PYRIMIDO[1,2-b]-1,2,4-TRIAZOLO[4,3-f]PYRIDAZINE, A NOVEL RING SYSTEM

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Abstract - The novel ring system pyrimido[1,2-b]-1,2,4-triazolo-[4,3-f]pyridazine was prepared either by ring closure of 6-(3-hydroxypropylamino)-1,2,4-triazolo[4,3-b]pyridazine 2a in polyphosphoric acid and the hydrazone 7 with bromine. Compound 1 showed a positive inotropic effect.

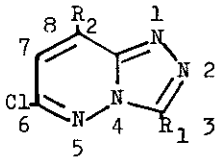
Few literature data are available on tricyclic ring systems comprising triazole, pyrimidine and pyridazine rings.[1,2,3] One of them, pyridazino[4,3-e]-1,2,4-triazolo-[1,5-a]pyrimidine is an analogue of the hypotensive bumepidil (8-tert-butyl-7,8-dihydro-5-methyl-6H-pyrrolo[3,2-e]-1,2,4-triazolo[1,5-a]pyrimidine) and is itself a hypotensive.[1]

With the aim to find compounds having cardiovascular activity we synthesized the novel 6H-pyrimido[1,2-b]-1,2,4-triazolo[4,3-f]pyridazine ring system.

The first approach to this ring system comprised the cyclization of 6-(3-hydroxy-propylamino)-1,2,4-triazolo[4,3-b]pyridazine 2a in polyphosphoric acid at 150 °C for 3 h giving compound 1 [mp 203 °C; 39 %; ν max (KBr) cm^{-1}: 1630, 1595, 1530; δ ($CDCl_3$) ppm: 2.14 (2H,m,C_7-2H), 3.57 (2H,t,C_8-2H), 4.0 (2H,t,C_6-2H), 6.53 (1H,d,C_{10}-H), 7.25 (1H,d,C_{11}-H), 8.42 (1H,s,C_3-H)]. It has to be noted that the corresponding 3-chloro-propyl analogue prepared from 2a by boiling with thionyl chloride was not cyclized to 1 even under forced conditions.

Bromination of 1 affects the triazole ring giving the 3-bromo compound 3.3HBr [mp 190 °C; 63 %; ν max (KBr) cm^{-1}: 3300-2300; δ ($CDCl_3$ - DMSO-d_6) ppm: 2.2 (2H,m, C_7-2H), 3.5 (2H,t,C_8-2H), 4.8 (2H,t,C_6-2H), 7.1 (1H,d,C_{10}-H), 8.2 (1H,d,C_{11}-H)].

Cyclization of the amides 2b and 2c was accompanied by the loss of the amide group giving again 1. In order to have access to some other substituted derivatives of the same ring system as above, other reactions for the ring formation was undertaken.

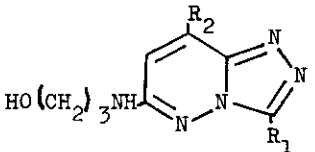
(I) 

$R_1 = R_2 = H$ 4

$R_1 = CONH_2$, $R_2 = H$ 5

$R_1 = H$, $R_2 = CONH_2$ 6

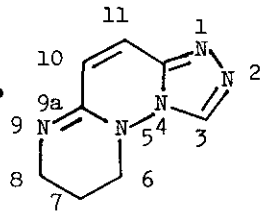
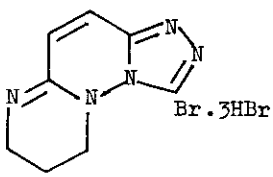
$HO(CH_2)_3NH_2$ →



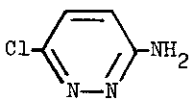
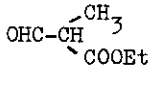
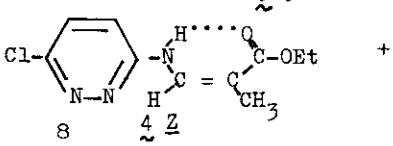
2a mp 210 °C

2b mp 230 °C

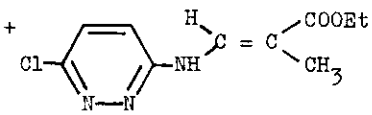
2c mp 248 °C

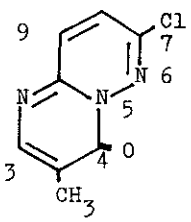
(II) 2a —PPA, 150 °C, 3 h→  —Br_2/AcOH, 25 °C→ 

