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Studies in the Field of Pyridazine Compounds, 20[1]. 6*H*-1,2,4-Triazino[4,3—*b*]1,2,4-triazolo[3,4—*f*]pyridazine, a Novel Angular Ring System

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The novel ring system, 6*H*-1,2,4-triazino[4,3—*b*]1,2,4-triazolo[3,4—*f*]-pyridazine was prepared either by ring closure of 1-(1-ethoxycarbonylethylene)-2-(1,2,4-triazolo[4,3—*b*]pyridazinyl-6)-hydrazine derivatives (**4**, **5**, **7**) in polyphosphoric acid or of a hydrazine **15** derived from pyridazino-1,2,4-triazine under the action of triethyl orthoformate. Compound **8** showed a positive inotropic effect.

(Keywords: Cyclization; Inotropic effect; Pyridazino-triazine; Triazino-triazolo-pyridazine; Triazolo-pyridazine)

Über Pyridazinring enthaltende Verbindungen, 20. 6H-1,2,4-Triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazin, ein neues angulares Ringsystem

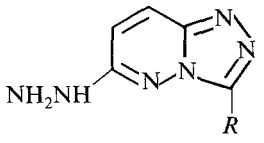
Das neue Ringsystem 6*H*-1,2,4-Triazino[4,3—*b*]1,2,4-triazolo[3,4—*f*]-pyridazin wurde entweder durch Ringschluß der 1-(1-Ethoxycarbonylethylen)-2-(1,2,4-triazolo[4,3—*b*]pyridazinyl-6)-hydrazin-Derivate (**4**, **5**, **7**) **4**, **5**, **7** in Polyphosphorsäure, oder aus einem von Pyridazino-1,2,4-triazin abgeleiteten Hydrazin **15** durch Ringschluß mit Orthoameisensäuretriethylester hergestellt. Verbindung **8** zeigte einen positiven inotropen Effekt.

Introduction

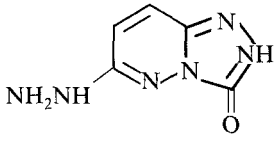
As a continuation of our studies on tricyclic compounds with positive inotropic effect incorporating a pyridazine ring[2,3] some representatives of the novel angular tricyclic ring system, 6*H*-1,2,4-triazino[4,3—*b*]1,2,4-triazolo[3,4—*f*]pyridazine, were prepared.

Results and Discussion

The 6-hydrazino-1,2,4-triazolo[4,3—*b*]pyridazines **1**[4], **2**[5] and **3** were transformed by ethyl pyruvate to the corresponding hydrazones **4**, **5**, **7** which were heated in polyphosphoric acid in the hope (based on literature data[6]) that the 7-methyl derivatives of the title ring system would be obtained. In fact the new ring system was formed, but by further reaction, owing to pyruvate exchange with the starting material, instead of the methyl derivatives the acrylates **8**, **9** and **10** were isolated by column chromatography in 20–30% yield. In addition ~ 20% of the hydrazines **1**–**3** and ~ 10% of the corresponding 6-amino derivatives were obtained. Interestingly, addition of ethyl pyruvate did not increase the yield of the acrylates.



1 $R=H$
2 $R=Ph$



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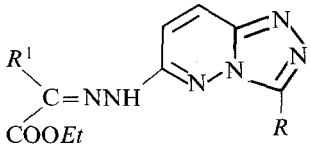
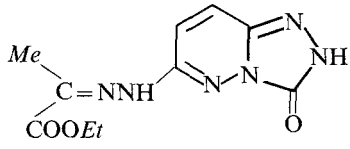


4 $R=H$, $R^1=Me$
5 $R=Ph$, $R^1=Me$
6 $R=R^1=H$



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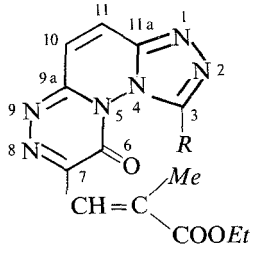
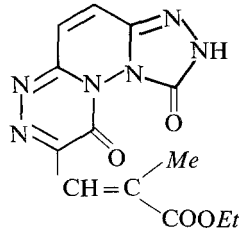
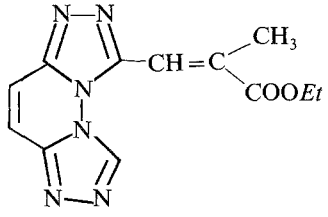


