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VINYLACETYLENE CHEMISTRY

LXXII Synthesis of Some Substituted 7-Aza-4-Ketodecahydroquinolines

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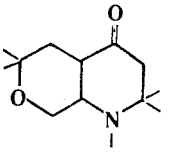
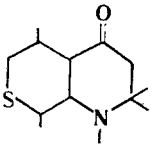
It is shown that heating vinylacetylenic piperidols I with phosphorus oxychloride in pyridine solution gives dienynes II, the structure of which is determined, in the case of II (R = H), by means of IR spectra and PMR. Hydration of the dienynes II (R = H, Me) in the presence of mercuric sulfate in methanol solution gives β-methoxyketones III (R = H, Me). It is also shown that III and aqueous solutions of ammonia or primary amines give the bicyclic piperid-4-ones IV. In the synthesis of IV (R = H, R_1 = i-Pr, Bu) imines V are obtained, which on hydrolysis give piperidones IV (R = H, R_1 = i-Pr, Bu). When the β-methoxyketone III (R = H) is heated with 5% sulfuric acid in the presence of mercuric sulfate, chroman-4-one is formed.

Over a period of years, this laboratory has done systematic research on the synthesis of various heterocyclic compounds from acetylene derivatives. In particular, it was shown that biheterocyclic compounds containing oxygen, sulfur, and nitrogen, can be synthesized from acetylenic tetrahydropyranols [1, 2] and tetrahydrothiopyranols [3].





The present work aimed to synthesize biheterocyclic compounds with both hetero atoms nitrogen atoms, and the synthesis started from known 4-vinylethynyl-4-piperidols [4, 5].

It is shown that dehydration of the α-stereoisomer (mp 93° C) of 1, 2, 5-trimethyl-4-vinylethynyl-4-piperidol [4] (I, R = H) with phosphorus oxychloride in piperidine solution gives 1, 2, 5-trimethyl-4-vinylethynyl-$\Delta^{4,5}$-dehydropiperidine (II, R = H). The structure of the latter is determined using IR and PMR spectra.

The IR spectrum of dienyne II (R = H) shows strong bands of double bonds conjugated to an acetylenic bond (1600 and 1625 cm^{-1}), while a conjugated acetylenic linkage is revealed in the 2180 cm^{-1} region.

Peaks at −0.89, −0.75, −0.65, −0.56, −0.42 in the PMR spectrum* (fig.) can be ascribed to an unsubstituted vinyl group. Peaks at 1.92, 1.96, and 3.13 indicate the presence of the Me−(C=) grouping. The peak at 2.71 is characteristic of the N−Me grouping, while peaks at 3.94 and 4.06 are characteristic of Me−(CH). So dehydration of the piperidol leads to formation of a tetrasubstituted vinyl group in the piperdine ring.

Dehydration of 1, 2, 5, 6-tetramethyl-4-vinylethynyl-4-piperidol [5] (I, R = Me) proceeded similarly, and gave 1, 2, 5, 6-tetramethyl-4-vinylethynyl-$\Delta^{4,5}$-dehydropiperidine (II, R = Me).

