PYRROLES FROM KETOXIMES AND ACETYLENE.

NO. 36.* 4,4,6,6-TETRAMETHYL-4,5,6,7-TETRAHYDRO-5-AZAINDOLE, ITS NITROXYL AND VINYL DERIVATIVES, AND SPIN-LABELLED COPOLYMER

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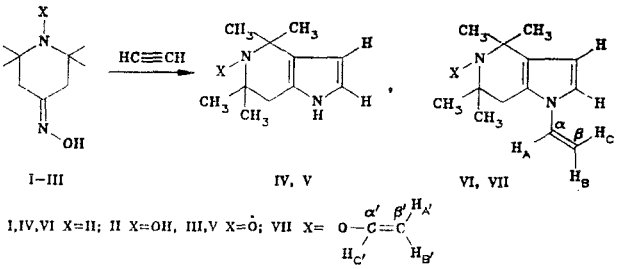
An oxime containing a nitroxyl functional group site, 2,2,6,6-tetramethyl-1-nitroxyl-4-hydroxyiminopiperidine, has been shown for the first time to engage in productive pyrrole synthesis via reaction with acetylene in KOH–DMSO. The behavior of 2,2,6,6-tetramethyl-4-piperidone oxime and its 1-hydroxy derivative in this reaction has also been investigated. The corresponding 5-azaindole and its 5-nitroxyl and 1-vinyl derivatives have been synthesized in this manner. 1-Hydroxy-4-piperidone oxime reacts at 50-60°C under the general reaction conditions undergoing oxidative conversion to 5-azaindole, while at 105°C in the presence of excess acetylene reduction of the hydroxy group also takes place. The formation of a pyrrole ring does not involve radical chains, although vinylation of the resulting pyrroles apparently involves one-electron transfer. 1-Vinyl-4,4,6,6-tetramethyl-4,5,6,7-tetrahydro-5-azaindole has been used for the preparation of a spin-labelled polyvinyl alcohol copolymer.

In previous papers in this series we have shown that reactions of ketoximes with acetylene in an alkali metal hydroxide–polar aprotic solvent system make it possible to prepare pyrroles and their 1-vinyl derivatives containing alkyl, aryl, and hetaryl substituents in the pyrrole ring, as well as condensed pyrrole systems, such as tetrahydroindoles, cyclopentano[b]-pyrroles, and dihydrobenzo[g]indoles [2].

In this behavior we discuss the characteristics of the reactions of 2,2,6,6-tetramethyl-4-piperidone oxime (I, X = H) and its N-oxidized derivatives (II, X = OH; III, X = O·) with acetylene in the system KOH–DMSO; we also report full experimental details for the synthesis of tetrahydroazaindoles IV-VI, for which only brief [3] or general [4] information has been available up until now.



The following fundamentally important facts have been revealed.

1. Oxime III consisting of a nitroxyl functional group can be converted to azaindole V without disruption of the free radical site (65% yield, with conditions not optimized). There are two important conclusions to be drawn from this observation: a) the presence of a nitroxyl functional group within the composition of the ketoxime does not inhibit its pyrroli-

*For Communication No. 35, see [1].

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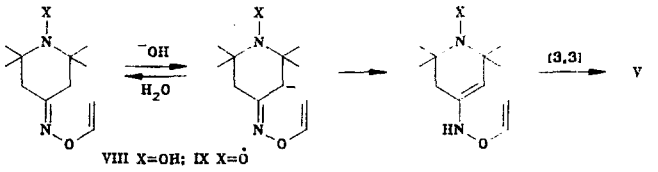
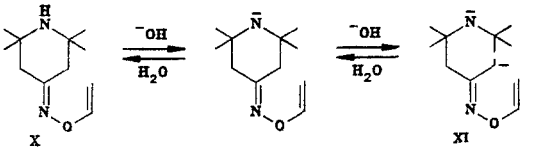
zation via reaction with acetylene in superbasic media; b) pyrrolization of ketoximes upon reaction with acetylene in the presence of a hyper-strong base does not involve pronounced radical chains, since if that were the case the nitroxyl sites would be expected to act as spin traps and suppress the reaction.

2. Ketoximes II and III are more easily converted to pyrroles than the nonoxidized form I. Thus, whereas II and III react at 50-60°C to give azaindole V in 48 and 65% yield, respectively, compound I under the same reaction conditions does not react to give azaindole IV until 90-95°C and gives only a 24% yield. This is probably due to more facile isomerization of the intermediate O-vinyloximes VIII and IX as a consequence of the enhanced acidity of the CH_2 groups in the presence of the strong electron withdrawing inductive effect of an N—OH or N—O· endocyclic functional group.



