SYNTHESIS AND NITRATION OF NH- AND N-VINYL-4,5,7-TRIMETHYL-4,5,6,7-TETRAHYDROPYRROLO[3,2-c]PYRIDINES

T. N. Borisova, I. A. Stazharova, A. É. Aliev, N. S. Prostakov, and A. V. Varlamov

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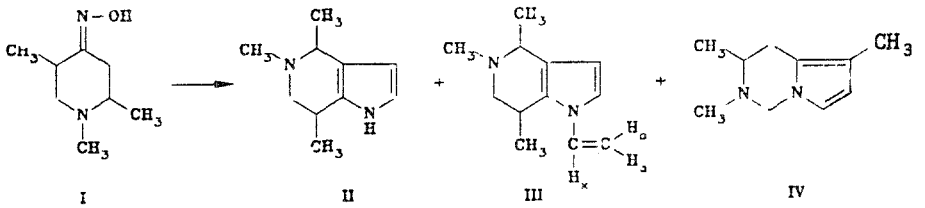
It has been shown that the most efficient catalysts for the synthesis of 4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine from 1,2,5-trimethylpyridin-4-one and acetylene under Trofimov conditions are rubidium and potassium hydroxides. Use of Triton B or a mixture of trimethylbenzylammonium chloride with rubidium hydroxide as catalyst gives O-alkylated oxime. Their configurations and conformations were established through separation of the individual isomers of 1-vinyl-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridines. Acetyl nitrate nitration of the cis isomer of this compound gave the 2- and 3-nitro derivatives. Similar nitration of 4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine gave the 2-nitro-7-hydroxy derivative.

Heterocyclization by acetylene in superbasic medium of 1,2,5-trimethylpiperidin-4-one oxime (I) with *trans*-diequatorial methyl groups at the C-2 and C-5 atoms gives NH- and N-vinyl-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridines (II and III) as well as 2,3,5-trimethyl-1,2,3,4-tetrahydropyrrolo[1,2-c]pyrimidine (IV). The *trans* methyl group orientation is preserved in the tetrahydropyridine fragment of II and III [1].



I II III IV

It is known that the ratio of NH- and N-vinylpyrroles formed upon heterocyclization of ketoximes under Trofimov conditions depends on the type and quantity of base, the solvent, and the reaction conditions [2].

We have studied the optimization of the heterocyclization of oxime I with acetylene using, as catalysts, potassium or rubidium hydroxides, Triton B, and mixtures of trimethylbenzylammonium chloride (TMBAC) with rubidium hydroxide and tetrabutylammonium iodide (TBAI) with potassium hydroxide. The reaction was carried out in DMSO at 95-98°C and the course of the reaction monitored by TLC from the degree of conversion of oxime I (see Table 1).

The most active catalyst appears to be potassium hydroxide but the best yield of II is obtained with rubidium hydroxide (Table 1). Portionwise addition of catalyst has no effect on yield.

It is known that a 1-5% water content in the reaction mixture significantly slows the vinylation while the rate of formation of the pyrrole ring remains fundamentally the same [3]. In order to limit the vinylation we carried out the heterocyclization in the presence of 4% water. However, the yield of II was approximately 1.5 times less than in the analogous experiment without addition of water.

In the presence of Triton B or a mixture of TMBAC with rubidium hydroxide a quantitative O-alkylation of the oxime I occurs to give a mixture of O-methyl- and O-benzyloximes V and VI (1:0.8 by PMR spectroscopy) instead of heterocyclization.

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TABLE 1. Yield of Pyridine II

Catalyst	Amount of catalyst, %	Yield, %	Catalyst	Amount of catalyst, %	Yield, %
KOH	50	27	KOH+TBAI	100	26
	65	36			
	80*	19	RbOH	90	43

*In the presence of 4 vol. % water relative to DMSO.

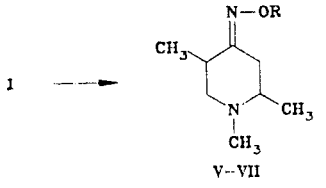
TABLE 2. Chemical Shifts of O-Alkylated Oxime Protons for V-VII

Compound	δ, ppm										
	2a	3a	3e	5a	6a	6e	2-CH_3	5-CH_3	N—CH_3	OCH_2	C_6H_5
V**	1,81	1,66	3,31	2,45	1,75	2,62	0,89	1,14	1,98	—	—
VI	1,83	1,65	3,33	2,44	1,73	2,60	0,85	1,12	1,96	5,20	7,08...7,37
VII	2,04	1,70	3,18	2,52	1,96	2,92	1,06	1,14	2,28	4,02***	—

*Spectra of VII recorded in $CDCl_3$, V and VI in C_6D_6.
**Spin—spin coupling constants for V and VI identical: $^2J_{3a3e} = -14.0$; $^2J_{6a6e} = -11.1$; $^3J_{2a3a} = 11.4$; $^3J_{2a3e} = 3.1$; $^3J_{5a6a} = 4.9$; $^3J_{2,2\text{-Me}} = 6.1$; $^3J_{5,5\text{-Me}} = 6.9$ Hz. For V, δ 3.85 ppm (OCH_3).
***β-CH_2 1.62; γ-CH_2 1.38; CH_3 0.94 ppm.