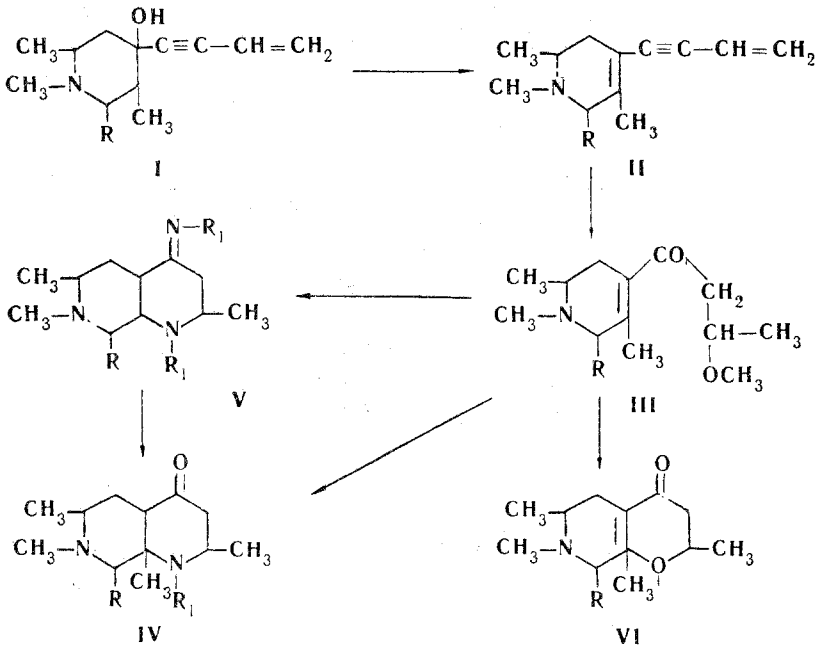
Hydration of dienynes II (R = H, Me) in the presence of sulfuric acid and mercuric sulfate in aqueous methanol solution results in hydration of the triple bond, and formation of the corresponding β-methoxyketones III (R = H, Me), the structure of which is shown by spectrum analysis of the typical dienone III (R = H). The conjugated carbonyl in the α, β unsaturated ketone III (R = H) is characterized by intense bands at 1665, 1629 cm^{-1}, and the other group by bands at 1095 and 1257 cm^{-1}.

Heating β-methoxyketones III (R = H, Me) with aqueous solutions of ammonia or primary amines, on a boiling water bath, gives the bicyclic piperid-4-one IV (R = H, Me).

The piperidone IV (R = R_1 = H) gives three stereoisomers (2 crystalline, 1 liquid), isolated chromatographically pure, and characterized by crystalline derivatives.

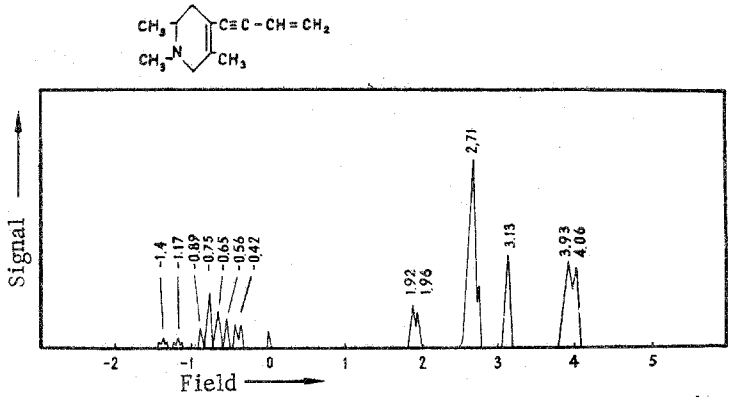
*This spectrum was measured by V. B. Lebedev with an IMN-3 instrument.

It is of interest to mention that when concentrated amine solutions (over 50%) are used when preparing piperidones IV (R = H, R_1 = i-Pr, Bu), the expected piperidones are not formed, but instead the imines V (R = H, R_1 = i-Pr, Bu), hydrolysis of which gives piperidones IV (R = H, R_1 = i-Pr, Bu). Heating β-methoxypropyl (1,2,5-trimethyl-$\Delta^{4,5}$-dehydropiperidyl-4) ketone (III, R = H) for an hour at 85° C with 5% sulfuric acid containing mercuric sulfate, gives chroman-4-one (VI).



