AN UNEXPECTED SYNTHESIS OF 1,5,5-TRISUBSTITUTED 3,4-DIBROMO-3-PYRROLIN-2-ONES FROM AN OPEN-CHAIN TAUTOMER γ-KETOAMIDE

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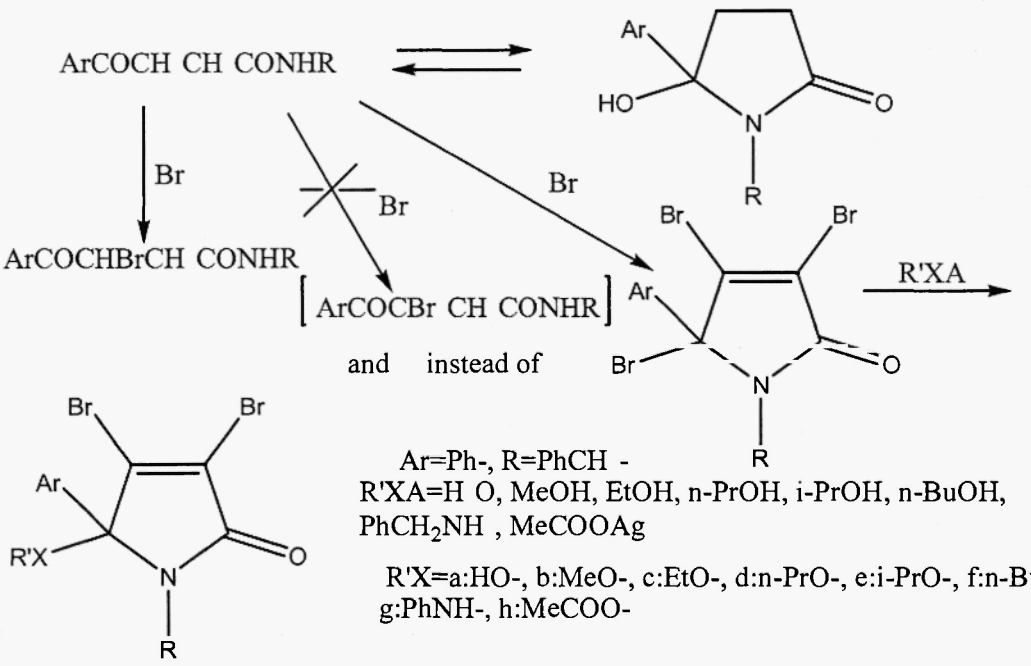
Abstract : The unexpected synthesis of 1,5,5-trisubstituted 3,4-dibromo-3-pyrrolin-2-ones **6**, from the reaction of the 1-benzyl-5-phenyl-3,4,5-tribromo-3-pyrrolin-2-one **5**, resulting from the reaction of 3-benzoylpropionamide **1** using a threefold excess of bromine, with different nucleophiles, is described.

The γ-butyrolactam skeleton exists throughout nature and is present in many bioactive natural products.[1] It also serves as a key intermediate in the synthesis of biologically and pharmaceutically useful molecules.[1] As far as compounds with herbicidal characteristics are concerned, exhibited remarkable bio-activity, at extremely low doses.[2] Especially, mono- and polybrominated pyrrolinones were described` as tolerated to marine antibiotics. Furthermore 2,3,4-trisustituted brominated pyrroles have demonstrated potent cytotoxicity[4] against leukemia and lymphomas.

On the basis of structural analogies of the above reported structures to the refered herein, additional to the convenience of the preparation method, probably these substituted 3,4-dibromo-3-pyrrolin-2-ones must be considered to be of interest as potential prodrugs, or other syntheses.