VIII X=OH; IX X=O·

In this regard it is probable that in superbasic medium ionization of the NH bond in O-vinyloxime X would be expected to hinder deprotonation of the CH_2 group, due to thermodynamic instability of a dianion XI as a consequence of repulsion of proximate negative charges.



X XI

3. 1-Hydroxy-2,2,6,6-tetramethyl-4-piperidone oxime (II) reacts with acetylene in the presence of KOH-DMSO at 50-60°C to form azaindole V containing a nitroxyl functional group (48% yield), i.e., an oxidative-reductive process is taking place under the reaction conditions:

$$\text{II} + HC{\equiv}CH + Me_2SO \xrightarrow{KOH} \text{V} + H_2O + Me_2S$$

4. At higher temperatures (105°C) in the presence of excess acetylene oxime II is converted to 1-vinylazaindole VI, apparently via intermediate formation of nitroxyl V (cf. 3 above). Thus, under harsher conditions the KOH—DMSO system behaves as a reducing agent relative to nitroxyl radical, possibly via conversion of dimethyl sulfoxide to dimethyl sulfone or methane-sulfonate (with more extensive degradation).

$$\text{V} + HC{\equiv}CH \xrightarrow{KOH/DMSO} \text{VI} + Me_2SO_2$$

5. During the course of redox-pyrrolization of oxime II a small amount of 1-vinyl-5-vinyloxy-4,4,6,6-tetramethyl-4,5,6,7-tetrahydro-5-azaindole (VII) is also formed. This is the first known example of nucleophilic addition of hydroxylamine to a triple bond which is not activated due to the presence of electron withdrawing substituents.

6. It was not possible to prepare a 1-vinylazaindole containing a nitroxyl functional group from oximes II or III. In both cases at 50-65°C only the N-unsubstituted derivative V was formed. As the temperature was increased to 95°C oxime III was converted to 1-vinylazaindole VI, with forfeiture of the radical site. This may be regarded as evidence that the process of pyrrole vinylation in the KOH—DMSO system involves one-electron transfer, for example:

$$HC{\equiv}CH + \text{IV} \longrightarrow [HC{\equiv}CH]^{\cdot-} + [\text{IV}]^{\cdot+},$$

which is inhibited by nitroxyl radicals (in which the acetylene anion radical can act as a reducing agent of nitroxyl V).

With respect to purely preparative results, the best yield (90%) of azaindole VI is achieved using a molar ratio of oxime I—KOH—DMSO equal to 1:3:43 (105°C, 8 h). At 95°C and almost identical conditions azaindole VI is formed after 5 h and 30 min in 87% yield, while

at an equimolar ratio of oxime I–KOH (at 90-95°C, 6 h) a mixture, consisting of azaindole IV (24% yield) and starting oxime, is obtained. Reaction of the same oxime I with acetylene under pressure (14 atm, 100°C, 3 h, equimolar ratio of oxime I–KOH) is accompanied by substantial resinification, which lowers the yield of azaindole VI to 38%.

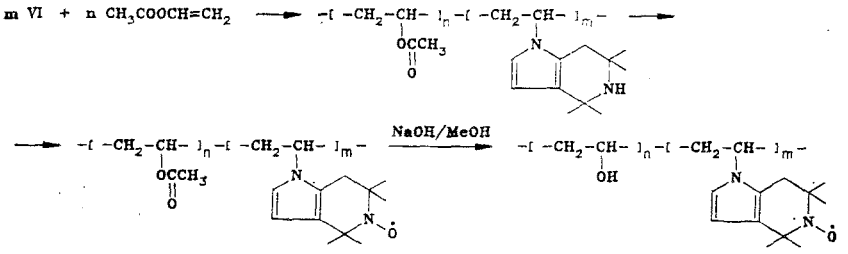
Azaindole V is the sole reaction product formed upon reaction of oxime II with acetylene at 50-60°C. Increasing the reaction temperature to 105°C leads to the formation of a mixture of azaindoles: VI (55%), IV, V, and VII (~1%).