8 $R=H$
9 $R=Ph$



10

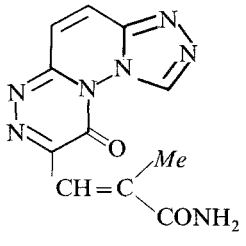
The hydrazones **4**–**7** failed to cyclize to the expected compounds on heating, on the addition of base or of acidic catalysts other than polyphosphoric acid. Cyclization of **4** can be effected by $BF_3 \cdot Et_2O$ but this leads, by ring contraction, to a bis-1,2,4-triazolo[4,3—*b*; 3′,4′—*f*]-pyridazine derivative (**11**).



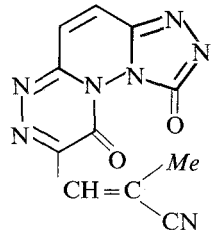
11

In contrast to the pyruvate hydrazones **4** and **5** the hydrazone **6** prepared from **1** and ethyl glyoxalate was recovered unchanged in 72% yield as the only isolable product after treatment with polyphosphoric acid. This is in accord with the findings of *Tisler* and coworkers[6] made in the course of the synthesis of similar heterocycles. They, however, did not observe the secondary condensation of the methyl group to acrylates.

The ester group of **8** is very reactive and can be readily transformed by action of methanolic ammonia at room temperature to the amide **12**, which on dehydration with phosphoryl chloride gives the nitrile **13**.



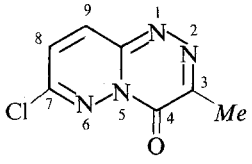
12



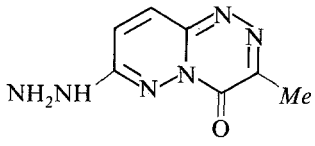
13

Our original target compound **21** was finally synthesized by constructing the ring in a different order. The known 7-chloro-pyridazino[6,1—*c*]-1,2,4-triazine derivate **14**[7]—the preparation of which we improved substantially (see Experimental)—was reacted under mild conditions with

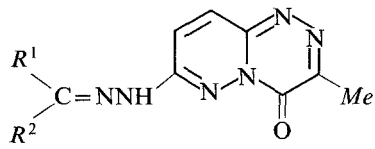
hydrazine hydrate to give **15**. **15** was condensed with a series of oxo compounds but none of the hydrazones **16**–**19** was amenable to cyclization under a variety of conditions (heating in tetraline, oxidation with bromine or lead tetraacetate). On oxidation of **16** and **17** with lead tetraacetate the corresponding 6-hydrazino-1,2,4-triazolo[4,3—*b*]pyridazines could be isolated. When the same hydrazones were treated with bromine in the presence of sodium acetate only the bromo compound **20** could be isolated.



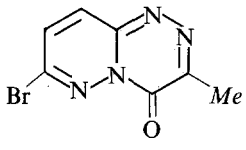
14



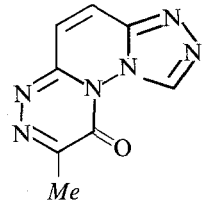
15



16 $R^1 = Me$, $R^2 = H$
17 $R^1 = Ph$, $R^2 = H$
18 $R^1 = COOEt$, $R^2 = H$
19 $R^1 = Ph$, $R^2 = Me$



20



21

Finally, the direct cyclization of the hydrazine **15** by treatment with triethyl orthoformate for a short period but at high temperature, i.e. at 190 °C in diphenylether, provided the required tricyclic compound **21** in 27% yield. **15** failed to undergo cyclization with CS_2, $COCl_2$, isothiuronium sulfate, acetic anhydride or even with triethyl orthoformate at its boiling point.