1 3.3HBr

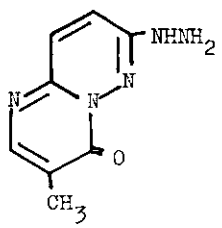
(III)  +  —TsOH, C_6H_6, 80 °C, 3h→  +

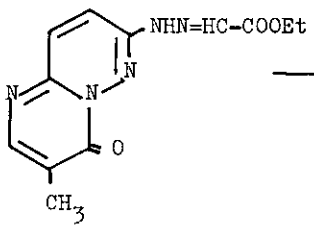
4 Z

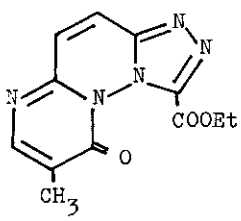


4 E —PPA, 100 °C, 1 h→  —$N_2H_4 \cdot H_2O$, 0 °C, 3 h→

5 →



6 —OHC-COOEt, 25 °C, 3 h→  →

7 —1. Br_2/AcOH, NaOAc; 2. Et_3N, iPrOH, 80 °C→ 

8

First the ester 4 was prepared as a 1:6 mixture of E [mp 137 °C; 11 %; ν max (KBr) cm^{-1}: 3320, 1710, 1630, 1590, 1550, 850; δ (DMSO-d_6) ppm: 1.25 (3H,t,$CH_2\underline{CH_3}$), 1.88 (3H,s,CH_3), 4.17 (2H,q,$\underline{CH_2}CH_3$), 7.45 (1H,d,C_4-H), 7.70 (1H,d,C_5-H), 8.50 (1H,d,CH=), 9.50 (1H,broad,NH)] and Z [mp 177 °C; 79 %; ν max (KBr) cm^{-1}: 3280, 1680, 1630, 1590, 850; δ (DMSO-d_6) ppm: 1.28 (3H,t,$CH_2\underline{CH_3}$), 1.86 (3H,s,CH_3), 4.22 (2H,q,$\underline{CH_2}CH_3$), 7.72 (2H,s,C_4-H,C_5-H), 7.93 (1H,d,CH=), 10.2 (1H,d,NH)] stereoisomers. These isomers could be separated by chromatography on Kieselgel 60 with methanol. Z form was assigned according to the literature[8] to the compound showing the higher chemical shift(Δδ= 0.57 ppm) for the vinyl proton. The predominant Z stereoisomer is stabilized by intramolecular hydrogen bond. In hot polyphosphoric acid both stereoisomers of 4 gave rise to the pyrimidopyridazine 5 [mp 145 °C; 70 %; ν max (KBr) cm^{-1}: 3080, 1700, 1620, 1575, 1530, 1490, 840; δ (DMSO-d_6) ppm: 2.3 (3H,s,CH_3), 7.4 (1H,d,C_8-H), 7.8 (1H,d,C_9-H), 8.2 (1H,s,C_2-H)]. The reaction of 5 with hydrazine hydrate at 0 °C provided hydrazino compound 6 [mp 260 °C; 52 %; ν max (KBr) cm^{-1}: 3260, 1680, 1575, 1510, 850; δ (DMSO-d_6) ppm: 2.1 (3H,s,CH_3), 7.3 (1H,d,C_8-H), 7.7 (1H,d,C_9-H), 8.2 (1H, s,C_2-H)] and the reaction of 6 with ethyl glyoxylate afforded hydrazone 7 [mp 245 °C; 76 %; ν max (KBr) cm^{-1}: 3200, 3060, 1740, 1690, 1590, 1550, 1490, 870; δ (DMSO-d_6) ppm: 1.3 (3H,t,$CH_2\underline{CH_3}$), 2.15 (3H,s,CH_3), 4.25 (2H,q,$\underline{CH_2}CH_3$), 7.45 (1H,s,N=CH), 7.7-8,0 (2H,ABq,C_8-H,C_9-H), 8.15 (1H,s,C_2-H)]. Under the action of bromine in acetic acid containing sodium acetate, the hydrazone 7 readily cyclized to 7-methyl-6-oxo-pyrimido[1,2-b]-1,2,4-triazolo[4,3-f]pyridazine 8 [mp 205 °C; 63 % ; ν max (KBr) cm^{-1}: 3070, 1750, 1690, 1600, 1560, 1510; δ ($CDCl_3$ - DMSO-d_6) ppm: 1.35 (3H,t,$CH_2\underline{CH_3}$), 2.2 (3H,s,CH_3), 4.4 (2H,q,$\underline{CH_2}CH_3$), 7.35 (1H,d,C_{10}-H), 7.9 (1H,d,C_{11}-H), 8.1 (1H,s,C_3-H)]. Compound 1 exerted a positive inotropic effect when tested according to the literature.[9]

NOTES

1. All new compounds had satisfactory elementary analyses and gave the expected molecular ion peaks in the mass spectrum.
2. Melting points were not corrected.
3. IR spectra were recorded on a Perkin-Elmer 577 instrument, ^{1}H-NMR spectra on a JEOL 60 HL spectrometer at 60 MHz, with TMS as internal standard.

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