SYNTHESIS OF ISOMERIC PYRIDO-PYRROLO[1,2-a]PYRIMIDINES

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Abstract - 5-Oxo derivatives of three new isomeric pyridopyrrolo[1,2-a]pyrimidines were synthesized from the corresponding carbalkoxy 2- or 3-[N-pyrrolo]pyridines. These were transformed into the corresponding hydrazides and further to acylazides which decomposed into acylnitrenes followed by insertion into C-H bond with ring closure.

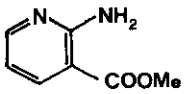
Our recent interest in pyridopyrimidines[1-4] stimulated our interest in extending investigations on some related systems. Our previous attempt to prepare a pyridopyrrolopyrimidine derivative failed.[4] Treatment of the ester 2 (R = OMe) with polyphosphoric acid resulted only in destruction of the pyrrole ring although a similar synthetic approach was reported to be successful in the mitomycin series.[5-7]

Therefore, we have considered other synthetic approaches and a feasible one should involve ring closure to the pyrrole part by generating an acylnitrene from the corresponding acyl azides. A variety of reactions involving carbonyl nitrenes are described [8] and acylnitrene cyclizations with insertion into C-H bonds were used for the syntheses of many new systems.[9]

3-Carbomethoxy-2-[N-pyrrolo]pyridine (2, R = OMe) was prepared from (1) and 2,5-diethoxytetrahydrofuran as described previously.[4] In a similar manner were synthesized in 40-65% yield the isomeric 2-carbethoxy- (4, R = OEt) (bp 170°/10 mm Hg) and 4-carbethoxy-3-[N-pyrrolo]pyridine (6, R = OEt) (bp 165°/10 mm Hg) or 3-carbethoxy-4-[N-pyrrolo]pyridine (8, R = OEt) (bp 170°/11 mm Hg). These esters were transformed into the corresponding hydrazides in 68-80% yield upon heating in an ethanolic solution of hydrazine hydrate for 30 minutes. In this manner were obtained compound 2 (R = $NHNH_2$), mp 191-193° (from ethanol); m/e 202 (M^+) and nmr δ (DMSO-d_6) 7.90 (dd, H_4), 7.38 (dd, H_5), 8.60 (dd, H_6), 7.35 (m, $H_{2',5'}$), 6.28 (m, $H_{3',4'}$), $J_{4,5}$ = 7.2, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.5, $J_{2',3'}$ = $J_{2',4'}$ = 2.0 Hz; compound 4 (R = $NHNH_2$)

had mp 106-107° (from n-propanol); m/e 202 (M^+) and nmr δ ($CDCl_3$) 7.80 (dd, H_4), 7.58 (dd, H_5), 8.63 (dd, H_6), 6.93 (m, $H_{2',5'}$), 6.42 (m, $H_{3',4'}$), $J_{4,5}$ = 7.8, $J_{4,6}$ = 1.5, $J_{2',3'}$ = $J_{2',4'}$ = 2.0 Hz; compound 6 (R = $NHNH_2$), mp 124-125° (from n-propanol), m/e 202 (M^+) and nmr δ ($CDCl_3$) 8.75 (d, H_2), 7.65 (dd, H_5), 8.75 (d, H_6), 7.90 (m, $H_{2',5'}$), 6.43 (m, $H_{3',4'}$), $J_{5,6}$ = 4.8, $J_{2,5}$ = 0.6, $J_{2',3'}$ = $J_{2',4'}$ = 2.0 Hz.

Under the same reaction conditions the reaction with 8 (R = OEt) did not afford the corresponding hydrazide and instead pyrazolo[4,3-c]pyridine-3-one (9) was obtained in 91% yield, mp 295-298° (from water; lit. [10] gives mp 292-294°, but the compound is described in its tautomeric form as 3-hydroxy derivative); m/e 135 (M^+) and nmr δ (DMSO-d_6, 70°) 8.65 (s, H_4), 7.70 (d, H_6), 7.03 (d, H_7),



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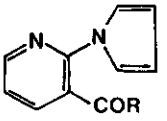

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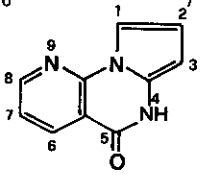

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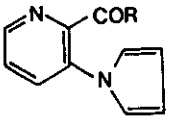

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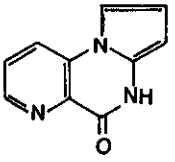

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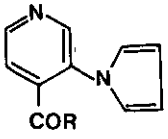

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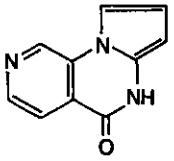

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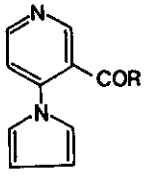

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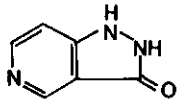

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$J_{6,7}$ = 6.5 Hz. Its formation can be explained by displacement of the pyrrole ring with hydrazine and subsequent cyclization. If the reaction was conducted at room temperature only the starting material was recovered.

If a solution of the hydrazide 2 (R = $NHNH_2$) in glacial acetic acid was treated with isoamyl nitrite at room temperature, the solution left aside for 5 hours, diluted with water and left on ice for several hours, a precipitate of pyrido[3,2-e]pyrrolo[1,2-a]pyrimidin-5-one (3) was obtained in 28 % yield, mp 292-293° (from ethyl acetate and n-hexane); m/e 185 (M^+) and δ nmr (DMSO-d_6, 130°) 8.13 (dd, H_1), 6.68 (dd, H_2), 7.13 (dd, H_3), 7.70 (dd, H_6), 7.33 (dd, H_7), 8.25 (dd, H_8), $J_{1,2}$ = 3.6, $J_{1,3}$ = 1.5, $J_{2,3}$ = 2.8, $J_{6,7}$ = 7.8, $J_{7,8}$ = 4.5, $J_{6,8}$ = 1.5 Hz.

In a similar manner the isomeric pyrido[2,3-e]pyrrolo[1,2-a]pyrimidin-5-one (5) was prepared from 4 (R = $NHNH_2$) in 22% yield, mp 300°; m/e 185 (M^+) and nmr δ (DMSO-d_6, 150°) 8.35 (dd, H_1), 6.75 (dd, H_2), 7.10 (dd, H_3), 8.15 (dd, H_7), 7.30 (dd, H_8), 8.45 (dd, H_9), $J_{1,2}$ = 3.6, $J_{1,3}$ = 1.5, $J_{2,3}$ = 2.8, $J_{7,8}$ = 4.5, $J_{7,9}$ = 1.5, $J_{8,9}$ = 7.5 Hz.

Compound 6 (R = $NHNH_2$) was treated in a similar manner, but at the end the reaction mixture was evaporated in vacuo almost to dryness to give pyrido[4,3-e]-pyrrolo[1,2-a]pyrimidin-5-one (7) in 14% yield, mp 291-293°; m/e 185 (M^+) and nmr δ (DMSO-d_6) 8.35 (dd, H_1), 6.75 (dd, H_2), 7.10 (dd, H_3), 7.25 (d, H_6), 8.40 (d,H_7), 9.40 (s, H_9), $J_{1,2}$ = 3.6, $J_{1,3}$ = 1.5, $J_{2,3}$ = 2.8, $J_{6,7}$ = 4.8 Hz. Thus, the above reactions have opened a new synthetic approach for the above mentioned tricyclic systems. Satisfactory analyses (C, H, N) were obtained for all compounds.

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