Experimental

1,2,5-Trimethyl-4-vinylethynyl-$\Delta^{4,5}$-dehydropiperidine (II, R = H). A 0.5 *l* flask was fitted with mechanical stirrer, reflux condenser, dropping funnel, and thermometer, a solution of 20 g (~ 0.1 mole) 1,2,5-Me_3-4-vinylethynyl-4-piperidol (I, mp 83° C) in 35 ml piperidine placed in it, stirred vigorously, and 15 ml $POCl_3$ in 15 ml pyridine added at such a rate that the temperature of the reaction mixture did not rise above 115° C (if the reaction temperature does not rise, heat must be applied); this was accompanied by darkening. Then the reaction products were heated for an hour at 120°–125° C, cooled, crushed ice added, and the mixture saturated with K_2CO_3. It was then repeatedly extracted with ether, the ether solution washed with water and dried over $MgSO_4$. After distilling off the ether and pyridine, the residue was vacuum-distilled, to give 7.5 g (41%) dienyne II (R = H), bp 72° (1 mm); d_4^{20} 0.9058; n_D^{20} 1.5365. Found: N 7.84%; MR_D 60.42. Calculated for $C_{12}H_{17}N$: N 8.00%; MR_D 56.42. Picrate mp 161° C (ex EtOH). Found: N 14.17%. Calculated for $C_{12}H_{17}N \cdot C_6H_3N_3O_7$: N 13.86%.



PMR Spectrum.

1,2,5,6-Tetramethyl-4-vinylethynyl-$\Delta^{4,5}$-dehydropiperidine (II, R = Me). 50 g (~ 0.24 mole) 1,2,5,6-Me_4-4-vinylethynyl-4-piperidol [5] in 90 ml pyridine, and 40 ml $POCl_3$ on 40 ml pyridine, reaction temperature 115°–120° C, time 35 min, proceeding as above, gave 15 g (33%) dienyne II (R = Me), bp 94° C (2.5 mm), d_4^{20} 0.9118; n_D^{20} 1.5335. Found: N 7.89%; MR_D 64.38. Calculated for $C_{13}H_{19}N$: N 7.40%. Oxalate: mp 60° C (washed with Et_2O).

β-Methoxypropyl (1,2,5-Me_3-$\Delta^{4,5}$-dehydropiperidyl-4) ketone (III, R = H). A mixture of 7 g (0.04 mole) dienyne II (R = H), 45 ml methanol, 7.5 ml water, 3.2 ml H_2SO_4, and 1.2 g $HgSO_4$, was stirred for 11 hr at 63°–65° C. After distilling off most of the MeOH under slightly reduced pressure, 15 ml water was added, the mixture neutralized with K_2CO_3, and extracted with ether. Yield 6 g (56%) β-methoxyketone III (R = H) bp 102°–103° C (1 mm); d_4^{20} 0.9732; n_D^{20} 1.4920. Found: N 6.89%; MR_D 67.07. Calculated for $C_{13}H_{23}NO_2$: N 6.22%; MR_D 65.57. Picrate: mp 144°–145° C (ex EtOH). Found: N 12.04%. Calculated for $C_{13}H_{23}NO_2 \cdot C_6H_3N_3O_7$: N 12.33%.

β-Methoxypropyl (1,2,5,6-Me_4-$\Delta^{4,5}$- dehydropiperidyl-4) ketone (III, R = Me). 15 g (~ 0.08 mole) dienyne II (R = Me) was hydrated in 24 ml water, 8 ml H_2SO_4, 100 ml MeOH, and 3 g $HgSO_4$ at 60°–63° C, time 12 hr. The product was worked up in the usual way, to give 14 g (74%) β-methoxyketone III (R = Me) bp 114°–115° C (1.5 mm); d_4^{20} 0.9753; n_D^{20} 1.4980. Found: N 6.02%; MR_D 71.10. Calculated for $C_{14}H_{25}NO_2$: N 5.85%; MR_D 69.78.

