STUDIES IN THE FIELD OF PYRIDAZINE COMPOUNDS, 28.[1] SYNTHESIS OF 5-SUBSTITUTED 6(5H)-1,2,4-TRIAZOLO[4,3-b]PYRIDAZINONES

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Abstract - The unknown 5-hydroxy-6(5H)-1,2,4-triazolo[4,3-b]pyridazinones (4) were prepared by rearrangement of 6-hydroxyalkoxy-1,2,4-triazolo[4,3-b]-pyridazines (1) in polyphosphoric acid. The reaction was accompanied by the formation of bis(triazolopyrydazine) derivatives (2). The products (4) were transformed to chloro derivatives (5).

5-Substituted 6(5H)-1,2,4-triazolo[4,3-b]pyridazinones could not be synthesized by direct alkylation of 6-hydroxy-1,2,4-triazolo[4,3-b]pyridazine. According to spectral evidence the latter compound exists only in the hydroxy form and therefore its alkylation by conventional methods afforded only O-alkylated derivatives.[2] It was reported that 1-hydroxyethoxyphthalazine[3] and 3-hydroxyethoxypyridazine[4] derivatives in the presence of thionyl choride in chloroform resulted N-chloroethylphthalazinones and pyridazinones by an O→N alkyl rearrangement *via* an oxazolinium intermediate which was subsequently attacked by the chloride ion. In the case of pyridazine derivatives[4] the mechanism of the rearrangement was followed by ^{1}H nmr spectroscopy and an intramolecular process was confirmed.

The synthesis of 1 was described earlier.[5] 6-Chloro-1,2,4-triazolo[4,3-b]pyridazine reacted with 1,2-ethane- or 1,3-propanediol in the presence of sodium hydride to give 6-hydroxyalkoxy-1,2,4-triazolo[4,3-b]pyridazines (1) and by-products:the bis(triazolo-pyridazine) derivatives (2) with recovery of the starting material. However, the formation of 2 was supressed (1-2 % yields) under diluted conditions.[5]

In avoiding direct alkylation we attempted to apply the above O→N rearrangement to 6-hydroxyalkoxy-1,2,4-triazolo[4,3-b]pyridazines (1) but only 6-chloroalkoxy derivatives

(3) were isolated. On the basis of Hückel[6] and CNDO/2[7] calculations of 1,2,4-triazolo-[4,3-b]pyridazine ring system the electron density of N-5 seems not to be enough to stabilize an oxazolo- or 1,3-oxazinotriazolopyridazinium ion intermediate (n=2 or n=3).

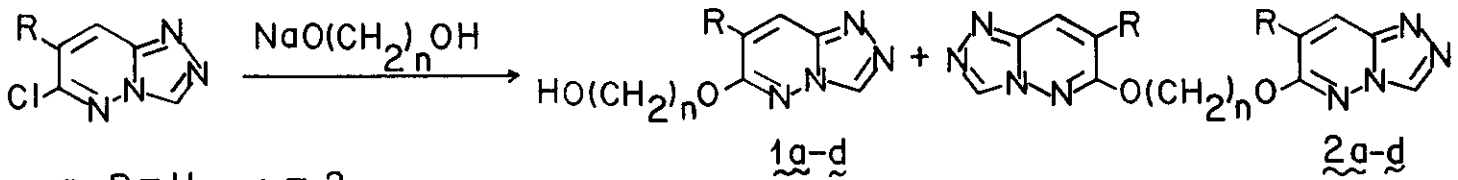
It was found that on heating in polyphosphoric acid at 120 °C 1 gave 5-substituted 6(5H)-1,2,4-triazolo[4,3-b]pyridazinones (4) and the bis-derivatives (2) (Scheme 1). On the basis of ir, ^{1}H nmr and uv data the N- and O-hydroxyalkyl derivatives could be well distinguished. The spectral data of 1b and 4b were compared in detail. Rearrangement of 1b to 4b caused a red shift of the absoption maximum in uv spectra from λ_{max} 272 nm to 279 nm, smaller than that observed with pyridazine derivatives.[4] Compound (4b) showed a characteristic carbonyl stretching band at 1660 cm^{-1}. ^{1}H Nmr spectra also supported the constitutions of 1b and 4b: a Het-NCH_2 triplet at 4.35 ppm (4b) and a Het-OCH_2 triplet at 4.50 ppm (1b) were characteristic (Table).