TABLE 3. Spin—Spin Coupling in Pyrrolopiperidines II, III, VIII-X

Compound	Spin—spin coupling, Hz									
	2.3	4,7	4.4-CH_3	6a6e	6a7.	6e7	7, 7-CH_3	XA	XB	AB
II	2,9	2,3	6,3	−11,2	9,9	5,1	6,8	—	—	—
cis-III	3,2	1,2	6,4	−11,4	3,9	1,8	6,7	8,9	15,7	0,9
trans-III	3,2	1,2	6,4	−11,5	5,4	4,9	6,6	8,9	15,8	0,9
VIII*	—	0,8	6,4	−11,8	3,7	2,7	6,9	8,2	15,6	0,8
IX*	—	1,2	6,5	−12,0	8,5	5,8	6,7	8,1	15,6	0,8
X*	—	—	6,4	−12,0	—	—	—	—	—	—



I → V–VII

V R=CH_3; VI R=$CH_2C_6H_5$; VII R=C_4H_9

The spin—spin coupling of the protons in the PMR spectrum of the piperidine ring (Table 2) point to a *trans*-diequatorial configuration for the methyl groups at C-2 and C-5. The low field shift of the 3e-H proton is due to the *cis*-orientation of the N-alkoxyl group (E-configuration for the oxime).

Evidently, the presence of the benzyl radical in TMBAC in the reaction facilitates the formation of an ammonium ylide which can exist in two forms. Breakdown of the latter forms carbene and phenylcarbene which can alkylate the oxime [4, 5].

$$:CHC_6H_5 \xleftarrow{-(CH_3)_3N} (CH_3)_3\overset{+}{N}-\overset{-}{C}HC_6H_5 \longleftrightarrow \overset{-}{C}H_2-\overset{+}{N}(CH_3)_2CH_2C_6H_5 \xrightarrow{-N(CH_3)_2CH_2C_6H_5} CH_2:$$

TABLE 4. Chemical Shifts of Pyrrolopiperidine Protons in II, III, VIII-X

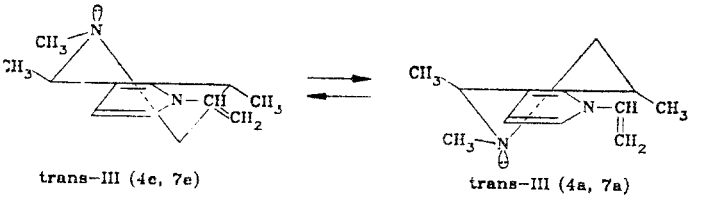
Compound	δ, ppm*											
	2-H	3-H	4-H	6a-H	6e-H	7-H	4-CH_3	5-CH_3	7-CH_3	H_X	H_a	H_B
II**	6,33	6,10	3,27	2,11	2,77	2,96	1,44	2,33	0,80	—	—	—
cis-III	6,77	6,05	3,06	2,51	2,44	2,44	1,39	2,28	1,25	6,50	4,29	4,80
trans-III	6,77	6,04	3,54	2,08	2,81	2,68	1,19	2,29	1,09	6,53	4,28	4,79
VIII	—	6,87	2,70	2,28	2,28	2,32	1,09	2,13	1,04	6,48	4,66	4,59
IX	7,04	—	3,24	2,24	3,09	3,23	1,33	2,43	1,20	7,20	5,39	5,31
X***	—	6,83	3,12	2,63	2,83	—	1,38	2,48	1,53	—	—	—

*Spectra of II, III recorded in C_6D_6, VIII-X in $CDCl_3$.
**6.79 ppm (NH).
***9.66 ppm (NH).

When a mixture of TBAI and KOH is used as heterocyclization catalyst the probability of formation of the ammonium ylide is much less and O-alkylation does not in effect occur. The yield of 1,2,5-trimethyl-4-butoximinopipridine (VII) is 0.8% but the tetrahydropyrrolopyridine II is formed in 29% yield.

