (s, NMe); 2,28 (m, 4a-Hand4e-H); 1,96 (s, 5-Me); 1,23 (d, J=6,5, 3-Me)

TABLE 3. ^{13}C-NMR Spectra of Pyrrole and N-Vinylpyrrole Derivatives

Compound	Chemical shift, δ, ppm from TMS									
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(\alpha)}$	$C_{(\beta)}$	Other signals
VIa	116,84	104,87	58,27	63,31	29,82	130,02	121,12			43,05, 20,16, 17,31 (Me)
VIb	116,62	104,84	57,19	59,16	28,59	129,80	120,64			43,11, 19,97, 19,91 (Me)
VIIa	116,71	110,58	55,59	51,15	42,18	131,20	115,56			160,18, 142,18, 107,10, 106,53 (Fur); 33,15, 29,80, 26,48, 26,26 ($(CH_2)_4$)
VIIc	116,50	110,61	61,27	53,71	42,14	130,55	117,22			159,26, 141,97, 2×105,97 (Fur); 33,34, 29,80, 26,51, 26,29 ($(CH_2)_4$)
IXa	117,83	107,74	48,33	55,61	42,42	129,92	125,41	133,83	97,74	22,91 (Me); 33,92; 32,94, 31,40, 29,27 ($(CH_2)_4$)
IXb	115,58	108,06	46,84	48,07	34,63	132,41	123,11	130,91	95,65	23,50 (Me); 26,80, 26,62, 26,13, 20,99 ($(CH_2)_4$)

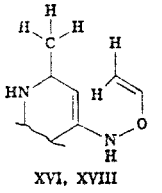
or via partial transformation of the annelated six-membered rings from a trans- to a cis-conformation. Considering the ease or facility of configuration inversion at the 7-position during the course of pyrrole synthesis, which was noted for products VIa,b and VIIIa, b, and based on Scheme 1, we feel that the latter alternative should be given preference in terms of explaining the observed isomerization process, i.e., isomerization is probably due to partial transformation of the trans-annelated six-membered rings to a cis-coupled conformation (Scheme 2).

Scheme 2



Reversible prototropic isomerization of intermediate XV should lead to the formation of hydroxylamines XVI and XVII. The latter can isomerize to hydroxylamine XVIII with the cyclohexane ring in a "boat" conformation (cis-annelation, 6a-H–7e-H). Intermediates XVI and XVIII are then converted to pyrroles IXa and IXb, respectively, via [3.3]-sigmatropic shift.

The difficulty encountered upon attempted pyrrole formation in the presence of an equatorial substituent (Me, 2-furyl) in the 2-position of decahydroquinolin-4-one oximes (Table 1, experiments 4, 6) is noteworthy. The problem may be due to steric hindrance for the [3.3]-sigmatropic shift exerted by a substituent oriented in the plane of the piperidine ring in intermediates of the type XVI and XVIII.



The observed results can also be rationalized based on the $A^{1,2}$-allyl strain hypothesis [10], which predicts that an equatorial orientation of the substituent R^1 should be unfavorable.

Following our results and discussion, we conclude that heterocyclization of substituted piperidin-4-one oximes with acetylene proceeds to form pyrrolo[3,2-c]-piperidines with both axial and equatorial arrangements of substituents in the 7-position. In the case of ketoximes with a rigid structure, such as compounds II-V, the presence of an equatorial substituent in the 2-position inhibits or obstructs the reaction course. As a consequence, formation of the corresponding pyrrolopyrimidines has not been observed upon reaction of these ketoximes.

EXPERIMENTAL

PMR spectra (200.13 MHz) and ^{13}C-NMR spectra (50.3 MHz) were recorded using a Bruker WP 200 SY spectrometer. Commercial grade DMSO was used (1.4% H_2O); Al_2O_3 (0.2% H_2O) was dehydrated prior to use by calcination at 550°C, while chemically pure grade KOH was used (14% H_2O). Preparative TLC was carried out using 20 × 20 cm plates (experiment 1, Table 1), or column chromatography was performed on a 40 × 2 cm Al_2O_3 column using 3:1 hexane–ether solvent system. Composition of reaction mixtures, as well as quality control during the course of compound separation and purification, were determined by GLC on an LKh-80 chromatograph equipped with a 2 m long, 3 mm diameter column filled with DC-550 liquid phase on N AW-HMDS chromatone, using helium carrier gas at a column temperature of 100-180°C. Mass spectra were measured on a MAT-212 spectrometer. Satisfactory IR spectra in either CCl_4 or $CDCl_3$ solution could not be obtained, due to the presence of intense idle bands arising from trace amounts of ammonium salts formed from the pyrrole products and solvent.

1,2,5-Trimethylpiperidin-4-one Oxime (I). Prepared according to the literature procedure [2].

2-Methyl- and 2-(2-Furyl)decahydroquinolin-4-one Oximes (II-V). Prepared by mixing the appropriate ketones, hydroxylamine hydrochloride, and sodium acetate, in a 1:2:2 molar ratio, in a water–diethyl ether mixture, which was then allowed to stand in an open flask for 8 h. The resulting solution was basified with KOH, and the precipitate was removed by filtration, washed with water, and dried. Yield of oximes II-V, 92-99%.

4,5,7-Trimethylpyrrolo[3,2-c]piperidines (VIIIa, b, $C_{10}H_{16}N_2$) and 1-Vinyl-4,5,7-trimethylpyrrolo[3,2-c]piperidines (VIIIa, b). A. A mixture of 4 g (26 mmoles) oxime I and 1.5 g (26 mmoles) powdered KOH in 40 ml DMSO (1.4%) at 85°C was bubbled with acetylene for 7 h. Remaining KOH was neutralized with CO_2, the precipitate was removed by filtration, and the filtrate was distilled on a water bath at 60-65°C (5-7 mm Hg pressure). According to GLC analysis, the distillate contained only DMSO and a trace amount of oxime I. The pot residue was then recrystallized from hexane. Yield 2.6 g (62% based on oxime used) of pyrrolopiperidine VIa, fine white crystals, mp 143°C. Mass spectrum: M^+ 164. Preparative TLC on the residue also gave 0.55 g (16%) of pyrrolopiperidine VIb, coarse white crystals, mp 127-129°C. Mass spectrum: M^+ 164. Vinylpyrrole VIIIa (0.3 g, 6%) (M^+ 190) was also isolated, along with 0.39 g (10%) recovered unreacted oxime I. The results of elemental analysis for these newly isolated compounds agreed with calculations.

B. A mixture of reagents in the same molar ratio as in method A was heated at 85-95°C in a rotating autoclave for 3 h at an initial acetylene pressure of 12 atm. After being cooled the reaction mixture was discharged, 2 volumes of water were added, and the mixture was then extracted with ether (4 × 25 ml). The combined ether extracts were washed with water and dried over Na_2SO_4. The ether was evaporated and the mixture purified by column chromatography. The GLC yields of the isolated products are reported in Table 1. Their molecular ion masses (M^+) corresponded to their calculated molecular weights. The purity of the samples used to record their NMR spectra was 90-95%, with the exception of pyrroles (VIa, b) (99.5%). The results of elemental analysis for pyrroles VIa, b agreed with calculations.

Pyrrolization of oximes II-V was carried out using method B.

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