CYCLIZATION OF 3-FORMYL-2-

ACETYLENYLINDCLE CXIMES

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The cyclization of ortho-substituted arylacetylenes is the basis for the synthesis of various condensed heterocyclic systems [1]. In the present work, we studied the possibility of cyclizing oximes of 2-acetylenyl-N-methylindol-3-aldehydes (I). Information on the intramolecular addition of the aldoxime group to an adjacent acetylenic group in aromatic compounds was lacking. Anderson and Sharp [2] reported that sulfonylhydrazones and aroylhydrazones of 2-ethynylbenzaldehyde cyclize in the presence of a base to give isoquinoline-N-imines, while the semicarbazone and 2,4-dinitrophenylhydrazone of this aldehyde and all these derivatives of 2-(phenylethynyl)benzaldehyde either do not react at all or are converted to polymer products. These results obviously cast doubt on the possibility of carrying out the cyclization of oximes of vicinal aromatic acetylenylaldehydes. In addition, it is difficult to predict the direction of such a cyclization since the functional group in the starting compounds have N- and O-nucleophilic reaction sites and reaction is likely at either of these sites as well as at both the β - and α -carbon atoms of the acetylenyl substituent.

We have found that aldoximes (I) which contain various acetylenic groups are readily cyclized upon heating to give the N-oxides of γ -carbolines (II)



Oximes (Ia) and (Ib) undergo rapid cyclization even under the conditions for their formation from aldehydes (IIIa) and (IIIb) upon heating at reflux in ethanol with NH₂OH to give N-oxides (IIa) and (IIb) in 85% and 45% yield, respectively. Oxide (IIb) was isolated as the stable hydrate $C_{17}H_{19}N_3C_2 \cdot H_2O$ which retains water upon prolonged heating at 80°C at 2 mm. Ring closure of the pyridine-N-oxide ring in (Ic) occurs with considerably greater difficulty. Heating (IIIc) with NH₂OH in ethanol for 2.5 h gives oxime (Ic) in 73% yield; about 20% (IIc) forms in addition to (Ic). The cyclization of (Ic) to (IIc) proceeds completely upon heating for several hours in pyridine or toluene at 110-115°C. The presence of KOH or Cu(I) compounds does not have a significant effect on the reaction rate. In order to confirm the structure, products (II) were reduced by PCl₃ to γ carbolines (IV) in 62-72% yields. The analytical and spectral data correspond to the structure of the compounds synthesized.

We propose that this reaction may be rather general in light of the high nucleophilicity of the oxime group and the lack of steric hindrance to addition at the triple bond.

EXPERIMENTAL

The NMR spectra were taken on a Varian XL-200 spectrometer in $CDCl_3$ and the IR spectra were taken on a UR-20 spectrometer in $CHCl_3$.

Institute of Chemical Kinetics and Combustion, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2602-2604, November, 1984. Original article submitted December 9, 1983. 2-Hexyn-1'-yl-1-methylindole (V). A sample of 7.7 g 2-iodo-1-methylindole and 5.5 g n-BuC = CCu in 50 ml pyridine was heated in an argon atmosphere at 110°C for 2.5 h and then diluted with 0.5 liter ether and filtered. The ethereal solution was washed with aqueous ammonia and water and dried over Na₂SO₄. Chromatography on alumina (grade II activity) and crystallization from hexane gave 5.1 g (80.6%) (V), mp 32.5-33.5°C. Found: C 85.30; H 8.10; N 6.87%. C₁₅H₁₇N. Calculated: C 85.26; H 8.11; N 6.63%. IR spectrum (ν , cm⁻¹): 2230 (C = C). PMR spectrum (δ , ppm): 0.98 t (CH₃-C), 1.4-1.7 m (β - and γ -CH₂), 2.52 t (α -CH₂), 3.78 (CH₃-N), 6.67 (H³), 7.1-7.3 m (H⁴⁻⁶), 7.57 d (H⁷).

<u>3-Formyl-2-hexynyl-1-methylindole (IIIa)</u>. A sample of 5.4 g (3.2 ml) POCl₃ was added gradually to 5 ml DMF with cooling and then 5.7 g (V) in 5-7 ml DMF was added. The mixture was stirred for 5.5 h at 40-45°C, poured onto 200 g ground ice, then made basic with aqueous NaCH, and rapidly heated to reflux and maintained at this temperature for 1 min. The product crystallized upon cooling (6.2 g). The solid was filtered, washed with water, dried in a dessicator over P_2O_5 , and recrystallized from hexane to give 5.6 g (IIIa) (86.7%), mp 44.5-45.5°C. Found: C 80.25; H 7.41; N 5.76%. C₁₆H₁₇NO. Calculated: C 80.30; H 7.16; N 5.85%. IR spectrum (ν , cm⁻¹): 1625 (C = O), 2230 (C = C). PMR spectrum (δ , ppm): 0.97 t (CH₃-C), 1.5-1.7 (β - and γ -CH₂), 2.58 t (α -CH₂), 3.78 (CH₃N), 7.2-7.4 (H⁴⁻⁶), 8.28 d (H⁷), 10.13 (CHO).

