

SYNTHESIS OF SOME PYRIMIDO[1,2-b]PYRIDAZIN-2- AND -4-ONES.

STUDIES ON PYRIDAZINE COMPOUNDS, XV¹.

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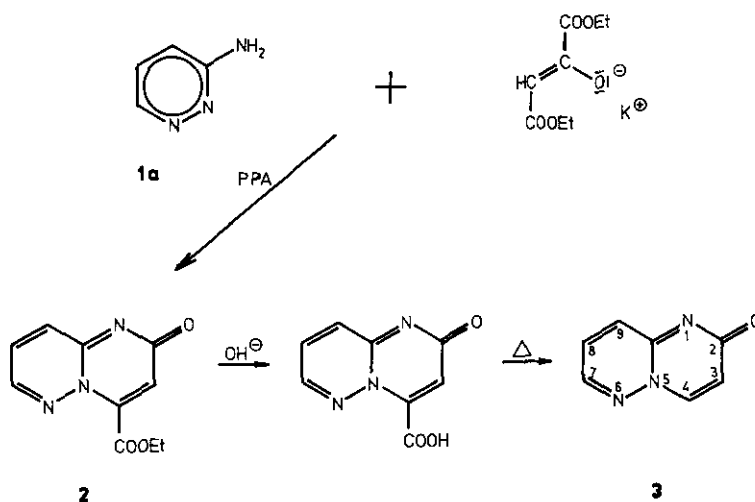
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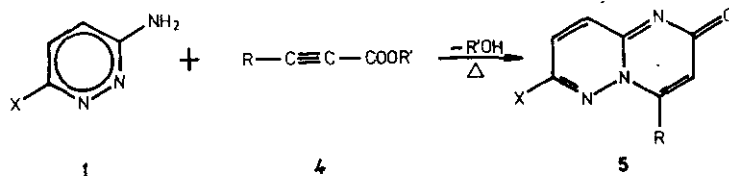
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Abstract - Some pyrimido[1,2-b]pyridazin-2- and -4-ones were synthesized. On the basis of their spectral data the structure of some known derivatives is revised.

It has been reported that the reaction of 3-aminopyridazine (1a) with the potassium enolate of diethyl oxaloacetate in polyphosphoric acid gives 4-carbethoxypyrimido[1,2-b]pyridazin-2-one (2) according to its ¹H-NMR spectrum, which is converted into compound 3².



It has also been reported that the reactions of 2-aminopyridine and 2-aminopyrimidine with acetylenic esters form the corresponding pyrido[1,2-a]pyrimidin-2-one³ and pyrimido[1,2-a]pyrimidin-2-one⁴ derivatives, respectively. We have extended this reaction to 3-aminopyridazines. Thus, the reactions of the compounds 1b,c with acetylenic esters (4a,b) afforded pyrimido[1,2-b]pyridazin-2-ones (5a-d)⁵.



b: X = Cl

c: X = Mph

(Mph = morpholino)

a: R = H

R' = Et

b: R = COOMe

R' = Me

a: X = Cl, R = H

b: X = Cl, R = COOMe

c: X = Mph, R = H

d: X = Mph, R = COOMe

The $^1\text{H-NMR}$ data of these compounds together with those of 6a,b and 7a,b are given in the table below.

T A B L E ^a

$^1\text{H-NMR}$ data of compounds 5a-d, 6a, b and 7a, b in DMSO-d_6
($\delta_{\text{TMS}} = 0$ ppm, coupling constants in Hz) at 60, 90 or 250 MHz

Com- pound	CH_3 <u>s</u> ^b	H-3 (1H) ^c	H-4(2) <u>d</u> (1H) ^d	H-6(7) <u>dd</u> (1H) ^e	H-8 (1H) ^f	H-9 (1H) ^f	NCH_2 <u>m</u> (2H)	OCH_2 <u>m</u> (2H)	NCH <u>s</u> (1H)	NH <u>s</u> (1H)
<u>5a</u>	-	6.40	8.40	-	7.72	7.78	-	-	-	-
<u>5b</u>	3.95	6.80	-	-	7.74	7.81	-	-	-	-
<u>5c</u>	-	6.30	8.15	-	7.45	7.75	3.48	3.72	-	-
<u>5d</u>	3.95	6.57	-	-	7.53	7.80	3.47	3.73	-	-
<u>6a</u>	1.75	-	-	9.15	7.81 ^g	8.03 ^h	-	-	9.34	~11.4
<u>6b</u>	1.75	-	-	-	8.10 ^g	7.98 ^h	-	-	9.20	~11.45
<u>7a</u>	-	6.60	8.30	8.88	7.80	8.05	-	-	-	-
<u>7b</u>	-	6.70	8.30	-	7.85	8.05	-	-	-	-

^a IR data (KBr, cm^{-1}): Ester $\nu\text{C=O}$ band: 1745 (5b), 1750 (5d), 1730 (6a) and 1690 (6b); $\nu\text{C=C}$ band: 1615 (6a) and 1625 (6b); $\nu\text{C-O}$ bands: 1270, 1240, 1100 (6a) and 1275, 1140 (6b).