The low yields of 4 were attributed to the formation of the by-products (2). Poor solubility of compounds 4 in organic solvents made their isolation difficult. Compounds (4) were transformed by thionyl chloride to chloro derivatives (5).

The first step of the rearrangement of 6-hydroxyalkoxy-1,2,4-triazolo[4,3-b]pyridazines (1) to 5-hydroxyalkyl-6(5H)-1,2,4-triazolo[4,3-b]pyridazinones (4) in polyphosphoric acid seems to involve an usual protonation and dehydratation process[8] with the formation of an alkyl cation. The stabilization of the alkyl cation might be carried out in two different ways: "a" - a nucleophilic attack by N-5, hydratation and deprotonation to the formation of 4; "b" - a nucleophilic attack by oxygen of another hydroxyalkoxy derivative (1), hydratation and deprotonation leads to the formation of 2 and alkanediol (Scheme 2). Heating of the mixture of 1b and 1c in polyphosphoric acid resulted in the formation of only 4b and 4c and no mixed 5-substituted triazolopyridazinones were detected. This crossover reaction suggests that the formation of the compounds (4) is an intramolecular reaction.

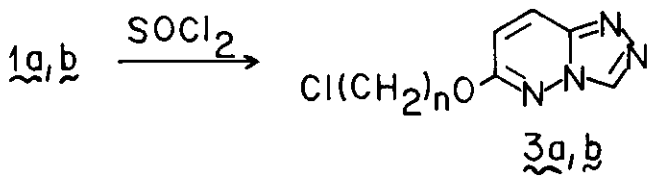
EXPERIMENTAL

Melting points were determined on a Boethius apparatus. Melting points are not corrected. The following apparatus were used to obtain spectral data: ir: Perkin-Elmer 577; ^{1}H nmr: Varian EM-390 90 MHz, using TMS as an internal reference; uv: Cary 1180 instrument.

