Cyclization of \( N \)-acetyl-ortho-cycloalkenylanilines on treatment with bromine and \( N \)-bromosuccinimide

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The reaction of \( N \)-acetyl-2-(cyclohex-1'-enyl)aniline with \( \text{Br}_2 \) or \( \text{N-bromosuccinimide} \) at 20 °C is accompanied by intramolecular cyclization to give brominated 3,1-benzoxazines or 4-acetyl-(3-bromo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[\( b \)]indole).

Key words: 2-(cyclohex-1'-enyl)aniline, \( N \)-acetyl-2-(cyclohex-1'-enyl)aniline, 2'-bromo-2-methylspiro[(4H-3,1-benzoxazine)-4.1'-cyclohexane], \( N \)-acetyl-2-(cyclopent-2'-en-1'-yl)-2-methylaniline, \( N \)-bromosuccinimide, intramolecular cyclization, 4-acetyl-(3-bromo-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[\( b \)]indole).

To continue our research\(^1,2\) dealing with heterocyclization of ortho-alkenylarylamines, we studied the reaction of their acetyl derivatives with molecular bromine and \( N \)-bromosuccinimide. Previously, it has been reported\(^1\) that 3,1-benzoxazine is formed on bubbling of gaseous HCl into a solution of \( N \)-acetyl-2-(cyclopent-1'-en-1'-yl)-6-methylaniline (1) in \( \text{CH}_2\text{Cl}_2 \) and that 2-(cyclopent-2'-en-1'-yl)-6-methylaniline hydrochloride (2) undergoes cyclization\(^2\) at 200 °C to give 8-methylperhydrocyclopenta[\( b \)]indole. Both reactions afford compounds containing no functional groups in the side chains of the heterocycles.

In this study, we extended for the first time the known halocyclization reaction\(^3\) to derivatives of ortho-alkenylarylamines,\(^4\) in order to open a way to bromine-substituted benzoxazines and indolines. Thus, the addition of a \( \text{CCl}_4 \) solution of \( \text{Br}_2 \) at 20 °C to a \( \text{CCl}_4 \) solution of \( N \)-acetyl-2-(cyclohex-1'-enyl)aniline (3), prepared from amine 4 by a procedure described previously,\(^1\) gives rise to 3,1-benzoxazine hydrobromide 5 (Scheme 1), whose treatment with a 10% solution of \( \text{NaHCO}_3 \) affords base 6 (yield 97%). It is known that halogenation of amido-derivatives of cyclohexene\(^5\) and related six-membered rings\(^6,7\) yields heterocycles with the trans-arrangement of the halogen and oxygen atoms. Apparently, in the benzoxazine that we prepared, these atoms are also arranged in this way.

Intramolecular cyclization of acetanilide 7 on treatment with NBS in \( \text{CCl}_4 \) gives indoline 8 in a high yield (Scheme 2), whereas the reaction of compound 7 with molecular bromine in \( \text{CCl}_4 \) affords isomeric dibromides 9 and 10 in 1:1 ratio (according to \( ^{1} \text{H} \) and \( ^{13} \text{C} \) NMR spectra).

In the \(^{1} \text{H} \) NMR spectrum of indoline 8 recorded using the double resonance method, the H(3a) proton is exhibited at \( \delta \) 4.92 as a doublet of doublets with

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J_{\text{H(3a),H(5b)}} = 7.99 \text{ Hz}, \text{ pointing to the cis-arrangement of the H(3a) and H(5b) atoms; the low value of the vicinal constant, } J_{\text{H(3a),H(2)}} = 2.33 \text{ Hz, attests to the trans-orientation of the H(3a) and H(3) protons.}^8 \text{ The substituents at the C(1') and C(2') atoms of the cyclopentyl fragment in molecule 9 occupy trans-positions; the conformation with the pseudoaxial orientation of substituents predominates, and the H(1') and H(2') protons are pseudoequatorial. This is indicated by the small spin–spin coupling constant of the H(2') proton (a narrow multiplet at 4.74 ppm).}^9,10 \text{ In addition, apparently, due to the cis-effect of the electron-withdrawing substituents on the H(1') and H(2') protons in compound 9, the signals of these protons occur in a low field (4.02 and 4.74 ppm, respectively), whereas similar protons in compound 10 are manifested in a higher field (3.55 and 4.68 ppm, respectively). The substituents at}}

the C(1') and C(2') atoms in molecule 10 are cis-arranged and the spin-spin coupling constants should be medium (4.5–6.5 Hz), which is actually observed for the H(2') proton in the 1H NMR spectra (6.08 Hz). 9,10

Experimental

1H and 13C NMR spectra were recorded on a Bruker AM-300 instrument (300 and 75 MHz, respectively). IR spectra were measured on a UR-20 instrument. Mass spectra were run on a MX 1320 mass spectrometer (El, 70 eV). The purity of the product was measured on a UR-20 instrument. Mass spectra were run on a PYE UNICAM spectrometer with an El source (70 eV).