Compound **8** exerted a positive inotropic effect when tested according to the literature[8].

Acknowledgements

Thanks are due to Dr. *J. Reiter* for helpful discussions and to Mrs. *L. Vass* and Miss *K. Antal* for technical assistance.

Experimental

M.p.s are uncorrected; IR spectra (KBr pellets) were recorded on a Perkin-Elmer 577 instrument; ^{1}H-NMR spectra were taken in *DMSO-d_6* with *TMS* as internal standard on a Varian EM-390 spectrometer at 90 MHz; mass spectra were run on a Varian-MAT-SM-1 spectrometer ($R = 1\,250$). Elementary analysis for C, H, and N agreed within $\pm 0.2\%$ with the calculated values. Recrystallizations were usually carried out in ethanol; **12**, **13**, and **21** were crystallized from methanol.

2H-2,3-dihydro-6-hydrazino-3-oxo-1,2,4-triazolo[4,3—b]pyridazine (**3**)

2*H*-2,3-dihydro-6-chloro-3-oxo-1,2,4-triazolo[4,3—*b*]pyridazine[9] (1.40 g, 8.3 mmol), 98% hydrazine hydrate (4.90 ml) was refluxed in methanol (15 ml) for 1.5 h. Next day the product was filtered off and washed with water, 0.92 g (67%), m.p. 268 °C (dec.). IR (cm^{-1}): 3 290, 3 160, 1 720, 1 630, 875. ^{1}H-NMR (δ, ppm): 6.67 and 7.40 [ABq, C(7)-H and C(8)-H], 8.03 (t, NHNH$_2$), 12.10 [s, N(2)-H]. $C_5H_6N_6O$.

1-(1-Ethoxycarbonylethylene)-2-(1,2,4-triazolo[4,3—b]pyridazinyl-6)-hydrazine (**4**)

1 (3.0 g, 20 mmol)[4] and ethyl pyruvate (2.32 g, 20 mmol) were stirred in ethanol (90 ml) for 24 h at room temperature. The product was filtered off, 3.87 g (78%), m.p.: 256 °C. MS (*m/z*, %): 176 (10.7), 175 (100), 134 (5), 120 (2.9), 42 (5.5). IR (cm^{-1}): 3 070, 1 700, 1 625, 1 290, 1 150, 865. ^{1}H-NMR (δ, ppm): 1.30 (t, CH$_3$CH$_2$), 2.21 (s, CH$_3$), 4.20 (q, CH$_3$CH$_2$), 7.42 and 8.22 [ABq, C(7)-H and C(8)-H], 9.30 [s, C(3)-H], 10.92 (bs, NH). $C_{10}H_{12}N_6O_2$.

1-(1-Ethoxycarbonylethylene)-2-(3-phenyl-1,2,4-triazolo[4,3—b]-pyridazinyl-6)-hydrazine (**5**)

5 was obtained from **2**[5] in 75% yield as described for **4**, m.p.: 222 °C. MS (*m/z*, %): 324 (79), 252 (20), 251 (100), 104 (15), 103 (29), 44 (21). IR (cm^{-1}): 3 080, 1 700, 1 630, 1 270, 1 150, 860. ^{1}H-NMR (δ, ppm): 1.32 (t, CH$_3$CH$_2$), 2.20 (s, CH$_3$), 4.22 (q, CH$_3$CH$_2$), 7.40 and 8.30 [ABq, C(7)-H and C(8)-H], 7.45–7.60 [m, C(3)-H—C(5)-H, phenyl], 8.41–8.50 [m, C(2)-H, C(6)-H, phenyl], 11.10 (bs, NH). $C_{16}H_{16}N_6O_2$.

