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On Triazoles XIX [1]: The Reaction of 5-Amino-1,2,4-triazoles with Functionalized Acetoacetic Esters [2]

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Summary. Different "functionalized" alkyl 3-oxo-butyrates (**2**) were reacted with 5-amino-3-*Q*-1*H*-1,2,4-triazoles (**1**) to yield **3** and **4** type 1,2,4-triazolo[1,5-a]pyrimidinones. In case of **2** (R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl) beside the corresponding derivative **4** the unexpected 5,6-dihydro-6,8-dimethyl-7-ethoxycarbonyl-3-methylthio-1,2,4-triazolo[4,3-a]-1,3-diazepin-5(9*H*)-one (**7**) was isolated, representing a novel ring system.

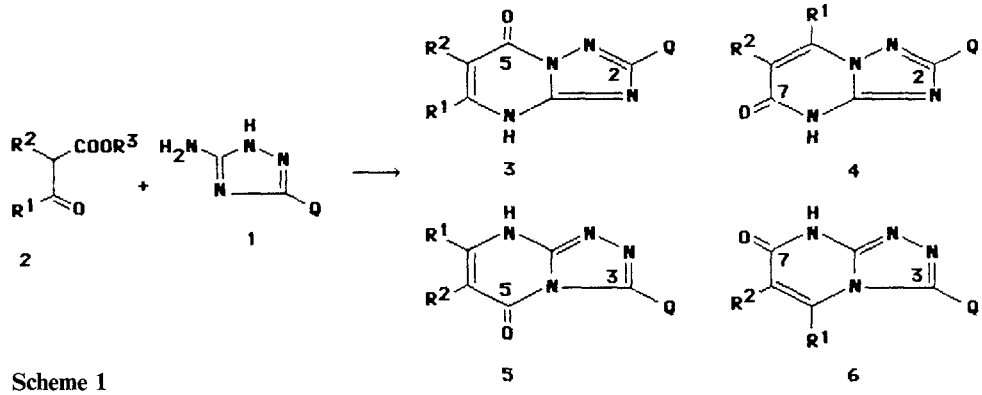
Keywords. 1,2,4-Triazolo[1,5-a]pyrimidinones; 1,2,4-Triazolo[4,3-a]-1,3-diazepinone; Novel ring system; IR-; UV-; ^{1}H-NMR; ^{13}C-NMR.

Über Triazole, 19. Mitt.: Die Reaktion von 5-Amino-1,2,4-triazolen mit funktionalisierten Acetoessigestern

Zusammenfassung. Verschiedene „funktionalisierte" 3-Oxo-buttersäurealkylester (**2**) wurden mit 5-Amino-3-*Q*-1*H*-1,2,4-triazolen (**1**) umgesetzt, wobei 1,2,4-Triazolo[1,5-a]pyrimidinone der Typen **3** und **4** erhalten wurden. Im Fall von **2** (R^1 = Methyl, R^2 = 1-Ethoxycarbonylethyl, R^3 = Ethyl) wurde neben dem erwarteten Derivat **4** das unerwartete 5,6-Dihydro-6,8-dimethyl-7-ethoxycarbonyl-3-methylthio-1,2,4-triazolo[4,3-a]-1,3-diazepin-5(9*H*)-on (**7**) isoliert, welches ein neues Ringsystem darstellt.

Introduction

In a previous paper of this series [3] we have reported on the reaction of methyl and ethyl 3-oxo-butyrates (**2**, R^1 = methyl, R^2 = H, R^3 = methyl and ethyl) with 5-amino-3-methylthio- and 3-morpholino-1*H*-1,2,4-triazoles (**1**, Q = methylthio and morpholino, respectively) that might in principal lead to any of the **3**–**6** type triazolo-pyrimidinone derivatives (Scheme 1). It was shown that provided that the reaction took place in acetic acid, dimethylformamide or their mixtures as solvent, the **3** type 7-methyl-2-methylthio- and 2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-5(8*H*)-ones (**3**, R^1 = methyl, R^2 = H, Q = methylthio and morpholino, respectively) were the main products of the reaction beside a small amount of the corresponding **4** type derivatives [5-methyl-2-methylthio and 2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-7(8*H*)-ones (**4**, R^1 = methyl, R^2 = H, Q = methylthio and morpholino, respectively)].