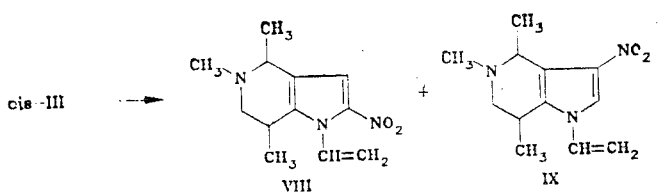
Heterocyclization of oxime I at increased acetylene pressure in the presence of KOH leads to quantitative vinylation of the formed NH-pyrrole. Under these conditions, a mixture of isomers attributable to the methyl groups in the piperidine ring of oxime I gives a mixture of N-vinylpyrrolotetrahydropiperidines III with *cis*- and *trans*-orientations of the methyl groups at atoms C-4 and C-7. The individual isomers of III were separated chromatographically. In addition to III a small amount of the pyrrolopyrimidine IV is formed.

The observed spin—spin couplings for the 6*a*-H and 6e-H protons (Table 3) in the PMR spectra of these isomers point to a half-chair conformation for the tetrahydropyrimidine fragment. The presence of two small 6*a*-H and 6e-H couplings in the *cis* isomer suggests an axial orientation of the methyl group at C-7. The analogous coupling in the *trans* isomer points to the existence of a conformational equilibrium of the type *trans*-III (4e, 7e)/*trans*-III (4*a*, 7*a*) as shown below.



Calculation as method [6] with use of the boundary values for the $^3J^0$ spin—spin couplings of 6e, 7e = 1.8 and 6*a*, 7*a* = 9.9 Hz (from the PMR spectra of *cis*-III and II respectively) gives a conformer population for the *trans* isomer III of $n_{III(4e7e)} \simeq 0.4$ and $n_{III(4a7a)} \simeq 0.6$.

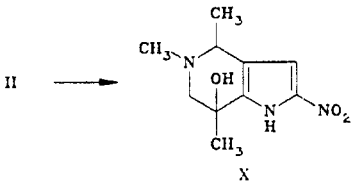
Taking into account the high lability of N-vinylpyrroles in acid [7], acetyl nitrate was chosen as nitrating agent for the *cis*-isomers of II and III. Nitration of *cis*-III occurs primarily in th α-pyrrole position to give 2-nitro-1-vinyl-3,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine (VIII, 21%). The corresponding 3-nitro derivative IX was also isolated from the reaction mixture in 16% yield.



The mass spectra of nitro derivatives VIII and IX show molecular ion peaks* at 235 (11% for VIII, 8% for IX) corresponding to their empirical formula. The basic ion fission for M^+ is through elimination of the C-4 methyl, which is a characteristic of the ionization of similar compounds [8].

As seen from the $^3J_{67}$ spin—spin couplings, the conformations of VIII and IX are different. In the 3-nitro derivative IX the predominant conformer has an equatorial orientation of the C-7 methyl group and axial orientation at C-4 as shown by the greater value of 8.5 Hz for $^3J_{67}^{trans}$ (Table 3). This is evidently connected with a steric interaction of the adjacent substituents at C-3 and C-4 leading to inversion of the parent half-chair. The $^3J_{67}$ value shows that the 4e, 7*a* configuration of the methyl groups in cis-III is preserved in VIII.

Nitration of II gives 2-nitro-7-hydroxy-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine (X) as the main product in 15% yield.



X

Evidently the reaction occurs to give the 2-NO_2 derivative which is oxidized by acetyl nitrate to give the hydroxy compound X. The IR spectrum of X shows a broad, strong band for hydroxyl at 3138 cm^{-1}. The mass spectrum shows a molecular ion peak m/z 225 (32%) corresponding to the molecular formula. Fragmentation of M^+ occurs via successive elimination of the methyl group and water to give an ion with m/z 192 (24%) which is apparently an azaindolium cation radical. The singlet nature of the 3-H proton and its low field shift (by 0.85 ppm) in the PMR spectrum show that the nitro group is at position 2. The singlet signal for the methyl group at C-7 is due to the presence of the geminal OH group (which shows a broad signal at δ 3.56 ppm) (Tables 3 and 4).

EXPERIMENTAL

PMR spectra were recorded on a Bruker WM-400 spectrometer with TMS as internal standard and mass spectra on an MK-1303. IR spectra were taken on a UR-20 spectrometer (KBr tablets) and TLC on Alufol and Silufol UV-254 plates. Column chromatography was performed using Brockmann grade II activity Al_2O_3 and L 40/100 silica gel.

Elemental analytical data for C, H, and N agreed with those calculated.