2,6,7,9-Tetramethyl-7-aza-4-ketodecahydroquinoline (IV, R = R_1 = H). NH_3 gas was passed into a mixture of 6 g (~ 0.025 mole) β-methoxyketone III (R = H) and 50 ml 17% NH_4OH until it gained 7 g in weight. The mixture was then heated in a sealed tube for 25 hr at 95°–96° C. Working up in the susal way gave 4 g (53.7%) piperidone IV (R = = R_1 = H) which crystallized after being distilled. The liquid isomer was obtained pure after removing it by suction filtration, bp 104° C (1.5 mm); n_D^{20} 1.4990. Found: N 12.85%.* Dipicrate: mp 140°–141° C (ex EtOH). Found: N 16.80%.**

Fractional crystallization of the crystals gave the two stereosimoeric piperidones. II isomer: mp 90° C (ex Et_2O). Found: N 12.78%.* Dipicrate: mp 184° C (ex EtOH). Found: N 17.21%.** III isomer: mp 96° C. Dipcrate: mp 192° C. Found: N 17.10%.**

The crystalline isomers give a depressed mixed mp (83°–86° C).

2,6,8,9-Pentamethyl-7-aza-4-ketodecahydroquinoline (IV, R = Me, R_1 = H). By the method described above, 2.5 g (~ 0.01 mole) β-methoxyketone III (R = Me) and 25 ml saturated NH_4OH solution reacted for 14 hr gave 1.5 g (56%) piperidone IV (R = CH_3, R_1 = H); bp 120°–121° C (1.5 mm): n_D^{20} 1.5110. Found: C 69.63; H 10.81; N 12.01%. Calculated for $C_{13}H_{24}N_2O$: C 69.64; H 10.71; N 12.50%. Methiodide: mp 48° C (washed with ET_2O). Found: N 3.95%. Calculated $C_{14}H_{27}IN_2O$: N 3.82%.

1,2,6,7,9-Pentamethyl-7-aza-4-ketodecahydroquinoline (IV, R = H, R_1 = Me). A mixture of 5 g (~ 0.02 mole) β-methoxyketone III (R = H) and 45 ml water was saturated, with cooling, with 30 g $MeNH_2$, and the reaction mixture then heated for 20 hr at 95° C, in a sealed tube. Yield 2.5 g (43%) piperidone IV (R = H, R_1 = Me), bp 113°–114° C (1.5 mm); d_4^{20} 0.9644; n_D^{20} 1.5065. Found: N 12.71%; MR_D 69.13. Calculated for $C_{13}H_{24}N_2O$: N 12.50%; MR_D 66.14. Dipicrate: mp 133° C (ex EtOH). Found: C 44.15; H 5.20; N 15.82%. Calculated for $C_{13}H_{24}N_2O \cdot 2C_6H_3N_3O_7$: C 43.98; H 4.38; N 16.42%.

1,2,6,7,8,9-Hexamethyl-7-aza-4-ketodecahydroquinoline (IV, R = R_1 = Me). A mixture of 2.5 g (~ 0.01 mole) β-methoxyketone III (R = Me), 5 ml MeOH, and 25 ml water, was saturated with 15 g $MeNH_2$, and the whole then heated in a sealed tube for 14 hr at 93° C, to give 1.7 g (60%) piperidone IV (R = R_1 = Me), bp 128° C (1.5 mm); d_4^{20} 0.9880; n_D^{20} 1.5115. Found: C 70.56; H 11.03; N 11.65%; MR_D 72.61. Calculated for $C_{14}H_{26}N_2O$: C 70.58; H 10.92; N 11.76%; MR_D 70.34. Methiodide: mp 72° C. Found: N 3.87%. Calculated for $C_{15}H_{29}IN_2O$: N 3.53%.

2,6,7,8,9-Pentamethyl-1-ethyl-7-aza-4-ketodecahydroquinoline (IV, R = Me, R_1 = Et). 2 g (~ 0.019 mole) β-methoxyketone III (R = Me) and 20 ml 30% $EtNH_2$ gave 1 g (42%) piperidone IV (R = Me, R_1 = Et); bp 129°–130° C (1 mm); d_4^{20} 0.9899; n_D^{20} 1.5160. Found: C 72.10; H 10.75; N 11.47%; MR_D 76.92. Calculated for $C_{15}H_{28}N_2O$: C 71.42; H 11.11; N 11.11%; MR_D 74.96.