Scheme 1

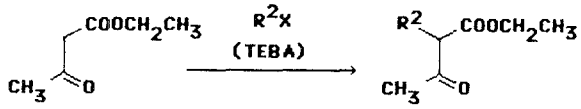
It was also pointed out that although the IR and ^{1}H NMR spectra of these products were consistent with the structures **3–6** they were not characteristic for any of them. On the other hand the structure of these derivatives could be easily proved on the basis of their UV spectra taken in neutral conditions (e.g. in methanol or ethanol) where derivatives **3** and **4** were characterized with two absorption maxima appearing at about 230 and 270 nm, and at about 208 and 290 nm, respectively, while those of the corresponding derivatives **5** and **6** were characterized with three and one maxima, respectively.

The unequivocal differentiation between structures **3–6** offered also the ^{13}C NMR spectra where the carbon atoms 2 of the **3** and **4** type derivatives appeared at about 163 ppm in contrary to those of the corresponding carbon atoms 3 of the **5** and **6** type derivatives appearing at about 143 ppm. In addition, the carbonyl carbon atoms of the "ring acylated" derivatives **3** and **5** appeared at about 154 ppm, and those of the corresponding "acylamino" derivatives **4** and **6** appeared at about 160 ppm, respectively.

We will now report on the preparation of different **3** type derivatives "functionalized" on the pyrimidinone ring and considered for biological screening.

Results and Discussion

Ethyl 3-oxo-butyrate (**2**, R^1 = methyl, R^2 = H, R^3 = ethyl) was C-alkylated with different alkyl halides, ethyl bromoacetate and ethyl 2-bromopropionate in the presence of a phase transfer catalyst (tetrabutylammonium hydrogen sulfate) to yield the corresponding "functionalized" ethyl 3-oxo-butyrates (**2**, R^1 = methyl, R^2 = methyl, ethoxycarbonylmethyl and 1-ethoxycarbonylethyl, R^3 = ethyl) (Scheme 2). These were – together with the commercially available ethyl 2-chlorothem. On the other hand the UV spectra nicely followed the UV rule elaborated R^1 = chloromethyl, R^2 = H) – condensed in acetic acid with different **1** type 5-amino-3-*Q*-1*H*-1,2,4-triazoles (**1**) to yield the corresponding "functionalized" derivatives **3** and small amounts of the corresponding derivatives **4**. With the exception of **4/1** and **4/2** the latter were not isolated. To enable their easy separation, derivatives **3** were in some cases converted to their sodium salts that were much less soluble in water than the corresponding sodium salts of derivatives **4**.