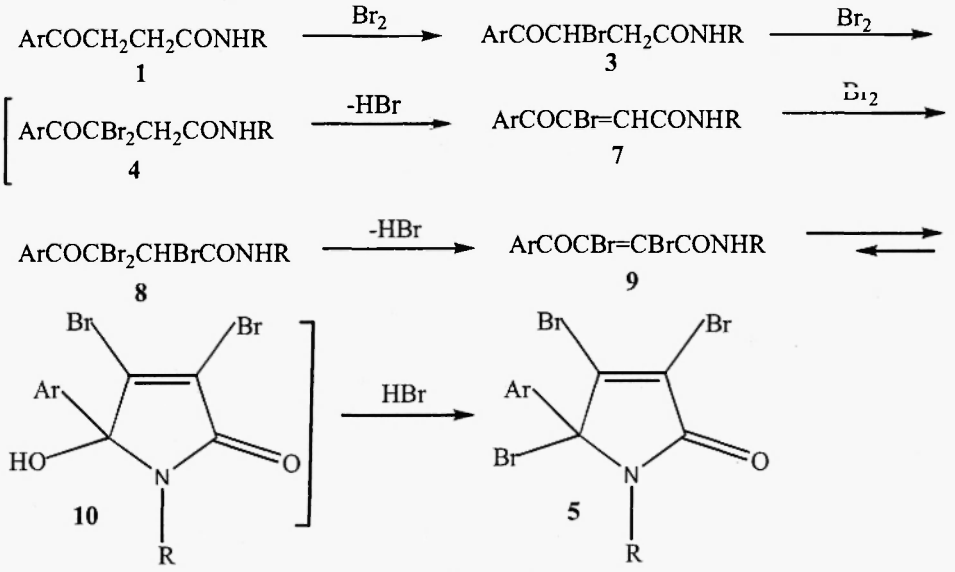


Scheme-1

Herein, we wish to report our preliminary results on the synthesis of 1,5,5-trisubstituted 3,4-dibromo-3-pyrrolin-2-ones **6**, which were prepared starting from a simple bromination reaction of N-benzyl 3-benzoylpropionamide[5] **1** afforded the very reactive bromide[6] **5**, and then on reaction with different nucleophiles (e.g. water,[7] alcohols,[8] amines,[9] carboxylic acid salts[10]).

γ-Keto amides of the general formula **1** are known[11,12] to exhibit ring-chain tautomerism, (Scheme 1), addionally substituted γ-ketopropionamides on methylene

carbons just as 3-aroylacrylamides have been shown[13,14] to favor the cyclic tautomeric form **2**. In a recent work[5] we prepared the N-benzyl 3-benzoyl-3-bromopropionamide[5] **3** with a simple bromination reaction of the corresponding 3-benzoylpropionamide **1**, its structure was determined (spectroscopically) as the open-chain tautomer. Now in a reaction on the same γ-keto amide using a twofold of bromine, a mixture of the β-bromo-γ-keto amide **3** and the tribromopyrrolinone **5** was detected (TLC, NMR). This reaction was made in an attempt to prepare the β,β-dibromo-γ-keto amide **4**, but the result has shown that after monobromination reaction and prior the quantitative β-dibromination, a faster reaction takes place to the direction of tribromopyrrolinone **5**, (Scheme 2). On the basis of this result we used a third mol of



Scheme-1

bromine in order to drive the reaction to the tribromopyrrolinone **5**, so the quantitative transformation to the product **5** was succeded. A probable mechanism was proposed (Scheme 2), including successive brominations (substitutions and additions) and dehydrobrominations, it must be pointed out that after the monobromination step, the intermediate γ-keto amides **4**, **7**, **8** and **9** could exist as cyclic tautomers, in analogy to disubstituted γ-keto amides[13] and γ-aroylacrylamides,[14] just as the substitution of the C5 OH, of intermediate **10**, by bromine could be possible on every earlier step in which a 5-hydroxy(pyrrolin- or pyrrolidin-)-2-one, cyclic tautomers of the γ-keto amides **4**, **7**, **8**, could occurr. The bromination-dehydrobromination steps could take place on these cyclic tautomers, as well.

The magnetic non equivalency of N-benzyl methylene protons just as the α-methylene protons to C-5 oxygen or nitrogen of the products **6**, must be explained because of hindered rotation of these protons.