The IR spectra of azaindoles IV and V both in the form of KBr pellets and nujol mulls contain stretching vibrational bands due to bound (associated) NH groups at 3280 cm^{-1} (intermolecular hydrogen bonding). The spectra in dilute solutions (CCl_4, $c = 3 \cdot 10^{-3}$ M) contain two bands: one at 3485 cm^{-1} which is assigned to a free NH group in the pyrrole ring (present at 3495 cm^{-1} in pyrrole [5]), and a second weaker band at 3330 cm^{-1} which corresponds to a band due to an NH group in piperidine (3347 cm^{-1} [6]). The fact that the frequency of the NH group vibration at 3330 cm^{-1} is constant in the spectra of 1-vinylazaindole VI in a thin film as well as in dilute solution (CCl_4) indicates that the NH group in the piperidine ring which is shielded by the methyl groups is unreactive with respect to the formation of intermolecular hydrogen bonds. The vinyl group in azaindole VI appears in the IR spectrum with bands at 865 (CH_2=), 1645 (C=C), and 3100 cm^{-1} (CH_2=). Bands at 1380, 1490, and 1550 cm^{-1} in the spectra of azaindoles IV-VII are typical of pyrrole rings [2].

The UV spectrum of 1-vinylazaindole VI (in ethanol) exhibits two bands: 202 (ε 12,500) and 247 nm (ε 12,600), which corresponds almost exactly with the spectrum of 1-vinyl-4,5,6,7-tetrahydroindole [2]. The spectra of azaindoles IV and V contain bands in the 213 (ε 7800) and 216 nm (ε 8600) regions, and thus are similar to the spectrum of 4,5,6,7-tetrahydroindole [7].

Azaindole V is paramagnetic. Its EPR spectrum* (in DMSO solvent) exhibits a characteristic triplet with an intensity ratio for its components of 1:1:1, and hyperfine splitting constant a_N = 16.04 Oe. The PMR spectrum of azaindole V consists of washed-out, broad signal bands, whose positions correspond to the signal positions in the PMR spectra of compounds IV and VI.

A spin-labelled polyvinyl alcohol derivative, which has cryoprotector properties [8], was synthesized by radical copolymerization of vinyl acetate with vinylazaindole VI in chlorobenzene, using an ampoule method, according to the following scheme:



Oxidation of the amine units to nitroxyl groups was accomplished using m-chloroperbenzoic acid. The composition of the spin-labelled polyvinyl alcohol was established based on double integration of its EPR spectra of frozen aqueous samples of the copolymer, and by determining the total spin concentration in a dry spin-labelled copolymer sample and then applying the spectral parameters (cf. Fig. 1, [9]). The results of these two methods revealed that the spin-labelled polyvinyl alcohol derivative contained $(3.2 \pm 0.8) \cdot 10^{19}$ spins/g, which corresponds to one label for every 250 copolymer units. The degree of saponification of the copolymer was 93%.

EXPERIMENTAL

DMSO grade "chemically pure" was used in all of the experiments; the KOH had a water concentration of 14% (and was not recalculated for the amount of anhydrous sample material present). ^1H- and ^{13}C-NMR spectra were recorded on a Bruker WP-200 spectrometer, IR and UV

*The authors are indebted to T. I. Vakul'skii for recording EPR spectra.

Fig. 1. EPR spectrum of a 0.3% solution of spin-labelled polyvinyl alcohol derivative in water at −170°C.

spectra on UR-20 and Perkin–Elmer 402 spectrophotometers, respectively. EPR spectra of the copolymers were recorded on a Varian E-104 radiospectrometer.

4,4,6,6-Tetramethyl-4,5,6,7-tetrahydro-5-azaindole (IV). To a flask equipped with a stirrer, condenser, and tube for the addition of acetylene was added 5 g (29.4 mmole) oxime I, 1.7 g (30 mmole) finely divided KOH, and 70 ml DMSO. The mixture was stirred vigorously as acetylene (~580 ml/min) was bubbled through the system for 6 h at 90-95°C. After being cooled the contents of the flask were diluted with cold water (1:2 by volume) and extracted with ether (70 ml × 5). The ether extracts were combined, washed with water, and dried over potash. After removal of the solvent the residue was chromatographed through a thin layer of Al_2O_3 (hexane–ether–ethanol, 5:5:1) to give 1.26 g (24%) of azaindole IV, light cream-colored crystals, mp 128-129°C. PMR spectrum: 10.14 (1H, 1-H); 6.48 (1H, d, 2-H); 5.80 (1H, d, 3-H, $^3J_{23}$ = 2.5 Hz; 2.32 (2H, s, CH_2); 1.22 (6H, s, 4-CH_3); 1.08 (6H, s, 6-CH_3); 3.35 ppm (1H, 5-H, exchanges with H_2O). ^{13}C-NMR spectrum: 123.40 ($C_{(3a)}$); 122.39 ($C_{(7a)}$); 115.27 ($C_{(2)}$); 103.26 ($C_{(3)}$); 50.24 ($C_{(4)}$, $C_{(6)}$); 36.16 ($C_{(7)}$); 33.41 (4-CH_3); 30.28 ppm (6-CH_3). Found, %: C 74.2, H 10.2, N 15.7. $C_{11}H_{18}N_2$. Calculated, %: C 74.1, H 10.2, N 15.7.