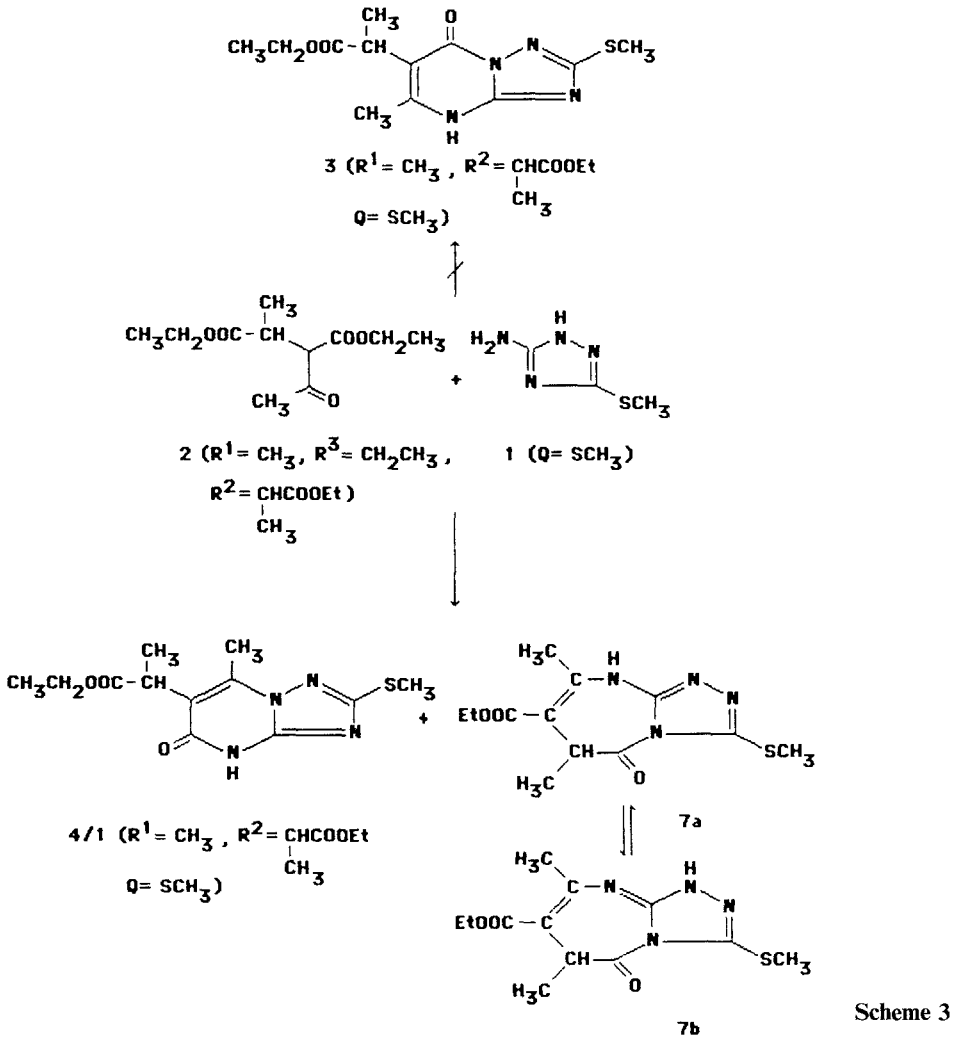
2 (R^2 = H) 2 (R^2 = alkyl) Scheme 2

The IR and ^{1}H NMR spectra of all derivatives **3** and **4** (Table 2) were again in accordance with the proposed structure, but were not characteristic for any of them. On the other hand the UV spectra nicely followed the UV rule elaborated recently [3] (compare the UV data taken in ethanol given in Table 2 with those required for structures **3** and **4**). In the ^{13}C NMR spectra taken in *DMSO-d_6* the carbon atoms 2 and 5 of derivatives **3** appeared with chemical shifts of 162.9–164.8 and 151.4–155.9 ppm, respectively, and those of carbon atoms 2 and 7 derivatives **4** appeared with chemical shifts of 161.8–164.8 and 159.1–159.3 ppm, respectively (Table 2); this was again in perfect agreement with the ^{13}C NMR rule elaborated previously [3].

From the reaction mixture of ethyl 4-oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl), that could be understood either as a 3-oxo-butyrate or a 4-oxo-valerate derivative (Scheme 3), and 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1**, Q = methylthio) the outcome was rather surprising: instead of the expected derivative **3** (R^1 = methyl, R^2 = = 1-ethoxycarbonylethyl, Q = methylthio), the corresponding isomer **4** (R^1 = = methyl, R^2 = 1-ethoxycarbonylethyl, Q = methylthio) and the unexpected 5,6-dihydro-6,8-dimethyl-7-ethoxycarbonyl-3-methylthio-1,2,4-triazolo[4,3-a]-1,3-diazepin-5(9*H*)-one (**7**) were isolated. **7** represents a novel ring system. The unexpected course of the reaction might be due to steric and electronic effects.

The IR spectrum of derivative **7** showed two carbonyl bands at 1 715 and 1 655 cm^{-1} (ester and amide, respectively) in accordance with the proposed structure but giving no evidence for it. The same was the situation with the MS spectra, where the relatively stable molecular ion M^+ appeared at 296. However, the fragmentation pattern was not informative enough for the unequivocal proof of structure **7**. In the ^{1}H NMR spectrum of **7**, besides the expected multiplicities of the SCH_3, (C-6)CH_3 and the ester CH_3 groups, the CH group 6 showed γ-coupling with the OCH_2 [of the (C-7) ethyl ester moiety] and the (C-8)CH_3 groups, which was in full accordance with the proposed structure. Structure **7** is also in accordance with the UV spectra obtained, showing two maxima at 231 and 300 nm, if taking in account that the analogous derivative **5** (Q = methylthio, R^1 = methyl, R^2 = H) prepared previously [3] showed three maxima at 231, 260 and 309 nm; the maximum appearing at 260 nm is probably due to the conjugation of the carbonyl band with the 6,7-double bond. The final and unequivocal proof of structure **7** offered again the ^{13}C NMR spectrum where the CH carbon atom 6 appeared at 61.1 ppm, the triazole carbon atoms C-3 and C-9a at 143.7 and 147.3, respectively, and the carbonyl carbon atom 5 at 157.6 ppm [compare with the corresponding carbon atoms C-3, C-8a and C-5 of **5** (Q = methylthio, R^1 = methyl, R^2 = H) appearing at 143.2, 150.4 and 156.7 ppm, respectively].