In conclusion, the reaction of the N-benzyl 3-benzoylpropionamide **1** using a threefold of bromine afforded the 1-benzyl-5-phenyl-3,4,5-tribromo-3-pyrrolin-2-one **5** and the subsequent reaction of the later with some nucleophiles gave the corresponding 5-substituted pyrrolinones **6**. The application of the method to other open-chain tautomers of 3-aroylpropionamides, as well as the use of other nucleophiles, is in our immediate plan.

References and Notes

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6. 1-Benzyl-5-phenyl-3,4,5-tribromo-3-pyrrolin-2-one **5**: a mixture of the keto amide **1** 1.74 g (6.50 mmol) in 15 ml of carbon tetrachloride and bromine 1 ml (19.50 mmol) was refluxed, under stirring, for 60 min. The resulting colorless solution was concentrated under vacuum to a light blue retinous mass. After trituration of the retinous residue with diethyl ether, the solid was recrystallized from dry benzene to give an analytical sample of product **5**, 1.85 g, yield 70%, mp 172-173 ^{0}C. Anal. Calcd for $C_{17}H_{12}Br_3NO$: C, 42.01; H, 2.49; Br, 49.32; N, 2.89. Found: C, 41.78; H, 2.30; Br, 49.11; N, 2.75. IR (Nujol mull, cm^{-1}): 1707, 1690, 1620, 1507. ^{1}H NMR ($CDCl_3$): δ 4.27 and 5.10 (two d, J=15 Hz, 2H, -CH_2Ph), 7.25-8.03 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 44.46, 93.80, 120.98, 126.64, 127.70, 128.60, 128.98, 129.22, 129.60, 134.80, 137.24, 145.52, 164.45.
7. 1-Benzyl-3,4-dibromo-5-hydroxy-5-phenyl-3-pyrrolin-2-one **6a**: a mixture of keto amide **1** 1.74 g (6.50 mmol) in 15 ml of glacial acetic acid and bromine 1 ml (19.50 mmol) was heated under stirring on an steam bath for 20 min. The resulting solution after cooling to room temperature was added to 75 ml of ice-water under stirring. The precipitated solid was filtered and washed with water, after recrystallization from ethanol an analytical sample of the product **6a** was separated: 1.90 g, yield 69%, mp 155-156 ^{0}C. Anal. Calcd for $C_{17}H_{13}Br_2NO_2$: C, 48.26; H, 3.10, Br, 37.77; N, 3.31. Found: C, 48.25; H, 3.11; Br, 37.52; N, 3.23. IR (Nujol mull, cm^{-1}): 3270, 1702, 1685, 1615, 1502. ^{1}H NMR ($CDCl_3$): 3.78 (s, 1H, -OH, exchangeable), 4.10 and 4.70 (two d, J=15 Hz, 2H, -CH_2Ph), 7.20 and 7.37 (two s, 10H, arom.). ^{13}C NMR (CDCl3): 44.67, 93.80, 121.21, 126.62, 126.80, 127.80, 128.45, 128.65, 129.06, 129.19, 134.74, 137.32, 145.35,164.28.
8. General procedure for the preparation of pyrrolinones **6b-f:** Following the procedure for the preparation of the tribromopyrrolinone **5** till the step of the concentration of the reaction's mixture. The reaction's concentrated residue was refluxed with 6 ml of the appropriate alcohol for 15 min. After cooling of the solution the crystallized solid was filtered and washed with diethyl ether. Recrystallization from the suitable solvent an analytical sample of the ether **6** was obtained. 1-Benzyl-3,4-dibromo-5-methoxy-5-phenyl-3-pyrrolin-2-one **6b**: yield 67%, mp 116-117 ^{0}C (MeOH). Anal. Calcd for $C_{18}H_{15}Br_2NO_2$: C, 49.46; H, 3.46; Br, 36.56; N, 3.20. Found: C, 49.58; H, 3.37; Br, 36.37; N, 3.19. IR (Nujol mull, cm^{-1}): 1714, 1618, 1502. ^{1}H NMR ($CDCl_3$): δ 2.87 (s, 3H, -OCH_3), 3.95 and 4.68 (two d, J=15 Hz, 2H, -CH_2Ph), 7.28 and 7.43 (two s, 10H, arom.). ^{13}C NMR ($CDCl_3$): 44.71, 49.73, 96.37, 119.61, 126.77, 127.39, 128.43, 129.11, 129.54, 129.61, 135.23, 136.91, 142.11, 164.37. 1-Benzyl-3,4-dibromo-5-ethoxy-5-phenyl-3-pyrrolin-2-one **6c**: yield 79%, mp 150-151 ^{0}C (EtOH). Anal. Calcd for $C_{19}H_{17}Br_2NO_2$: C, 50.58; H, 3.80; Br, 35.42; N, 3.10. Found: C, 50.34; H, 3.72; Br, 35.32; N, 3.09. IR (Nujol mull, cm^{-1}): 1710, 1613, 1495. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J=7 Hz, 3H, CH_3-), 2.68-3.45 (m, 2H, -CH_2-), 3.85-4.72 (two d, J=15 Hz, 2H, -CH_2Ph), 7.25 and 7.40 (two s, 10H, arom.). ^{13}C NMR ($CDCl_3$): 14.12, 44.79, 58.96, 97.48, 121.97, 126.77, 127.84, 128.56, 129.02, 129.62, 129.65, 135.17, 136.97, 142.96,164.54. 1-Benzyl-3,4-dibromo-5-phenyl-5-n-propyloxy-3-pyrrolin-2-one **6d**: yield 67%, mp 96-97 ^{0}C (EtOH). Anal. Calcd for $C_{20}H_{19}Br_2NO_2$: C, 51.64; H, 4.12; Br, 34.35; N, 3.01. Found: C, 51.39; H, 3.98; Br, 34.47; N, 3.11. IR (Nujol mull, cm^{-1}): 1713, 1616, 1498. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J=7.2 Hz, 3H, CH_3-), 1.15-1.40 (m, 2H, -CH_2-), 2.71-3.04 (m, 2H, -CH_2O-), 3.87 and 4.69 (two d, J=15.3 Hz, 2H, -CH_2Ph), 7.17-7.35 (m, 10H,