1-Vinyl-4,4,6,6-tetramethyl-4,5,6,7-tetrahydro-5-azaindole (VI). A. To a vigorously stirred suspension of 5 g (29.4 mmole) oxime I, 3.4 g (61 mmole) KOH, and 90 ml DMSO was added acetylene (~580 ml/min) at 105°C over a 4 h period; an additional 1.7 g (30 mmole) KOH was added and acetylene addition was continued with vigorous stirring for another 4 h. After workup as described above, followed by fractional vacuum distillation, 5.43 g (90%) of azaindole VI was obtained as a yellow liquid, which formed low melting crystals, mp 25-27°C, bp 103°C (~4 hPa), n_D^{20} 1.5303, d_4^{20} 0.9805. PMR spectrum: 7.03 (1H, d, 2-H) 6.02 (1H, d, 3-H, $^3J_{23}$ = 2.4 Hz); 6.68 (1H, q, H_A); 4.55 (1H, q, H_B); 5.10 (1H, q, H_C, $^3J_{AB}$ = 8.9, $^3J_{AC}$ = 15.8, $^2J_{BC}$ = 0.8 Hz); 2.39 (2H, s, CH_2); 1.25 (6H, s, 4-CH_3); 1.12 ppm (6H, s, 6-CH_3). ^{13}C-NMR spectrum: 130.47 ($C_{(\alpha)}$); 125.36 ($C_{(3a)}$); 124.65 ($C_{(7a)}$); 115.71 ($C_{(2)}$); 106.36 ($C_{(3)}$); 96.04 ($C_{(\beta)}$); 50.19 and 50.04 ($C_{(4)}$ and $C_{(6)}$); 34.77 ($C_{(7)}$); 32.79 (4-CH_3); 30.28 ppm (6-CH_3). Found, %: C 76.2, H 9.8, N 13.6. $C_{13}H_{20}N_2$. Calculated, %: C 76.4, H 9.9, N 13.7.

B. To a vigorously stirred suspension of 5 g (29.4 mmole) oxime I, 3.4 g (61 mmole) powdered KOH, and 100 ml DMSO acetylene was bubbled for 4 h at 95°C; an additional 1.7 g (30 mmole) KOH was added and the process was continued at the same temperature for another 1 h and 30 min. The mixture was allowed to stand overnight, then was poured into 300 ml of cold water and extracted with ether; the extracts were washed with water and dried over potash. The ether was removed and the residue was fractionated under vacuum. Yield 5.2 g (87%) of chromatographically pure azaindole VI (Tsvet-100 chromatograph, catharometer detector, 1 m column length, 3 mm diameter, chromatone N-AW support, 5% DS-550 as the liquid phase, helium carrier gas, thermostat temperature 164°C, injector (vaporizer) 300°C, detector 200°C), bp 92°C (3.3 hPa), n_D^{20} 1.5348; d_4^{20} 0.9742.

C. A 1 liter vibrating steel autoclave was heated (100°C, 3 h) with 34 g (0.2 mole) oxime I, 11.2 g (0.2 mole) KOH, and 300 ml DMSO; the mixture had been saturated initially (prior to experiment) with acetylene at room temperature and an initial pressure of 14 atm. The reaction mixture was diluted with a fourfold excess (by volume) of water and extracted with ether. The ether extracts were washed with water and dried over potash. After removal of the ether solvent the residue was distilled under vacuum. Yield 26 g of a damp material and 11.5 g of a dark orange resin. Repeat distillation under vacuum gave 15.5 g (38%) of azaindole VI.

D. In analogy with method C (autoclave, 80°C, 3 h), 10 g (59 mmole) of oxime I, 3.9 g (69 mmole) KOH, and 140 ml DMSO gave 7.6 g (63%) of practically pure azaindole VI (TLC, Silufol UV-254, hexane–ether, 3:1).