Derivative **7** may appear in tautomeric formes **7a** and **7b**. Taking in account the analogy of its UV and ^{13}C NMR spectra with those of **5** (Q = methylthio,



Scheme 3

R^1 = methyl, R^2 = H) with known tautomeric structure [3], the dominant tautomeric structure **7a** seems to be the favoured one in ethanolic and *DMSO-d_6* solution.

Experimental

Melting points were determined on a Kofler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The electron impact mass spectra were determined with a Varian MAS SM-1 spectrometer. The ultraviolet spectra were obtained by a Pye Unicam SP 8-150. The ^{1}H NMR and the ^{13}C NMR measurements were performed on a Varian EM-390 and Bruker WM-250 instrument at 90 and 250 MHz, respectively, in the CW or FT mode at ambient temperature using broad band and proton decoupling; internal standard was tetramethylsilane.

General Methods for the Preparation of Derivatives **3** *and* **4**

Method A. To a solution of 0.01 mol of the appropriate 5-amino-3-*Q*-1*H*-1,2,4-triazole (**1**) [4, 5] in 5 ml of acetic acid 0.012 mol of the appropriate ethyl 3-oxo-butyrate derivative (**2**) was added and

Table 1. Synthetic and analytical data

Compound no.	Q	R^1	R^2	Conditions of Preparation			Molecular formula (M.W.)	Analysis Calculated/Found				M.p. (°C) of the Na Salt
				Method	Yield (%)	M.p. (°C) (Cryst. from)		C	H	N	S	
3/1	Dimethylamino	Methyl	H	A	86	310–313 (*DMF*)	$C_8H_{11}N_5O$ (193.21)	49.73 49.70	5.74 5.71	36.25 36.30		343–345
3/2	Diethylamino	Methyl	H	C	45	220–221 (*DMF*)	$C_{10}H_{15}N_5O$ (221.26)	54.28 54.36	6.83 6.88	31.65 31.55		
3/3	Diallylamino	Methyl	H	A	83	232–235 (1-*Bu*OH)	$C_{12}H_{15}N_5O$ (245.29)	58.76 58.83	6.16 6.20	28.55 28.46		
3/4	Piperidino	Methyl	H	A	71	293–295 (*DMF*)	$C_{11}H_{15}N_5O$ (233.27)	56.64 56.48	6.48 6.38	30.02 30.11		280–284
3/5	4-Methylpiperazino	Methyl	H	D	64	286–288 (*DMF*)	$C_{11}H_{16}N_6O$ (248.29)	53.21 53.44	6.50 6.56	33.85 33.73		
3/6	*n*-Octylthio	Methyl	H	B	38	105–108 (2-*Pr*OH)	$C_{14}H_{22}N_4OS$ (294.42)	57.11 57.06	7.53 7.50	19.03 18.89	10.89 10.92	
3/7	Methylamino	Methyl	H	A	65	348–350 (*DMF*)	$C_7H_9N_5O$ (179.18)	46.92 47.09	5.06 5.11	39.09 38.96		330–340
3/8	Propylamino	Methyl	H	A	48	285–287 (*DMF*)	$C_9H_{13}N_5O$ (207.24)	52.16 52.08	6.32 6.35	33.79 33.68		
3/9	1-Methylethylamino	Methyl	H	A	50	264–267 (*Me*OH)	$C_9H_{13}N_5O$ (207.24)	52.16 52.20	6.32 6.34	33.79 33.85		
3/10	1,1-Dimethylethylamino	Methyl	H	B	43	275–279 (*DMF*+ CH_3CN)	$C_{10}H_{15}N_5O$ (221.26)	54.28 54.21	6.83 6.79	31.65 31.60		
3/11	Cyclohexylamino	Methyl	H	B	95	304–307 (*Me*OH)	$C_{12}H_{17}N_5O$ (247.30)	58.28 58.35	6.93 7.02	28.32 28.27		
3/12	Benzylamino	Methyl	H	A	76	324–327 (*DMF*)	$C_{13}H_{13}N_5O$ (255.28)	61.17 61.25	5.13 5.20	27.43 27.37		210–215