arom.). ^{13}C NMR ($CDCl_3$): 10.57, 22.13, 44.79, 64.79, 97.36, 121.97, 126.76, 127.80, 128.50, 129.00, 129.58, 129.66, 135.28, 136.93, 142.98, 164.58. 1-Benzyl-3,4-dibromo-5-phenyl-5-i-propyloxy-3-pyrrolin -2-one **6e**: yield 68%, mp 120-122 ^{0}C (EtOH). Anal. Calcd for $C_{20}H_{19}Br_2NO_2$: C, 51.64; H, 4.12; Br, 34.35; N, 3.01. Found: C, 51.55; H, 4.08; Br, 34.17; N, 3.21. IR (Nujol mull, cm^{-1}): 1712, 1610, 1495. ^{1}H NMR ($CDCl_3$): 1.03 and 1.27 (two d, J=6.3 Hz, 6H, two CH_3-), 3.76 (septet, J=6.3 Hz, 1H, >CH-), 4.20 and 4.48 (two d, J=16.5 Hz, 2H, -CH_2Ph), 6.93-7.21 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 23.48, 24.12, 45.05, 67.88, 97.08, 122.26, 126.89, 127.46, 128.26, 128.55, 129.24, 129.45, 135.58, 136.89, 143.50, 164.68. 1-Benzyl-5-n-butyloxy-3,4-dibromo-5-phenyl-3-pyrrolin-2-one **6f**: yield 70%, mp 69-71 ^{0}C (EtOH). Anal. Calcd for $C_{21}H_{21}Br_2NO_2$: C, 52.63; H, 4.42; Br, 33.35; N, 2.92. Found: C, 52.41; H, 4.19; Br, 33.47; N, 3.11. IR (Nujol mull, cm^{-1}): 1728, 1612 and 1495. ^{1}H NMR ($CDCl_3$): 0.82 (t, J=7.5 Hz, 3H, CH_3-), 1.05-1.39 (m, 4H, -CH_2CH_2-), 2.77-2.84 and 3.02-3.09 (two set of m, 2H, -CH_2O-), 3.86-4.69 (two d, J=14.7 Hz, 2H, -CH_2Ph), 7.19-7.35 (m, 10H, arom.). ^{13}C NMR ($CDCl_3$): 13.90, 19.26, 30.84, 44.72, 63.00, 97.33, 121.88, 126.69, 127.74, 128.46, 128.94, 129.52, 129.59, 135.20, 136.88, 142.92, 164.50.