1-Ethoxycarbonylmethylene-2-(1,2,4-triazolo[4,3—b]pyridazinyl-6)-hydrazine (**6**)

6 was prepared in 68% yield from **1**[4] and ethyl glyoxalate as described for **4**, m.p.: 218 °C. MS (*m/z*, %): 234 (25), 162 (14), 161 (100), 135 (15). IR (cm^{-1}): 3 080, 1 710, 1 620, 1 280, 1 145, 840. ^{1}H-NMR (δ, ppm): 1.30 (t, CH$_3$CH$_2$), 4.21 (q, CH$_3$CH$_2$), 7.42 and 8.02 [ABq, C(7)-H and C(8)-H], 7.50 (s, CH=), 9.41 [s, C(3)-H], 12.20 (bs, NH). $C_9H_{10}N_6O_2$.

1-(1-Ethoxycarbonylethylene)-2-(2H-2,3-dihydro-3-oxo-1,2,4-triazolo-[4,3—b]pyridazinyl-6)-hydrazine (**7**)

7 was obtained from **3** in 78% yield as described for **4**, m.p.: 288 °C. IR (cm^{-1}): 3 280, 1 720, 1 630, 860. ^{1}H-NMR (δ, ppm): 1.27 (t, CH$_3$CH$_2$), 2.10 (s, CH$_3$), 4.20 (q, CH$_3$CH$_2$), 7.27 and 7.80 [ABq, C(7)-H and C(8)-H], 10.97 (bs, NHN), 12.63 [s, N(2)-H]. $C_{10}H_{12}N_6O_3$.

Ethyl-[3-(6H-6-oxo-1,2,4-triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazinyl-7)-2-methylacrylate] (**8**)

4 (1.17 g, 5 mmol) was heated at 100 °C in polyphosphoric acid (10 g) for 5 h. The reaction mixture was poured onto ice (100 g), neutralized with $KHCO_3$ and the aqueous solution extracted with chloroform in a continuous extractor. Evaporation and chromatography on silica gel (eluant ethyl acetate) gave **8** (32%), **1** (20%) and 6-amino-1,2,4-triazolo[4,3—*b*]pyridazine[10] (9%). **8**: m.p.: 186 °C. MS (*m*/z, %): 300 (64.5), 255 (4.4), 227 (100), 94 (4). IR (cm^{-1}): 1 720, 1 690, 1 615, 1 270, 1 135, 865. ^{1}H-NMR (δ, ppm): 1.30 (t, CH_3CH_2), 2.21 (s, CH_3), 4.30 (s, CH_3CH_2), 7.61 and 8.61 [ABq, C(10)-H and C(11)-H], 7.90 (s, CH=), 9.82 [s, C(3)-H]. $C_{13}H_{12}N_6O_3$.

Ethyl-[3-(6H-6-oxo-3-phenyl-1,2,4-triazino[4,3—b]1,2,4-triazolo-[3,4—f]pyridazinyl-7)-2-methylacrylate] (**9**)

Following the procedure described for **8**, **5** gave **9** in 27% yield, m.p.: 229 °C. MS (*m*/z, %): 376 (100), 331 (1.2), 303 (6.9), 94 (2.8). IR (cm^{-1}): 1 715, 1 660, 1 610, 1 250, 1 130, 865. ^{1}H-NMR (δ, ppm): 1.40 (t; CH_3CH_2), 2.31 (s, CH_3), 4.40 (q, CH_3CH_2), 7.30 and 8.30 [ABq, C(10)-H and C(11)-H], 7.41–7.61 [m, C(3)-H—C(5)-H, phenyl], 7.80 (s, CH=), 8.30–8.50 [m, C(2)-H, C(6)-H, phenyl]. $C_{19}H_{16}N_6O_3$.

Ethyl-3-(2H,6H-2,3-dihydro-3,6-dioxo-1,2,4-triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazinyl-7)-2-methylacrylate (**10**)

Following the procedure described for **8**, **5** gave **10** in 20% yield, m.p.: 250 °C. MS (*m*/z, %): 316 (100), 244 (6.5), 243 (46), 182 (4.2), 169 (4.1), 131 (5), 119 (6.5), 69 (16.5). ^{1}H-NMR (δ, ppm): 1.30 (t, CH_3CH_2), 2.20 (s, CH_3), 4.33 (q, CH_3CH_2), 7.30 and 7.93 [ABq, C(10)-H and C(11)-H], 7.90 (s, CH=), 12.97 [s, N(2)-H]. $C_{13}H_{12}N_6O_4$.