Table 1 (continued)

Compound no.	Q	R^1	R^2	Conditions of Preparation			Molecular formula (M.W.)	Analysis Calculated/Found				M.p. (°C) of the Na Salt
				Method	Yield (%)	M.p. (°C) (Cryst. from)		C	H	N	S	
3/13	2-Phenyl-ethylamino	Methyl	H	B	85	283–286 (*DMF*)	$C_{14}H_{15}N_5O$ (269.31)	62.44 62.34	5.61 5.66	26.01 26.11		200–205
3/14	2-(3,4-Di-ethoxyphenyl) ethylamino	Methyl	H	A	47	219–222 (*W*+2-*Pr*OH)	$C_{18}H_{23}N_5O_3$ (357.41)	60.49 60.27	6.49 6.30	19.59 19.45		
3/15	3,3-Diphenyl-propylamino	Methyl	H	A	45	281–284 (*W*+*DMF*)	$C_{21}H_{21}N_5O$ (359.43)	70.17 69.93	5.89 5.79	19.48 19.22		
3/16	Phenylamino	Methyl	H	A	78	350–360 (*DMF*+*Me*OH)	$C_{12}H_{11}N_5O$ (241.25)	59.74 59.81	4.60 4.67	29.03 28.96		>360
3/17	Pyridine-3-yl-amino	Methyl	H	A	52	345–350 (*DMSO*+CH_3CN)	$C_{11}H_{10}N_6O$ (242.24)	54.54 54.42	4.16 4.07	34.69 34.75		
3/18	Methylthio	Phenyl	H	A	32	292–295 (*Ac*OH)	$C_{12}H_{10}N_4OS$ (258.31)	55.80 55.75	3.90 4.14	21.69 21.42	12.42 12.52	
3/19	Methylthio	Chloro-methyl	H	A	61	226–230 (*DMF*)	$C_7H_7ClN_4OS$ (230.68)	36.45 36.40	3.06 3.10	24.29 24.40	13.90 14.01	
3/20	Benzylamino	Chloro-methyl	H	A	62	315–320 (*DMF*)	$C_{13}H_{12}ClN_5O$ (289.73)	53.89 53.72	4.17 4.10	24.17 24.28		
3/21	Methylthio	Methyl	Methyl	A	76	278–280 (*Ac*OH)	$C_8H_{10}N_4OS$ (210.26)	45.70 45.41	4.79 4.77	26.65 26.48	15.25 15.41	
3/22	Morpholino	Methyl	Methyl	A	63	248–250 (*n-Bu*OH)	$C_{11}H_{15}N_5O_2$ (249.27)	53.00 53.18	6.07 6.02	28.10 28.17		
3/23	2-(3,4-Di-ethoxyphenyl) ethylamino	Methyl	Methyl	A	82	264–267 (*Ac*OH)	$C_{19}H_{25}N_5O_3$ (371.44)	61.44 61.24	6.78 6.65	18.85 18.83		

Table 1 (continued)

Compound no.	Q	R^1	R^2	Conditions of Preparation			Molecular formula (M. W.)	Analysis Calculated/Found				M.p. (°C) of the Na Salt
				Method	Yield (%)	M.p. (°C) (Cryst. from)		C	H	N	S	
3/24	Methylthio	Methyl	Ethoxy-carbonylmethyl	A	32	211–213 (*W*+*DMF*)	$C_{11}H_{14}N_4O_3S$ (282.32)	46.80 46.76	5.00 5.01	19.85 19.94	11.36 11.35	
3/25	Morpholino	Methyl	1-Ethoxy-carbonylethyl	*	36	253–256 (*Me*OH)	$C_{15}H_{21}N_5O_4$ (335.36)	53.72 53.66	6.31 6.27	20.88 20.96		
3/26	Methylthio	Methyl	Chloro	A	67	324–327 (*DMF*)	$C_7H_7ClN_4OS$ (230.68)	36.45 36.58	3.06 3.16	24.29 24.20	13.90 13.82	
3/27	Benzylamino	Methyl	Chloro	A	45	316–320 (*DMF*)	$C_{13}H_{12}ClN_5O$ (289.73)	53.89 53.99	4.17 4.30	24.17 24.10		
4/1	Methylthio	Methyl	1-Ethoxy-carbonylethyl	*	41	193–194 (2-*Pr*OH)	$C_{12}H_{16}N_4O_3S$ (296.35)	48.64 48.82	5.44 5.63	18.91 18.79	10.82 10.90	
4/2	Morpholino	Methyl	1-Ethoxy-carbonylethyl	*	24	149–152 (2-*Pr*OH)	$C_{15}H_{21}N_5O_4$ (335.36)	53.72 53.70	6.31 6.35	20.88 20.76		