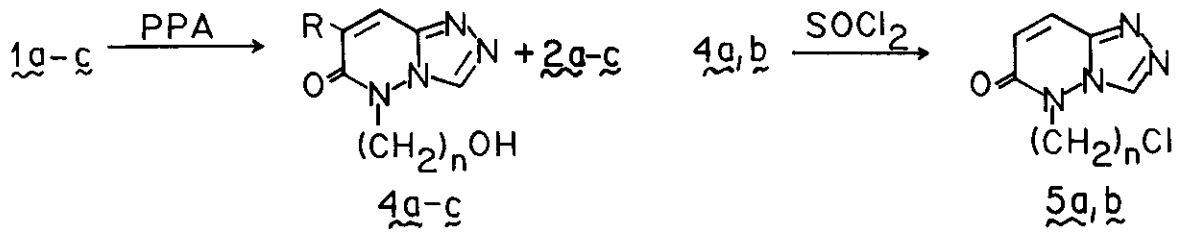


1a-d + 2a-d

a R = H n = 2
b R = H n = 3
c R = Me n = 2
d R = Me n = 3



3a,b



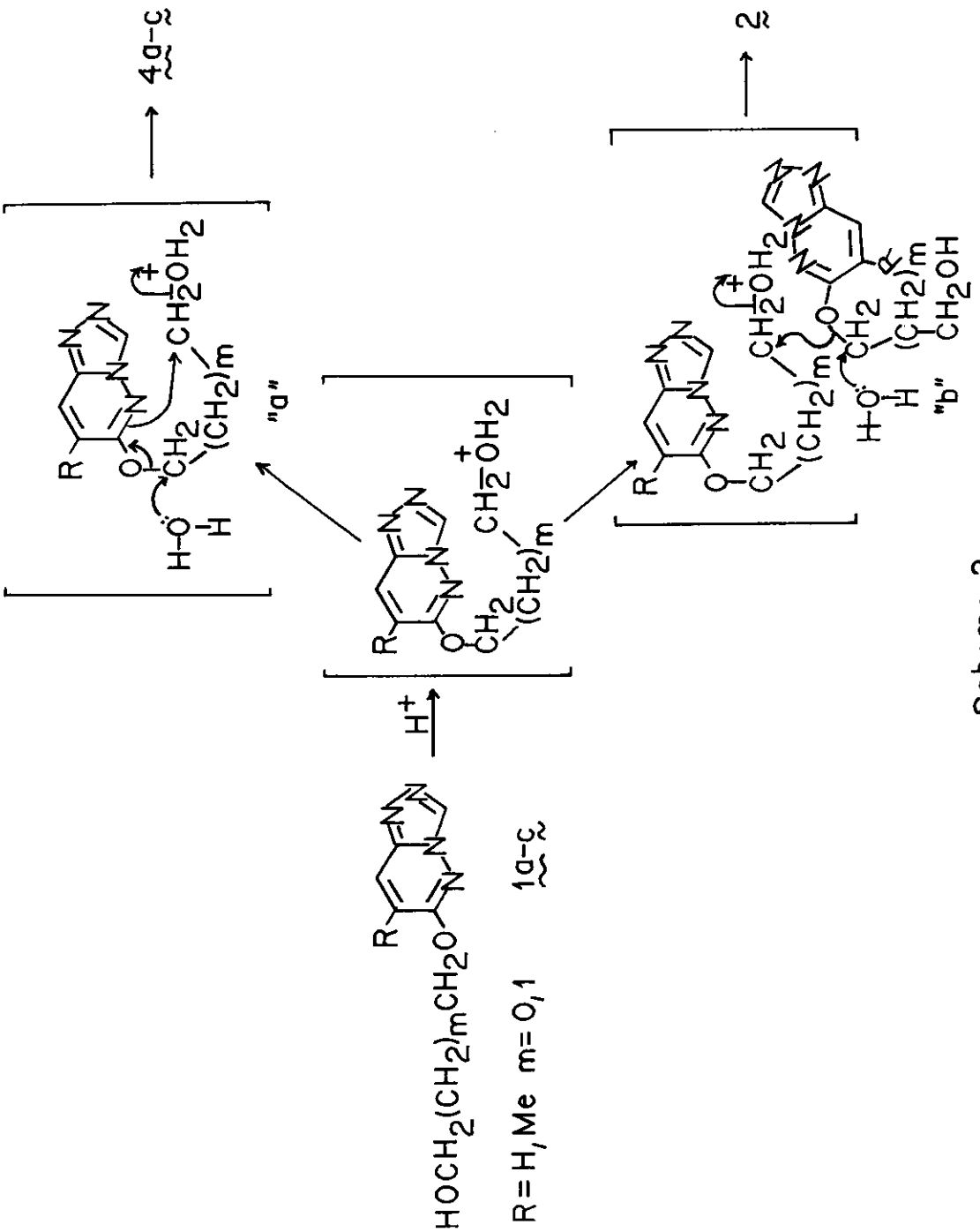
Scheme 1

Table

Characteristic ir (KBr, cm^{-1}), ^1H nmr ($CDCl_3$, δ ppm) and uv (96 % ethanol) data of compounds (1, 2, 3, 4 and 5)