Heterocyclization of 1,2,5-Trimethylpipridin-4-one Oxime. A. Acetylene was passed through a solution of the oxime I (32 mmoles) with *trans*-diequatorial methyl groups at atoms C-2 and C-5 with the calculated quantity of catalyst in DMSO (50 ml) at 96-98°C until TLC (Silufol, ammonia—isopropanol, 1:20) showed the disappearance of I. In the case of portionwise addition of catalyst, the calculated amount was added in three equal parts over 2 h. The product was poured into ice, extracted with ether, dried ($MgSO_4$), evaporated to about 20 ml, and cooled. The precipitate of NH-tetrahydropyrrolopyridine II was filtered off. After distillation, the melting point of an analytical sample corresponded to a standard [1].

When a mixture of KOH—TBAI was used the filtrate, after removal of II, was evaporated and the residue chromatographed on an Al_2O_3 column (h = 50 cm, d = 1.5 cm) using hexane eluent. Compound VII was obtained (40 mg, 0.8%) as a viscous oil with R_f 0.55 (Alufol, ethyl acetate—hexane, 1:5). Found: M^+ 212. Calculated: M^+ 212.

B. Heterocyclization of a mixture of oxime I isomers (30 g, 190 mmoles) was carried out in an autoclave at 85°C using KOH (11.2 g, 0.2 mole) and DMSO (300 ml). The initial acetylene pressure was 16 atm and the reaction was continued for 2.5 h. The product was poured into water, extracted with chloroform, and the extracts washed with water to remove DMSO. After removal of solvent the residue was twice distilled in vacuo collecting the fraction at 93-115°C (4 mm Hg) to give 13.4 g (37%) of a mixture of cis-III, *trans*-III, and IV. Chromatography was carried out on 1.6 g of the mixture on a silica gel column (h = 45 cm, d = 1.8 cm). The following fractions were collected: 0.24 g of a mixture of IV and *cis*-III; 0.5 g of *cis*-III, 0.4 g of a mixture of *cis*-III and *trans*-III, and 0.3 g of *trans*-III. R_f: 0.56 (IV), 0.8 (*cis*-III), 0.23 (*trans*-III) (Alufol, ethyl acetate—pentane, 1:7).

*Here and below, mass spectral values of m/z are given.

1,2,5-Trimethyl-4-methoximino- and 4-Benzyloximinopiperidines (V and VI, $C_9H_{18}N_2O$ and $C_{15}H_{22}N_2O$). A current of acetylene was passed through a solution of oxime I (5 g, 32 mmoles), rubidium hydroxide (3.28 g, 32 mmoles), and TMBAC (5.9 g, 32 mmoles) in DMSO (50 ml) at 96-98°C until disappearance of starting material by TLC. The residue (6 g) was chromatographed on an Al_2O_3 column (h = 40 cm, d = 3.5 cm) using hexane eluent to give 2.5 g of a mixture of V and VI.

2-Nitro- and 3-Nitro-1-vinyl-3,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridines (VIII and IX, $C_{12}H_{17}N_3O_2$). Nitric acid (ρ = 1.4 g/cm^3, 2.14 g, 24 mmoles) was added with intensive stirring to acetic anhydride (10 ml) at —20°C. After 15 min, *cis*-III (0.38 g, 2 mmoles) in acetic anhydride (10 ml) was added over 30 min. The solution was stirred at —20°C until the reaction was complete (TLC), held at room temperature for 30 min, and poured into ice/sodium carbonate. The product was extracted with ether (5 × 30 ml), dried ($MgSO_4$), the ether distilled, and the residue (0.32 g) chromatographed on an Al_2O_3 column (h = 35 cm, d = 1.5 cm) using hexane—ethyl acetate (1:30). There was obtained VIII (0.1 g, 21%, R_f 0.81 on Alufol using ethyl acetate—hexane, 1:7) as yellow crystals with mp 75-77°C from pentane and with IR spectrum 1520 cm^{-1} (NO_2). Next eluted was a mixture of VIII and IX (30 mg), and finally IX (75 mg, 16%) with R_f 0.41 (Alufol, ethyl acetate—hexane, 1:7) as yellow crystals with mp 54-55°C (from heptane) and IR spectrum 1500 cm^{-1} (NO_2).

2-Nitro-7-hydroxy-4,5,7-trimethyl-4,5,6,7-tetrahydropyrrolo[3,2-c]pyridine (X, $C_{10}H_{15}N_3O_3$). Nitric acid (ρ = 1.4 g/cm^3, 2 g, 30 mmoles) and acetic anhydride (15 ml) were used to nitrate II (0.5 g, 3 mmoles) by the above method. Ether was distilled off and the residue (0.3 g) crystallized from pentane—ethyl acetate to give X (0.1 g, 15%) as yellow crystals with mp 148-149°C and R_f 0.69 (Silufol, ammonia—isopropanol, 1:20).

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