* See Experimental

Table 2. Spectral data (IR, ^{1}H NMR, ^{13}C NMR, UV)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2(3)	C-6	C-7(5)	C-2	C-5	C-6	C-7	C-8a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
3/1	1688	2.97 s	5.66 s	2.24 s	164.8	155.0	98.3	148.4	150.4	18.1 37.4	228 (10.9) 272 (4.3)	227 (11.2) 269 (4.5)	233 (11.6) 280 (4.1)
3/2	1695	1.15 t 3.45 q	5.69 s	2.27 s	163.4	155.2	98.4	148.3	150.4	12.9 18.2 41.9	228 (22.1) 275 (8.9)	228 (22.2) 270 (8.8)	280 (9.3)
3/3	1691	4.03 d 5.17 t 5.87 m	5.70 s	2.27 s	163.7	155.1	98.5	148.6	150.4	18.3 49.5 116.6 133.9	229 (20.4) 273 (8.1)	228 (23.8) 271 (9.6)	278 (8.8)
3/4	1662	1.57 m 3.42 m	5.66 s	2.24 s	164.3	154.1	98.4	148.6	150.3	18.2 23.8 24.6 46.2	228 (23.2) 272 (9.4)	228 (23.2) 270 (9.7)	232 (26.5) 279 (8.7)
3/5	1681	2.25 s 2.44 t 3.40 t	5.66 s	2.24 s	164.2	155.2	98.2	149.4	150.8	18.5 45.2 45.5 53.7	227 (26.8) 270 (9.4)	222 (28.2) 266 (10.8)	230 (27.7) 278 (9.2)
3/6	1668	0.88 t 1.27–1.76 m 3.17 t	5.82 s	2.32 s							229 (17.3) 264 (7.8)	226 (7.9) 264 (4.4)	280 (7.1)
3/7	1689	2.75 d 6.42 q (NH)	5.64 s	2.23 s	164.1	155.0	98.2	148.4	150.2	18.2 28.9	224 (17.0) 278 (6.1)	223 (17.9) 267 (6.7)	229 (15.9) 269 (6.1)

Table 2 (continued)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2(3)	C-6	C-7(5)	C-2	C-5	C-6	C-7	C-8a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
3/8	1673	0.90 t 1.55 m 3.12 q 6.50 t (NH)	5.62 s	2.24 s	163.6	155.2	98.3	148.5	150.2	11.2 18.3 22.4 44.2	223 (20.1) 270 (7.0)	222 (21.7) 268 (8.0)	229 (20.1) 278 (7.1)
3/9	1675	1.14 d 3.70 qq 6.35 d (NH)	5.61 s	2.22 s	162.7	155.0	98.1	148.3	150.0	18.2 22.4 43.6	221 (22.4) 270 (8.6)	221 (23.4) 268 (9.0)	279 (7.8)
3/10	1684	1.34 s 6.23 s (NH)	5.63 s	2.23 s	162.3	155.1	98.2	148.4	149.6	18.2 28.7 50.2	222 (21.2) 270 (8.1)	222 (21.1) 267 (9.0)	230 (20.1) 278 (8.1)
3/11	1689	1.18–1.94 m 2.51 m 6.42 d (NH)	5.69 s	2.23 s	162.9	155.2	98.3	148.5	150.2	18.3 24.7 25.4 32.7 51.1	224 (25.2) 280 (8.2)	228 (30.3) 268 (9.6)	230 (24.7) 279 (8.6)
3/12	1675	4.41 d 7.00 t (NH) 7.20–7.36 m	5.62 s	2.23 s	163.5	155.0	98.3	148.4	150.2	18.1 45.7	226 (21.6) 268 (8.4)	225 (22.7) 268 (8.9)	279 (7.7)
3/13	1680	2.85 t 3.37 q 6.60 t (NH) 7.15–7.3 m	5.64 s	2.23 s	163.2	154.9	98.2	148.3	150.0	18.1 34.9 43.7	226 (22.0) 270 (8.5)	224 (23.1) 268 (9.0)	279 (7.7)