9. 1-Benzyl-5-benzylamino-3,4-dibromo-5-phenyl-3-pyrrolin-2-one **6g**: The reaction's concentrated residue, from the preparation procedure of the tribromopyrrolinone **5**, corresponding to 6.5 mmol of the tribromopyrrolinone **5** dissolved in 30 ml of dry diethyl ether and 1.5 ml (13.74 mmol) of benzylamine was added, after 30 min of stirring 30 ml of water was added to the mixture. The organic layer was washed sometimes with water, dried and concentrated to give a solid residue, which proved to be almost pure (^{1}H NMR) compound **6g**. Recrystallization from ethanol gave a yellow analytically pure crystalline solid, 2.33 g, (yield 70%), mp 156-158 ^{0}C. Anal. Calcd for $C_{24}H_{20}Br_2N_2O$: C, 56.27; H, 3.93; Br, 31.20; N, 5.47. Found: C, 56.49; H, 3.85; Br, 30.93; N, 5.32. IR (Nujol mull, cm^{-1}): 3360, 1723, 1617, 1505. ^{1}H NMR ($CDCl_3$): 2.03 (t, J=7 Hz, 1H, >NH, exchangeable), 2.73-3.55 (m, 2H, >NCH_2Ph), 3.88 and 4.95 (two d, J=15 Hz, 2H, -CH_2Ph), 6.82-7.53 (m, 15H, arom.). ^{13}C NMR ($CDCl_3$): 44.91, 51.11, 94.56, 121.78, 126.63, 127.43, 128.51, 128.87, 129.35, 135.47, 142.80, 164.60.

10. 5-Acetoxy-1-benzyl-3,4-dibromo-5-phenyl-3-pyrrolin-2-one **6h**: Following the procedure for the preparation of the tribromopyrrolinone **5** till the step of the concentration of the reaction's mixture. The reaction's concentrated residue corresponding to 6.5 mmol of the tribromopyrrolinone **5** dissolved in 20 ml of dry tetrahydrofuran, to the solution 1.2 g (7 mmol) of silver acetate were added and the mixture was stirred for 24 h at room temperature. The precipitated solid was filtered, the filtrate was partially concentrated and diluted with diethyl ether, after cooling the crystallized solid was filtered and recrystallized from ethyl acetate to give an analytical pure sample of the acetoxyderivative **6h:** yield 64%, mp 144-146 ^{0}C. Anal. Calcd for $C_{19}H_{15}Br_2NO_3$: C,49.06; H, 3.25; Br, 34.35; N, 3.01. Found: C, 48.93; H, 3.11; Br, 34.49; N, 2.87. IR Nujol mull, cm^{-1}): 1788, 1710, 1612, 1495. ^{1}H NMR ($CDCl_3$): 1.45 (s, 3H, CH_3-), 3.66 and 5.13 (two d, J=15.3 Hz, 2H, -CH_2Ph), 7.14-7.48 (m, 10H, arom.). ^{13}C NMR (CDCl3): 20.16, 44.70, 95.16, 121.23, 126.27, 126.64, 127.90, 128.80, 129.10, 129.23, 129.53, 130.25, 133.57, 136.47, 142.13, 164.93, 167.50.

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