Analogous preparations were carried out for: (IIIb), 63.9% yield, mp 160-161°C (dec, from benzene). Found: C 72.54; H 6.40; N 9.77%. Calculated for $C_{17}H_{18}N_2O_2$: C 72.32; H 6.43; N 9.92%. IR spectrum (ν , cm⁻¹): 1670 (C=O), 2230 (C=C). PMR spectrum (δ , ppm): 2.65 t (CH₂NCH₂), 3.68 (CH₂C=C), 3.75 t (CH₂OCH₂), 3.81 (CH₃N), 7.3-7.4 m (H⁴⁻⁶), 8.27 d (H⁷), 10.15 (CHO).

(IIIc), 88.5% yield, mp 120-121°C (from 1:5 benzene-petroleum ether). Found: C 83.14; H 5.01; N 5.27%. Calculated for $C_{18}H_{13}NO$: C 83.37; H 5.05; N 5.40%. IR spectrum (ν , cm⁻¹): 1675 (C=O), 2230 (C = C). PMR spectrum (δ , ppm): 3.91 (CH₃N), 7.3-7.7 m (Ph, H⁴⁻⁶), 8.35 d (H⁷), 10.28 (CHO).

<u>2-Butyl-9-methyl- γ -carboline N-Oxide (IIa)</u>. A solution of NH₂OH prepared by the neutralization of 1.5 NH₂OH·HCl by 1.1 g Na₂CO₃ in 15 ml was added to 3.2 g (IIIa) in 25 ml ethanol and the mixture was heated at reflux for 2.5 h, diluted with 30-40 ml water, and evaporated in vacuum to a small volume. The residue was filtered off, washed with water, dried over P₂O₅ and recrystallized from toluene to give 2.9 g (85.3%) (IIa), mp 182-183°C (from ethyl acetate). Found: C 75.58; H 7.16; N 10.98%. C₁₆H₁₈N₂O. Calculated C 75.56; H 7.13; N 11.01%. PMR spectrum (δ , ppm): 0.98 t CH₃C), 1.49 sext (γ -CH₂), 1.80 q (β -CH₂), 3.09 t (α -CH₂), 3.80 (CH₃N), 7.14 (H¹), 7.3-7.6 m (H⁵⁻⁷), 7.95 d (H⁸), 9.0 (H⁴).

By analogy, (IIIb) yielded 44.7% 2-(N-morpholino)methyl-9-methyl- γ -carboline N-oxide hydrate (IIb)hydrate), mp 189.5-190.5°C (from benzene). Found: C 64.63; H 6.80; N 13.17%. Calculated for: $C_{17}H_{21}N_3C_3$: C 64.74; H 6.71; N 13.32%. PMR spectrum (δ , ppm): 7.70 t (CH_2NCH_2), 3.87 (CH_3N), 4.04() C - CH_2 -N), 7.3-7.6 m ($H^{1,5-7}$), 7.99 d (H^8), 9.01 (H^4), 1.92 (the signal is broadened upon the addition of PhCO₂H and is not observed, H₂O).

3-Formyl-2-phenylethynyl-1-methylindole Oxime (Ic). A sample of 4.4 g (IIIc) in 40 ml ethanol and a solution of NH₂OH prepared by the neutralization of 1.9 g NH₂OH HCl by 1.4 g Na₂CO₃ in 10 ml water, heated at reflux for 2.5 h, diluted with water, and evaporated to a small volume in vacuum. The residue was filtered off, washed with water, dried, and recrystallized from 320 ml benzene. Chromatography of the product (4.4 g) consisting of (Ic) and (IIc) on silica gel using dichloroethane gave 3.4 g (73.2%) (Ic), mp 147-148°C (dec., from benzene). Found: C 78.77; H 5.32; N 10.17%. Calculated for $C_{18}H_{14}N_2O$: C 78.81; H 5.14; N 10.21%. IR spectrum (ν , cm⁻¹): 2220 (C = C), 3600, 3380 br (OH). PMR spectrum (δ , ppm): 3.86 (CH₃N), 7.2-7.4 m (Ph), 7.5-7.6 m (H⁴⁻⁶), 8.13 d (H⁷), 8.60 (CH = N).