Azaindole VI from Oxime II. Reaction of 5.4 g (29 mmole) oxime II and 5.1 g (91 mmole) KOH (added in 1.7 g portions every 3 h) in 95 ml DMSO (105°C, 8 h, acetylene bubbled through the mixture at atmospheric pressure) gave a mixture of compounds, which after preparative

chromatography on nonfixed layers of Al_2O_3 gave 3.2 g (55%) of azaindole VI, as well as azaindoles IV, V, and VII in about 1% amounts. PMR spectrum of azaindole VII: 6.94 (1H, d, 2-H) 5.90 (1H, d, 3-H, $^3J_{23}$ = 2.7 Hz; 6.78 (1H, q, H_A); 4.48 (1H, q, H_B); 4.96 (1H, q, H_C, $^3J_{AB}$ = 9.0, $^3J_{AC}$ = 15.8, $^2J_{BC}$ = 0.8 Hz); 2.43 (s, 7-CH_2); 1.26 (6H, s, 4-CH_3); 1.14 (6H, s, 6-CH_3); 6.52 (1H, q, $H_{A'}$); 3.82 (1H, q, $H_{B'}$); 4.20 ppm (1H, q, $H_{C'}$, $^3J_{A'B'}$ = 6.8, $^3J_{A'C'}$ = 13.5, $^2J_{B'C'}$ = 1.4 Hz). ^{13}C-NMR spectrum: 130.39 ($C_{(\alpha)}$); 96.81 ($C_{(\beta)}$); 157.84 ($C_{(\alpha')}$); 84.91 ppm ($C_{(\beta')}$).

Azaindole VI from Oxime III. A mixture of 3 g (16 mmole) oxime III and 2.6 g (46 mmole) KOH in 50 ml DMSO was vigorously stirred and heated to 95°C as acetylene was bubbled through the solution at atmospheric pressure for 3 h. Another 0.8 g (14 mmole) of KOH was added and acetylene addition was continued for 3 h and 30 min. After workup as described above and vacuum fractionation 2.7 g (82%) of azaindole VI was obtained.

4,4,6,6-Tetramethyl-5-nitroxyl-4,5,6,7-tetrahydro-5-azaindole (V) from Oxime II. To a stirred mixture of 5.4 g (29 mmole) oxime II and 3.4 g (61 mmole) KOH in 100 ml DMSO acetylene was bubbled at 50-60°C for 4 h; an additional 1.7 g (30 mmole) of KOH was added and the process was continued under the same conditions for another 4 h. After workup as described above and chromatography on Al_2O_3 plates (hexane–ether, 1:1) 2.7 g (48%) of azaindole V was obtained as dark orange crystals, mp 143-144°C. Found, %: C 68.7, H 8.3, N 14.3. $C_{11}H_{17}N_2O$. Calculated, %: C 68.4, H 8.9, N 14.5.

4,4,6,6-Tetramethyl-5-nitroxyl-4,5,6,7-tetrahydro-5-azaindole V from Oxime III. Reaction of 5.4 g (29 mmole) oxime III and 5.1 g (91 mmole) KOH (added in 1.7-g portions every 3 h) in 95 ml DMSO at 65°C for 8 h gave (after preparative chromatography on Al_2O_3 plates with hexane–ether, 1:1) 4.2 g (65%) of azaindole V.

Spin-labelled Polyvinyl Alcohol. A glass ampoule was charged with 5 g (58 mmole) vinyl acetate, 0.05 g (0.24 mmole) vinylazaindole VI, and 0.1 g azobisisobutyronitrile (2%) in 20 ml chlorobenzene, argon was purged through the system for 30 min, and the ampoule was sealed and thermostatted at 70°C for 40 h. The resulting product mixture was purified by threefold precipitation from chloroform (with hexane added as precipitating solvent). The copolymer was dissolved in 100 ml chloroform, cooled to 0°C, and a solution of 0.1 g m-chloroperbenzoic acid in 20 ml chloroform was added with stirring to the solution. The reaction mixture was maintained at 0°C for 20 h. The spin-labelled copolymer was precipitated from toluene with hexane. It was dried at room temperature. Yield 70%. M 6360 (ebullioscopic).

To a solution of 2 g spin-labelled copolymer in 50 ml methanol was added 10 ml of 20% sodium hydroxide in methanol solution and the mixture was refluxed for 5 h. The resulting white precipitate was filtered, washed with methanol, and dried in vacuo. The degree of saponification was determined using the standard method [10].

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