Compd	ir	^1H nmr								uv
		$ArOCH_2$	NCH_2	$CH_2CH_2CH_2$	CH_2OH	CH_2Cl	H-3	H-7	H-8	λ_{max}
		t(2H)	t(2H)	m(2H)	t(2H)	t(2H)	s(1H)	ABq(2H)		nm
1a	3235, 3100, 1630, 1550, 860, 840	4.50 (J=6 Hz)	-	-	3.90 (J=6 Hz)	-	9.30	7.05 (J=10 Hz)	8.25	272
1b	3230, 3100, 1620, 1547, 888, 835	4.50 (J=6 Hz)	-	2.20	3.45 (J=6 Hz)	-	8.90	6.85 (J=10 Hz)	8.02	272
1c	3227, 3095, 1539, 1502, 889, 870	4.45 (J=6 Hz)	-	-	3.60 (J=6 Hz)	-	9.01	-	8.00[a] (J=0 Hz)	271
1d	3230, 3090, 1600, 1545, 880, 840	4.50 (J=6 Hz)	-	1.80	3.40 (J=6 Hz)	-	8.90	-	8.10[a] (J=0 Hz)	270
2a	3123, 1620, 1548, 858, 825	4.75[b] (J=0 Hz)	-	-	-	-	8.90[c]	6.90[d] (J=10 Hz)	8.01[d]	272
2b	3100, 1623, 1540, 860, 830	4.75[b] (J=0 Hz)	-	2.00	-	-	8.90[c]	6.85[d] (J=10 Hz)	8.05[d]	273
2c	3100, 1600, 1570, 858, 830	4.75[b] (J=0 Hz)	-	-	-	-	9.00[c]	-	8.00[c] (J=0 Hz) 2.05[e]	272
2d	3110, 1630, 1600, 860, 840	4.80[b] (J=0 Hz)	-	1.90	-	-	8.90[c]	-	7.90[c] (J=0 Hz) 2.10[e]	270
3a	3136, 1618, 1547, 887, 831	4.65 (J=5 Hz)	-	-	-	3.90 (J=5 Hz)	8.90	6.90 (J=10 Hz)	8.05	273
3b	3126, 1622, 1558, 1543, 854, 827	4.52 (J=5 Hz)	-	2.25	-	3.73 (J=5 Hz)	8.95	6.80 (J=10 Hz)	8.02	273
4a	3230, 3095, 1657, 1625, 1530, 850	-	4.25 (J=7 Hz)	-	4.00 (J=7 Hz)	-	9.30	7.01 (J=10 Hz)	8.15	279
4b	3235, 3090, 1660, 1610, 1520, 840	-	4.35 (J=7 Hz)	1.80	3.55 (J=6 Hz)	-	9.40	6.75 (J=10 Hz)	8.10	279
4c	3225, 3090, 1656, 1615, 1530, 850	-	4.45 (J=7 Hz)	-	3.60 (J=7 Hz)	-	9.20	-	8.00[a] (J=0 Hz) 2.05	279
5a	3130, 1665, 1610, 1540, 860, 825	-	4.40 (J=6 Hz)	-	-	4.10 (J=6 Hz)	8.90	6.95 (J=10 Hz)	8.10	280
5b	3126, 1660, 1550, 865, 830	-	4.42 (J=6 Hz)	1.95	-	3.83 (J=5 Hz)	9.00	6.90 (J=10 Hz)	8.02	279

[a] s(1H); [b] s(4H); [c] s(2H); [d] ABq(4H); [e] s(6H)



Scheme 2

Recrystallizations were carried out using ethanol.

Preparation of compounds 1

To a suspension of NaH (0.5 g, 50 % dispersion in mineral oil, 0.01 mol) in 1,2-ethane- or 1,3-propanediol (10 ml), 6-chloro-1,2,4-triazolo[4,3-b]pyridazine (1.54 g, 0.01 mol) was added in small portions at 5 °C. The reaction mixture was stirred for 24 h at room temperature. The precipitate was filtered off. Chromatography on silica gel (eluant ethyl acetate) gave 1 along with 1-2 % of 2.