<u>2-Phenyl-9-methyl- γ -carboline N-Oxide (IIc)</u>. A sample of 4.1 g (Ic) in 60 ml pyridine was heated at reflux under argon for 4 h (until thin-layer chromatography on silufol with 2:1 dichloroethane – acetone as the eluent) indicated complete disappearance of (Ic) and evaporated to dryness in vacuum. The residue was recrystallized from ethanol to give 3.4 g (83%) (IIc), mp 221-222°C. Found: C 78.76; H 5.04; N 10.21%. Calculated for C₁₈H₁₄N₂O: C 78.81; H 5.14; N 10.21%. PMR spectrum (δ , ppm): 3.83 (CH₃N), 7.3-7.9 m (H^{1,5,6,7}, Ph), 7.99 d (H⁸), 9.08 (H⁴).

The introduction of KOH, CuCl or $CuC \equiv CPh$ to the reaction mixture or the replacement of pyridine by toluene did not affect the result of the reaction.

<u>2-Butyl-9-methyl- γ -carboline (IVa)</u>. A sample of 3.5 g (2.3 ml) PCl₃ was added to 3.1 g (IIa) in 40 ml CHCl₃ at 0-3°C, heated at reflux for 135 min and poured into ice water. The mixture was made basic with

aqueous NaOH. The organic layer was separated and the aqueous layer was extracted with CHCl₃. The chloroform solution was dried over Na₂SO₄. Recrystallization from hexane gave 2.1 g (72.5%) (IVa), mp 68-69°C. Found: C 80.62; H 7.72; N 11.78%. Calculated for $C_{16}H_{18}N_2$: C 80.63; H 7.61; N 11.75%. PMR spectrum (δ , ppm): 0.96 t (CH₃-C), 1.43 sext (γ -CH₂), 1.80 q (β -CH₂), 2.95 t (α -CH₂), 3.79 (CH₃N), 7.11 (H¹), 7.3-7.5 m (H⁵⁻⁷), 8.10 d (H⁸), 9.19 (H⁴).

Analogous preparations were carried out for: (IVb), 62.8% yield, mp 114-115°C (from 1:2 benzene – hexane). Found: C 72.47; H 6.60; N 15.05%. Calculated for $C_{17}H_{19}N_3O$: C 72.57; H 6.81; N 14.93%. PMR spectrum (δ , ppm): 2.57 t (CH₂NCH₂), 3.76 t (CH₂OCH₂), 3.81 (\supset CH₂N), 3.84 (CH₃N), 7.3-7.5 m (H^{1,5-7}), 8.12 d (H⁸), 9.22 (H⁴). (IVc), 62.1% yield, mp 106-107° (from hexane). Found: C 83.59; H 5.67; N 11.00%. Calculated for $C_{18}H_{14}N_2$: C 83.69; H 5.46; N 10.84%. PMR spectrum (δ , ppm): 3.85 (CH₃N), 7.3-8.1 m (H^{1,5-7}, Ph), 8.15 d (H⁸), 9.34 (H⁴).

CONCLUSIONS

3-Formyl-2-acetylenyl-1-methylindole oximes readily undergo intramolecular heterocyclization with closure of a pyridine ring and formation of substituted γ -carboline N-oxides.

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REACTIONS OF 15-CROWN-5 AND BIS-15-CROWN-5 ETHERS WITH METAL ACETYLACETONATE IONS IN THE GAS PHASE

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The composition and stability of complexes of crown ethers with metal ions in solution are determined to a significant extent by the nature of the solvent [1]. The reactivity of the macroring may be evaluated independently by carrying out the complexation in the gas phase in the absence of solvent by mass spectrometric methods. In our previous work [2, 3], we showed that 18-crown-6 and macrocyclic thiourea derivatives in the gas phase form 1:1 complexes with Group III elements. In the present work, we studied the gas-phase complexation reactions between 15-crown-5 (L^1) and bis-15-crown-5 (L^2) and cations containing transition metals, Group III metals, and rare-earth elements



Acetylacetonate complexes $(acac)_n M$, where M = Co (n = 3), Fe (n = 3), Cr (n = 3), Ni (n = 2), Mn (n = 2), Ga (n = 3), In (n = 3), Nd (n = 3) were used as the sources of metal-containing cations. The electron impact * Deceased.

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