Ethyl-[3-(bis-1,2,4-triazolo[4,3—b; 3',4'—f]pyridazinyl-1)-2-methylacrylate] (**11**)

4 (0.50 g, 2 mmol) and $BF_3 \cdot Et_2O$ (2.0 ml) was stirred at 100 °C. The solution was evaporated to dryness. The residue was solved in water (10 ml), neutralized with $KHCO_3$ and the aqueous solution extracted with chloroform. Evaporation and chromatography on silica gel (eluant ethyl acetate) gave 0.15 g (28%) **11**, m.p.: 102 °C. MS (*m*/z, %): 272 (100), 227 (56), 243 (14.8), 200 (14). IR (cm^{-1}): 1 720, 1 620, 1 267, 1 135, 842. ^{1}H-NMR (δ, ppm): 1.33 (t, CH_3CH_2), 2.43 (s, CH_3), 4.37 (q, CH_3CH_2), 6.83 (s, CH=), 7.60 and 8.23 [ABq, C(4)-H and C(5)-H], 9.03 [s, C(8)-H]. $C_{12}H_{12}N_6O_2$.

3-(6H-6-Oxo-1,2,4-triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazinyl-7)-2-methylacrylic amide (**12**)

8 (1.35 g, 5 mmol) was stirred in 14% methanolic ammonia for 48 h. The product was filtered off and washed with ether to afford **12** (0.98 g, 72%), m.p.: 314 °C. MS (*m*/z, %): 271 (100), 228 (12), 227 (77.5), 66 (6.5), 44 (7.5). IR (cm^{-1}): 3 340, 3 180, 1 700, 1 685, 1 610, 845. ^{1}H-NMR (δ, ppm): 2.17 (s, CH_3), 7.73 and 8.63 [ABq, C(10)-H and C(11)-H], 7.80 (bs, NH_2), 7.93 (s, CH=), 9.80 [s, C(3)-H]. $C_{11}H_9N_7O_2$.

3-(6H-6-Oxo-1,2,4-triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazinyl-7)-2-methylacrylonitrile (**13**)

12 (0.27 g, 1 mmol) was refluxed in phosphoryl chloride (0.5 ml) for 3 h. After pouring onto ice (5 ml) and neutralization with aqueous ammonia the product was filtered off and washed with water to give **13** (0.5 g, 58%), m.p.: 258 °C. MS (*m/z*, %): 253 (100), 227 (4), 127 (5,5), 45 (15.5), 44 (20.5), 28 (10.2). IR (cm^{-1}): 1 670, 1 610, 860. ^{1}H-NMR (δ, ppm): 2.17 (s, CH_3), 7.57 and 8.50 [ABq, C(10)-H and C(11)-H], 8.50 (s, CH=), 9.70 [s, C(3)-H]. $C_{11}H_7O$.

4H-7-Chloro-3-methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazine (**14**)

1-(1-Ethoxycarbonylethylene)-2-(6-chloro-3-pyridazinyl)-hydrazine[7] (2.43 g, 10 mmol) was heated in polyphosphoric acid (30 g) for 5 h at 100 °C. The usual work-up gave **14** (1.17 g, 60%), m.p.: 153° (dec.) > 260 °C [Lit.[7] m.p.: 150° (dec.) > 260 °C, yield 36%].

4H-7-Hydrazino-3-methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazine (**15**)

To a solution of **14** (1.40 g, 6.9 mmol) in methanol (15 ml) 98% hydrazine hydrate (4.2 ml) was added dropwise at 0 °C. Stirring was continued for 3 h at 0 °C and then 3 h at room temperature. The product was filtered off, washed with cold water, dried and triturated twice with hot chloroform (20 ml) to remove **14**. Yield 0.81 g (61%), m.p. 218 °C. MS (*m/z*, %): 192 (17), 164 (9), 79 (5.5), 43 (6.5), 28 (100). IR (cm^{-1}): 3 250, 1 675, 1 640, 850. ^{1}H-NMR (δ, ppm): 2.43 (s, CH_3), 4.47 (bs, NH_2NH), 7.17 and 7.67 [ABq, C(8)-H and C(9)-H], 8.93 (bs, NH_2NH). $C_7H_8N_6O$.

