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ISOXAZOLO[3,4-*d*]PYRIDAZIN-7(6H)-ONES. SYNTHESIS OF 3-UNSUBSTITUTED DERIVATIVES: A REINVESTIGATION

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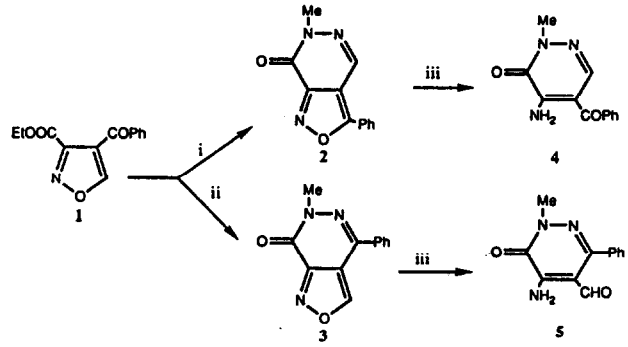
Abstract: The structure of the major product from 1 and methylhydrazine is established and a mechanism for the formation of 2 involving a preliminary nucleophilic attack at the isoxazole C-5 is proposed.

Key-words: 3-unsubstituted isoxazolo[3,4-d]pyridazinone; 4-unsubstituted isoxazolo[3,4-d]pyridazinone; reaction mechanism

In connection with our researches on the isoxazolo[3,4-*d*]pyridazin-7(6H)ones derivatives as useful intermediates to various functionalized nitrogen heterocycles (pyrazoles[1] , 1,2-diazepines[2] and pyridazines[3,4]),we became interested in the synthesis of some 3-unsubstituted compounds. Following the literature procedure [5] , we have found that the structure of 6-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin -7(6H)-one assigned in 1969 to the reaction product from the isoxazole **1** and methylhydrazine is incorrect. A re-examination of the reaction revealed that the major product (80%) in this condensation is the isomeric 6-methyl-3-phenylisoxazolo[3,4-*d*]pyridazin-7(6H)-one **2**, whereas the 4-phenyl derivative **3** can be obtained from the mother liquors (15%) or, as sole product (85%), carrying out the reaction in presence of polyphosphoric acid (PPA)[6].



i=$MeNHNH_2$; ii= $MeNHNH_2$, PPA ; iii= H_2, Pd/C

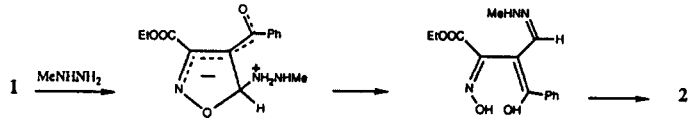
The spectroscopic properties of compounds **2** and **3** confirm these attributions[7]. In fact for compound **2** ^{1}H-NMR shows a signal at 8.30 ppm for the 4 CH, in good agreement with the ^{1}H-NMR of similar unsubstituted pyridazinones[8] and ftalazinones[9,10].

MS spectra are also in agreement with the proposed structures, showing a strong peak for compound **2** at m/e 105, $[PhCO]^+$, which is typical of a 3-phenylisoxazole moiety[11] .

This peak is absent in the MS spectrum of **3** and also in a series of 4-phenylisoxazolopyridazinones studied for comparison, whereas this typical fragmentation appears in other 3-arylsubstituted isoxazolo[3,4-*d*] pyridazinones [12].

The catalytic hydrogenation of **2** and **3**, leading to 4-amino-5-benzoylpyridazinone **4** and 4-amino-5-formylpyridazinone **5**, respectively, confirms the structures of this isomeric pair[13].

The formation of compound **2** from **1** and $MeNHNH_2$ as main product can be rationalized on the basis of the preferential nucleophilic attack of the $MeNHNH_2$ at 5 position of the isoxazole ring of **1**,which is favoured by the presence of an electron -withdrawing CO group at position 4.



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This mechanism closely resembles the one reported for the conversion of isoxazoles into pyrazoles by means of hydrazine [14]. Nevertheless, the presence in the intermediate **7** of a ethoxycarbonyl group gives rise to pyridazine closure and consequent ring closure of the isoxazole ring.

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6) Compound **3** is prepared as follows: a mixture of **1** (4mmol), methylhydrazine (10mmol), PPA (10 g) and EtOH 95° (5ml) is stirred at 110°C for 0.5 h. The work-up of the mixture affords compound **3**, m.p. 214 °C from EtOH. Anal. for $C_{12}H_9N_3O_2$ Calcd: C= 63.43; H=3.99; N=18.49; Found: C= 63.51; H 4.; N=18.23.
7) ^1H and ^{13}C-NMR spectra are recorded on Gemini 200 spectrometer (in $CDCl_3$); MS spectra are obtained by a GC(Perkin -Elmer 8420)-MS(Perkin Elmer ITD) instrument.
2: ^1H-NMR: 3.80 (s,3H,NCH_3); 7.50-8.00(m, 5H,ArH_5);8.30 (s,1H,CH); - ^{13}C-NMR (DMSO-d_6): 39.1(6-CH_3); 110.5 (C-3a); 126.4 (C-ipso); 127.9 and 130.0(C-ortho and meta);132.0 (C-para);133.0 (C-4);150.0(C-7a);153.2 (C-7);168.0 (C-3); - MS, m/e (%): 227,M(58);228,M+1(34);170(25); 142(17) ;105(45) ;77(100); 51 (74);43(39).
3: IR 1680 cm-^{1} (CO); - ^1H-NMR: 3.90(s,3H,NCH_3) ;7.50-7.80(m,5H,ArH_5); 9.30 (s, 1H,CH); - ^{13}C-NMR : 39.5 (6-CH_3); 115.0(C-3a); 127.0 and 130.9 (C-ortho and meta) ; 131.8 (C-para) 134.0 (C-ipso) ; 141.2(C-4); 152.0(C-7) ; 153.8 (C-7a) ; 158.0(C-3); - MS, m/e (%):227, M (100); 228, M+1 (31);142(22); 128(19); 115(21); 101(20); 77(92) ;51(79) ;43(44).
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13) Compounds **4** and **5** are prepared as follows : a mixture of **2** or **3** (1mmol), EtOH 95° (50ml) and palladium on charcoal 10% (80 mg) was shaken under hydrogen at room temperature and 2 bar for 10-20 min. The work-up of the mixture affords **4** or **5**.
4 : yield 83% ; mp 141°C from EtOH ; IR (nujol): 3400-3280(NH_2) , 1670 and 1630 cm-^{1} (2xCO).^1H-NMR($CDCl_3$):3.78(s,3H,NCH_3),7.40-7.65(m,5H,ArH_5),7.80(s,1H,CH),8.80(ex. broad s.,2H,NH_2). Anal. for $C_{12}H_{11}N_3O_2$ Calcd: C= 62.87; H=4.84; N=18.33; Found: C=63.11; H=5.01; N=18.05.
5 : yield 78% ,mp 157-9°C from EtOH ; IR (nujol): 3400-3260,NH_2;1670 and 1650 cm-^{1}(2xCO) ; ^1H-NMR ($CDCl_3$); 3.80 (s, 3H, NCH_3) , 7.45 (s, 5H, ArH_5) , 9.10(ex. broad s., 2H,NH_2); 9.72 (s ,1H,CHO). Anal. for $C_{12}H_{11}N_3O_2$ Calcd: C= 62.87; H=4.84; N=18.33; Found: C=62.98 ; H=5.10; N=18.47.
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