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Pyrrolo[2,1-c][1,4]Benzodiazepines : A Mild Conversion of Thiolactam into amidine.

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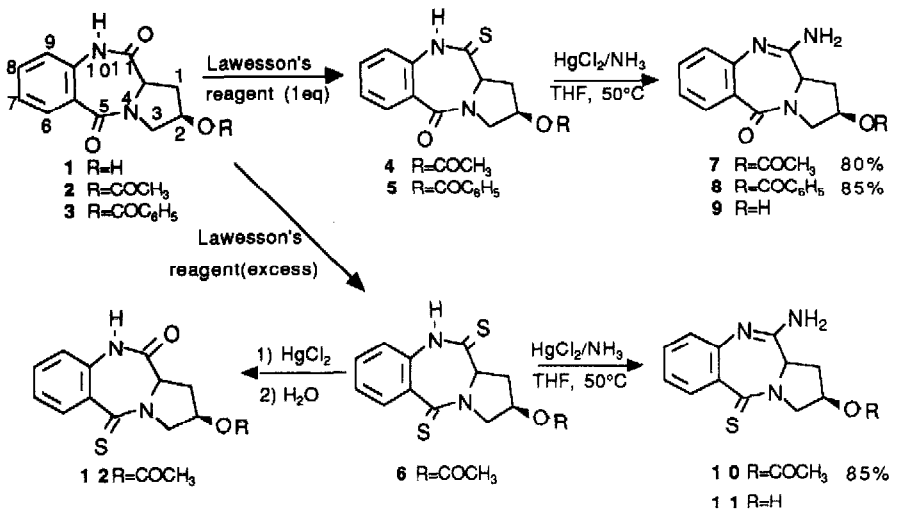
Key Words : Pyrrolo[2,1-c][1,4]Benzodiazepines; Thiolactam; Mercuric chloride; Amidine

Abstract : Reaction of 2-hydroxy pyrrolo [2,1-c] [1,4] benzodiazepines-5-one-11-thione or 5,11-dithiones with ammonia in presence of mercuric chloride affords new amidines in high yield.

The pyrrolo[2,1-c][1,4]benzodiazepines (PBD) such as anthramycin, tomaymycin, neothramycins A and B are thought to exert their antitumor activity[1] through a covalent binding via an aminal linkage from the electrophilic carbinolamine-bearing C-11 position to an N-2 of guanine within the minor grove of DNA[2]. In view of the importance of the carbinolamine functionality, we were interested in developing strategies for the synthesis of new PBD N-10 C-11 amidine derivatives. Although several groups had demonstrated the lack of reactivity of the N-10 C-11 lactam moiety of PBD[3] it can be easily converted into thiolactam which appears to be more reactive[4]. So, during the course of our study, we have found that N-10 C-11 thiolactam exhibits a great reactivity towards ammonia in the presence of mercuric chloride to give the new corresponding amidine. Mercuric or silver salts are known to favour this kind of reaction[5].



The precursors **2** and **3** were respectively prepared by esterification with acetic anhydride or benzoyl chloride of 2-hydroxy pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione **1** which in turn was synthesized by condensation of isatoic anhydride with trans-4-hydroxy-L-proline in boiling dimethylsulfoxide. The thiolactams **4**, **5** and the dithiolactam **6** were then obtained by thionation of **2** or **3** with respectively one or two equivalents of Lawesson's reagent in refluxing 1,4-dioxane[6]. Then, a solution of **4**, **5**, **6** in dry THF was warmed to 55°C, an ammonia stream was bubbled in the solution and finally 1.5 equivalent of mercuric chloride was added in one portion. After a few minutes the solution became black (formation of mercuric sulfide), the stream of ammonia was stopped after five minutes and the reaction mixture was stirred for one hour. Mercuric sulfide was filtered off, THF was rotoevaporated to dryness and the solid residue was washed with water and dried to give the amidines **7**, **8**, **10** in high yield (> 80%). It must be pointed out that in compound **6** only thiolactam N-10 C-11 is reactive. Ammonia is unreactive if mercuric chloride is added first. In this case, the reaction produces a mercury salt of PBD unable to react with ammonia. Starting with **6**, this salt conducts to the yet unknown 5-thioxo N-10 C-11 lactam **12** in boiling water. Finally, the 2-hydroxy group is recovered by treating acetoxy or benzoyloxy derivatives **7**,**8**,**10** with potassium carbonate in hot methanol to give 2-hydroxyamidines **9** and **11**.

IR, NMR and mass spectrum data are in agreement with all the proposed structures[7].

In conclusion, this conversion is an important key-step for the synthesis of new 11-amino derivatives of pyrrolo[2,1-c][1,4]benzodiazepines and extension of this reaction to primary amines is actually under development.

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7. For example : **7**: m.p;158°C.(diethyl ether / petroleum ether) ; IR (KBr) 3400, 3160, 1725, 1650, 1620, 1580, 1450, 1230 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 7.71, 1H, H-6; 7.36, 1H, H-7; 6.97, 2H, H-8 H-9; 5.27, 1H, H-2; 4.03, 1H, H-11a; 3.70, 2H, H-3a H-3b; 2.72, 1H, H-1a; 2.50 (exchangeable), 2H,NH_2; 2.28, 1H, H-1b; 2.04, 3H, CH_3.

10: m.p.182°C (diethyl ether) ; IR (KBr) 3405, 3160, 1730, 1650, 1580, 1460, 1230 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 8.17, 1H, H-6; 7.56, 1H, H-7; 7.20, 1H, H-8; 7.12, 1H, H-9; 5.50, 1H, H-2; 4,45,1H, H-11a; 4.30, 1H, H-3a; 4.00, 1H, H-3b; 3.50 (exchangeable), 2H, NH_2; 3.04, 1H, H-1a; 2.50, 1H, H-1b; 2.18, 3H, CH_3;

12: m.p.234°C (H_2O) ; IR (KBr) 3240, 1720, 1690, 1480, 1350, 1240 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ 10.80 (exchangeable), 1H, N-11; 8.07, 1H, H-6; 7.51, 1H,H-7; 7.24, 1H, H-8; 7.10, 1H,H-9; 5.29, 1H, H-2; 4.54, 1H, H-11a; 4.11, 2H, H-3a H-3b; 3.03, 1H, H-1a; 2.23, 1H, H-1b; 2.03, 3H,CH_3.

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