^b 3H (5b,d) or 6H (6a,b)

^c s (5b,d) or d, $\text{J} = 7.5$ (5a), $\text{J} = 8.0$ (5c), $\text{J} = 6.5$ Hz (7a,b)

^d H-4, $\text{J} = 7.5$ (5a) and 8.0 Hz (5c) or H-2, $\text{J} = 6.5$ Hz (7a,b)

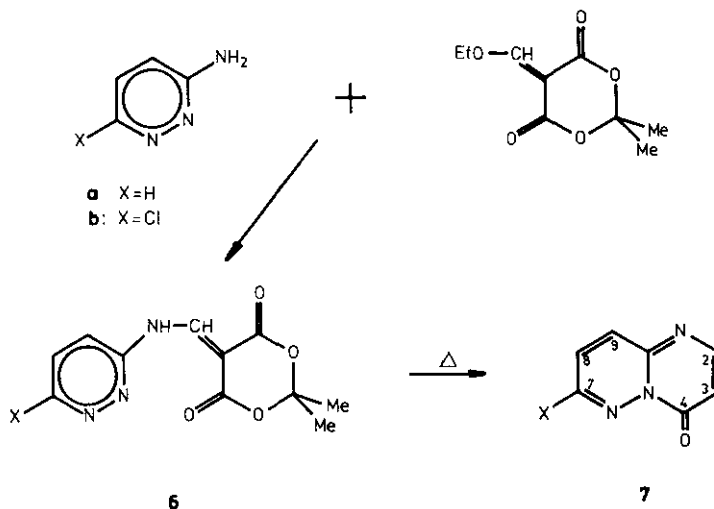
^e H-6, $\text{J} = 5$ and 1 Hz (6a) or H-7, $\text{J} = 4$ and 1 Hz (7a)

^f d, $\text{J} = 9$ (5a,b, 6b), 10 Hz (5c,d, 7b) or dd, $\text{J} = 9$ and 5 (6a), $\text{J} = 9$ and 4 Hz (7a)

^g H-5

^h H-4

The 4-one derivatives (7a, b) were easily synthesized by thermal cyclization of the 3-pyridazinylaminomethylenemalonates (6a, b)⁶.



Since the amide-I bands of 5a and 7a in the IR spectra appear at 1640 and 1710 cm^{-1} , respectively, as can be anticipated^{7,8} and they are significantly different and nearly independent from the substituents (1645 (5b,d), 1630 (5c) and 1700 cm^{-1} (7b), respectively), it is possible to determine the 2-one and 4-one structures even if only one of the isomers is available. For distinction between the isomers the $^1\text{H-NMR}$ spectra are not different enough and strongly depend on substituents. Moreover, it has been reported⁹ that the $^{13}\text{C-NMR}$ data may not be applied to this purpose. However, the other theoretically possible ring isomers could be ruled out on the basis of the above data.

On the basis of these results, the structures of 2 and 3² are revised to be pyrimido[1,2-b]pyridazin-4-ones (amide-I band: 1695 and 1709 cm^{-1} , respectively), and the pyrimido[1,2-a]pyrimidine, obtained from 2-aminopyrimidine and dimethyl acetylenedicarboxylate (amide-I: 1705 cm^{-1})⁴, is also revised to be a 4-one derivative.

REFERENCES AND NOTES

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5. Preparation of 5g-d.
The reaction of 1b (2,6 g, 20 mmol) with 4a (1,96 g, 20 mmol) in EtOH (30 ml) by heating at reflux temperature for 2 h afforded 1,5 g (41 %) 5a mp 218-220 °C.
5b-d were analogously prepared, 5b (mp 214-216 °C, 52 %), 5c (mp 165-167 °C, 39 %), 5d (mp 221-223 °C, 43 %).
6. Preparation of 6a,b and 7a,b.
2,2-Dimethyl-1,3-dioxane-4,6-dione (1,44 g, 10 mmol) was reacted with triethyl orthoformate (12 ml) at room temperature to 2,2-dimethyl-5-ethoxymethylene-1,3-dioxane-4,6-dione, of which reaction with 1a (0,95 g, 10 mmol) at room temperature for 20 h and at 80 °C for 30 min afforded 2,0 g (78,5 %) 6a, mp 235-238 °C (and analogously 6b, 220-221 °C, 81 %).
The heating of 6a (0,3 g, 1,2 mmol) in Dowtherm (7 ml) at 240 °C for 7 min led to 7a (0,1 g, 56,5 %), mp 155-157 °C (and 7b, mp 204-205 °C, 90,5 %, respectively).
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