1-(4H-3-Methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazinyl-7)-2-ethylidene-hydrazine (**16**)

Prepared (as described for **4**) from **15** and acetaldehyde in 59% yield, m.p. 298 °C. MS (*m/z*, %): 218 (100), 203 (37), 175 (33), 149 (32), 79 (21), 60 (9.2), 42 (13), 28 (22). IR (cm^{-1}): 3 050, 1 680, 1 630, 865. $C_9H_{10}N_6O$.

1-(4H-3-Methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazinyl-7)-2-phenylmethylene-hydrazine (**17**)

Prepared (as described for **4**) from **15** and benzaldehyde in 72% yield, m.p. > 360 °C. MS (*m/z*, %): 280 (86), 197 (15), 177 (26.5), 149 (100), 104 (25.5), 103 (14.5), 79 (21), 77 (17.5). IR (cm^{-1}): 3 045, 1 680, 1 640, 860. $C_{14}H_{12}N_6O$.

1-(4H-3-Methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazinyl-7)-2-ethoxycarbonylmethylene-hydrazine (**18**)

Prepared (as described for **4**) from **15** and ethyl glyoxalate in 66% yield, m.p.: 311 °C. MS (*m/z*, %): 276 (54), 203 (76), 175 (81), 64 (23), 44 (100), 30 (24.2), 29 (40). IR (cm^{-1}): 3 050, 1 715, 1 685, 1 635, 1 280, 1 160, 860. $C_{11}H_{12}N_6O_3$.

1-(4H-3-Methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazinyl-7)-2-(1-phenyl-ethylidene)-hydrazine (**19**)

Prepared (as described for **4**) from **15** and acetophenone in 87% yield, m.p.: 319 °C. MS (*m/z*, %): 294 (100), 266 (12.5), 265 (22), 119 (10.5), 118 (40), 105 (19), 77 (31), 43 (11.5), IR (cm^{-1}): 3 065, 1 690, 1 630, 850. $C_{15}H_{14}N_6O$.

4H-7-Bromo-3-methyl-4-oxo-pyridazino[6,1—c]1,2,4-triazine (**20**)

To a solution of **16** (0.22 g, 1.0 mmol), anhydrous sodium acetate (0.20 g, 2.5 mmol) in acetic acid (4.5 ml) a solution of bromine (0.16 g, 1.0 mmol) in acetic acid (0.5 ml) was added dropwise. After 3 h the reaction mixture was diluted with water (10 ml), neutralized with aqueous ammonia and the aqueous solution extracted with chloroform. After evaporation the residue was triturated with ether. Yield 0.10 g (41%), m.p. > 360 °C. MS (*m/z*, %): 241 (9), 240 (90), 215 (8), 214 (97), 213 (9), 212 (100), 196 (5.2), 64 (72). $C_7H_5BrN_4O$.

6H-7-Methyl-6-oxo-1,2,4-triazino[4,3—b]1,2,4-triazolo[3,4—f]pyridazine (**21**)

15 (0.25 g, 1.25 mmol) was refluxed for 30 min at 190 °C in a mixture of freshly distilled triethyl orthoformate (25 ml) and diphenylether (7.5 ml). After cooling and dilution with petroleum ether (b.p. 80–100 °C) the precipitate was collected and chromatographed on silica gel (eluant methanol—ethyl acetate 1 : 1) to give **21** (68 mg, 27%) and unchanged starting material (0.12 g, 48%). **21**: m.p.: 210 °C. MS (*m/z*, %): 202 (70), 175 (56), 174 (100). IR (cm^{-1}): 1690, 1620, 865. ^{1}H-NMR (δ, ppm); 2.53 (s, CH_3), 7.43 and 8.05 [AB q, C(10)-H and C(11)-H], 10.20 [s, C(3)-H]. C_8H_6O.

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