2,6,7,9-Tetramethyl-1-isopropyl-7-aza-4-ketodecahydroquinoline (IV, R = H, R_1 = i-Pr). A mixture of 3 g (~ 0.013 mole) β-methoxyketone III (R = H) and 10 g 67% aqueous i-$PrNH_2$, was heated at 90°–95° C in a sealed tube for 45 hr. The products were worked up in the usual way to give 2 g (51%) 2,6,7,9-Me_4-1-i-Pr-4-isopropylimino-7-azadecahydroquinoline (V, R = H, R_1 = i-Pr); bp 116°–117° C (1.5 mm); n_D^{20} 1.4960. Found: N 13.74%. Calculated for $C_{18}H_{35}N_3$: N 14.33%.

1.5 g imine V (R = H, R_1 = i-Pr) was heated with 20 ml 10% HCl at 70° C for 20 min, the products neutralized, and extracted with ether, to give 0.8 g (62%) piperidone IV (R = H, R_1 = i-Pr), bp 119°–120° C (2 mm); n_D^{20} 1.4945.

* Calculated $C_{12}H_{22}N_2O$: N 13.33%.

** Calculated for $C_{12}H_{22}N_2O \cdot 2C_6H_3N_3O_7$: N 16.76%.

Found: N 11.53%. Calculated for $C_{15}H_{28}N_2O$: N 11.11%.

2,6,7,9-Tetramethyl-1-butyl-7-aza-4-ketodecahydroquinoline (IV, R = H, R_1 = Bu). A mixture of 3 g (~ 0.013 mole) β-methoxyketone III (R = H), 10 g $BuNH_2$, 7 ml water, and 5 ml MeOH was reacted as above, to give 2 g (46%) 2,6,7,9-Me_4-1-Bu-4-butylimino-7-azadecahydroquinoline (V, R = H, R_1 = Bu); bp 119°–121° (1 mm); n_D^{20} 1.4940. Found: N 13.21%. Calculated for $C_{20}H_{39}N_3$: N 13.08%.

1.5 g imine V (R = H, R_1 = Bu) when treated in the usual way gave 0.7 g (58%) piperidone IV (R = H, R_1 = Bu), bp 123°–124° (2 mm); n_D^{20} 1.4990. Found: N 11.14%. Calculated for $C_{16}H_{30}N_2O$: N 10.52%.

2,6,7,9-Tetramethyl-1-p-methoxyphenyl-7-aza-4-ketodecahydroquinoline (IV, R = H, R_1 = p-$MeOC_6H_4$). A mixture of 6 g (~ 0.025 mole) β-methoxyketone III (R = H), 11 ml MeOH, 4 g p-anisidine, and 7 ml water was heated under reflux, at 64°–65° C for 11 hr. Then a small quantity of water was added, and the products extracted with ether, to give 3 g (32.6%) piperidone (IV) (R = H, R_1 = p-$MeOC_6H_4$), bp 240 (2 mm). Found: N 9.28%. Calculated for $C_{19}H_{28}N_2O_2$: N 8.86%. Dihydrochloride: mp 91° C (washed with ether). Found: N 6.88%. Calculated for $C_{19}H_{28}N_2O_2 \cdot 2HCl$: N 7.14%.

2,6,7,9-Tetramethyl-7-azahydrochroman-4-one (VI). 6.5 g (~ 0.027 g mole) β-methoxyketone III (R = = H) was dropped into a mixture of 70 ml 8% H_2SO_4 and 3 g $HgSO_4$ held at 85° C. The mixture was stirred for 2 hr at 90°–95° C, and during that time a further 3 g $HgSO_4$ was added in portions. The products were worked up in the usual way to give 2.5 g (40%) of chroman-4-one VI, bp 102°–103° C (1 mm); d_4^{20} 0.9867; n_D^{20} 1.5010. Found: N 7.05%. Calculated for $C_{12}H_{21}NO_2$: N 6.63%; MR_D 59.01.

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