2-Bromo-2-methylcyclo[(4H-3,1-benzoxazine)-4,1'-cyclohexane] hydrobromide (5). A solution of Br2 (0.1 m, 1.9 mmol) in 5 mL of CC14 was added dropwise with stirring to a solution of compound 3 (0.4 g, 1.86 mmol) in 20 mL of dry CC14. The hydrobromide precipitate was filtered off and washed with 10 mL of CC14. Yield 0.65 g (94%), m.p. 165–167°C. Found (%): C, 44.59; H, 4.31; Br, 42.40; N, 3.50. 

1H NMR (CDCl3, 300 MHz): δ: 2.07 (s, 3 H, Me); 1.66–2.37 (m, 8 H, 4 CH2); 5.76 (m, 1 H, CH); 7.00–7.20 (m, 3 H, Ar). 13C NMR (CDCl3, 75 MHz): δ: 20.94 (C(2')); 23.87 (Me); 29.30 (C(3')); 30.89 (C(1)); 34.83 (C(2')); 45.39 (C(8b)); 55.50 (C(3)); 74.76 (C(3a)); 121.09, 121.71, 128.26, 130.33, 136.17, 140.50 (C arom.); 169.60 (C=O).

A mixture of 1(3'S,2'S,3'R,5') and 1(3'R,2'R,3'S,5')-N-acetyl-2-(3,3'-dibromocyclo-1'-yl)-6-methylanilines (9 and 10). A solution of Br2 (0.1 mL, 1.9 mmol) in 15 mL of CC14 was added dropwise with stirring using a magnetic stirrer to a solution of anilide 7 (2.15 g, 10 mmol) in 30 mL of CC14. The mixture was stirred for an additional 1 h, diluted with 50 mL of CC14, and filtered. The filtrate was washed with 20 mL of 10% NaHCO3 and concentrated under reduced pressure to give 3.5 g (93%) of a mixture of isomers 9 and 10 as an oil. Yield 0.61 g (91%) of indoline 8, Rf 0.67. Found (%): C, 44.55; H, 4.39; Br, 42.29; N, 3.73. IH NMR (CDCl3, 600 MHz): δ: 1.60–2.70 (m, 8 H, 4 CH2); 2.20 (s, 3 H, Me); 2.39 (s, 3 H, Me); 4.04 (t, 1 H, H(3b), J = 7.99 Hz); 4.27 (t, 1 H, H(3a), J = 7.99 Hz); 4.92 (dd, 1 H, H(3a), JH(3a),H(3b)= 7.99 Hz); 6.95–7.30 (m, 3 H, Ar). 13C NMR (CDCl3, 150 MHz): δ: 20.94 (C(2')); 23.87 (Me); 29.30 (C(3')); 30.89 (C(1)); 34.83 (C(2')); 45.39 (C(8b)); 55.50 (C(3)); 74.76 (C(3a)); 121.09, 121.71, 128.26, 130.33, 136.17, 140.50 (C arom.).

MS, m/z: 294 [M]+. A mixture of 1(3'S,2'S,3'R,5') and 1(3'R,2'R,3'S,5')-N-acetyl-2-(3,3'-dibromocyclo-1'-yl)-6-methylanilines (9 and 10). A solution of Br2 (0.1 mL, 1.9 mmol) in 15 mL of CC14 was added dropwise with stirring using a magnetic stirrer to a solution of anilide 7 (2.15 g, 10 mmol) in 30 mL of CC14. The mixture was stirred for an additional 1 h, diluted with 50 mL of CC14, and filtered. The filtrate was washed with 20 mL of 10% NaHCO3 and concentrated under reduced pressure to give 3.5 g (93%) of a mixture of isomers 9 and 10 as an oil. Found (%): C, 44.55; H, 4.39; Br, 42.29; N,