Compound 1a: mp 172 °C; yield 54 %. Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4,48; N, 31.10. Found: C, 46.60; H, 4.50; N, 31.10.

Compound 1b: mp 135 °C; yield 72 %. Anal. Calcd for $C_8H_{10}N_4O_2$; C, 49.48; H, 5.19; N, 28.85. Found: C, 49.36; H, 5.22; N, 28.77.

Compound 1c: mp 180 °C; yield 64 %. Anal. Calcd for $C_8H_{10}N_4O_2$; C, 49.48; H, 5.19; N, 28.85. Found: C, 49.29; H, 5.30; N, 28.80.

Compound 1d: mp 152 °C; yield 70 %. Anal. Calcd for $C_9H_{12}N_4O_2$; C, 51.91; H, 5.81; N, 26.91. Found: C, 51.84; H, 5.80; N, 26.99.

Preparation of compounds 2 and 4

1 (0.01 mol) was heated at 120 °C in polyphosphoric acid (9 g) for 1 h. The reaction mixture was poured onto crushed ice, neutralized with solid $KHCO_3$ and the aqueous solution was extracted with chloroform. Evaporation and chromatography of the solid residue on silica gel (eluant methanol and ethyl acetate 1:9) gave 2 and 4.

Compound 2a: mp 254 °C; yield 21 %. Anal. Calcd for $C_{12}H_{10}N_8O_2$: C, 48.32; H, 3.38; N, 37.57. Found: C, 48.30; H, 3.42; N, 37.70.

Compound 2b: mp 197 °C; yield 19 %. Anal. Calcd for $C_{13}H_{12}N_8O_2$: C, 50.00; H, 3.87; N, 35.88. Found: C, 49.97; H, 3.89; N, 35.75.

Compound 2c: mp 199 °C; yield 20 %. Anal. Calcd for $C_{14}H_{14}N_8O_2$: C, 51.53; H, 4.32; N, 34.34. Found: C, 51.37; H, 4.30; N, 34.40.

Compound 2d: mp 176 °C; yield 5 %. Anal. Calcd for $C_{15}H_{16}N_8O_2$: C, 52.93; H, 4.74; N, 32.93. Found: C, 52.88; H, 4.70; N, 33.07.

Compound 4a: mp 186 °C; yield 15 %. Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.62; H, 4.50; N, 31.15.

Compound 4b: mp 166 °C; yield 15 %. Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85.

Found: C, 49.40; H, 5.25; N, 29.01.

Compound 4c: mp 180 °C; yield 11 %. Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.34; H, 5.12; N, 29.10.

Preparation of compounds 3 and 5

To a solution of 1a,b or 4a,b (5 mmol) in chloroform (50 ml), thionyl chloride (3.06 g, 0.026 mol) was added dropwise at 10 °C. The reaction mixture was refluxed for 1 h then poured onto crushed ice, neutralized by 10 % Na_2CO_3 and extracted with chloroform. The solvent was evaporated in vacuo and the residue was triturated with ether.

Compound 3a: mp 118 °C; yield 73 %. Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21. Found: C, 42.20; H, 3.63; N, 28.00.

Compound 3b: mp 97 °C; yield 57 %. Anal. Calcd for $C_8H_9N_4OCl$: C, 45.19; H, 4.27; N, 26.35. Found: C, 45.01; H, 4,35; N, 26.32.

Compound 5a: mp 128 °C: yield 65 %. Anal. Calcd for $C_7H_7N_4OCl$: C, 42.33; H, 3.55; N, 28.21. Found: C, 42.20; H, 3.62; N, 28.24.

Compound 5b: mp 104 °C; yield 59 %. Anal. Calcd for $C_8H_9N_4OCl$: C, 45.19; H, 4.27; N, 26.35. Found: C, 45.10; H, 4.31; N, 26.30.

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