Table 2 (continued)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2(3)	C-6	C-7(5)	C-2	C-5	C-6	C-7	C-8a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
3/14	1680	1.28 t 2.75 t 3.98 q 4.00 q 6.55 t (NH) 6.68 d, 6.82 d 6.80 s	5.65 s	2.22 s	163.5	155.2	98.4	146.6	150.1	14.8 18.3 34.7 44.0 63.7 63.8	226 (33.9) 273 (11.2)	225 (31.3) 272 (11.7)	278 (10.1)
3/15	1680	2.43 q 3.10 q 4.11 t 6.60 t (NH) 7.2–7.4 m	5.65 s	2.28 s	163.6	155.2	98.3	148.5	150.2	18.3 34.5 41.0 47.9	226 (34.4) 278 (10.2)	221 (35.4) 270 (10.9)	278 (7.0)
3/16	1675	6.65 t 7.26 t 7.67 d 9.56 s (NH)	5.72 s	2.25 s	159.7	155.1	98.4	149.2	149.4	18.2	230 (24.1) 283 (9.2)		
3/17	1675	7.37 q 8.17 q 8.85 d 9.85 s (NH)	5.81 s	2.33 s	159.4	154.8	98.5	149.2	149.7	18.3 122.9 137.5 138.9 141.0			
3/18	1675	2.01 s	5.64 s	6.9–7.4 m	163.3	154.9	97.6	151.7	150.5	13.4	237 (28.7) 279 (15.9)	235 (27.8) 281 (18.7)	280 (11.4)

Table 2 (continued)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2(3)	C-6	C-7(5)	C-2	C-5	C-6	C-7	C-8a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
3/19	1680	2.62 s	6.17 s	4.69 s	163.7	154.8	99.8	148.9	151.3	13.6	230 (22.3)	230 (22.3)	
										41.1	272 (8.4)	271 (10.8)	289 (8.6)
3/20	1680	4.49 d	6.08 s	4.63 s	162.3	155.1	100.3	148.9	150.3	41.9	233 (23.8)	232 (25.4)	
		7.19–7.40 m								45.8	280 (8.0)	276 (8.4)	288 (7.2)
										126.6			
										127.1			
										128.1			
										138.9			
3/21	1650	2.58 s	1.94 s	2.28 s	163.0	155.6	104.5	145.6	150.1	10.3	231 (27.0)	230 (28.5)	
										13.4	270 (7.4)	271 (8.2)	288 (7.2)
										17.0			
3/22	1655	3.30 t	1.98 s	2.34 s	164.4	155.9	104.4	144.1	149.4	10.3	231 (26.6)	229 (27.4)	
		3.75 t								16.6	274 (10.1)	274 (11.2)	285 (8.7)
										45.8			
										65.6			
3/23	1665	1.38 t	2.02 s	2.36 s	163.5	155.8	104.0	146.7	149.2	10.3	229 (33.2)	227 (33.9)	
		2.90 t								14.8	274 (11.7)	274 (12.5)	283 (9.0)
		3.55 q								16.8			
		4.12 q								34.7			
		4.15 q								44.0			
		6.60 t (NH)								63.6			
		6.9–7.2 m								63.8			

Table 2 (continued)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2 (3)	C-6	C-7 (5)	C-2	C-5	C-6	C-7	C-8 a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
3/24	1660 1730	2.56 s	1.19 t 3.49 s 4.04 q	2.29 s	163.7	155.2	103.6	148.0	150.4	13.5 14.0 17.0 30.4 60.4 170.4	230 (25.4) 268 (9.9)	231 (25.7) 268 (11.6)	286 (7.8)
3/25	1660 1745	3.40 t 3.70 t	1.09 t 1.26 d 3.25 q 4.02 q	2.35 s	164.4	154.4	110.2	144.6	149.3	13.8 14.3 36.2 45.7 59.9 65.3 172.7	232 (31.6) 274 (10.2)	232 (30.8) 274 (11.4)	234 (36.3) 287 (10.1)
3/26	1662	2.61 s		2.42 s	163.8	151.4	105.1	148.0	149.8	13.4 18.2	234 (23.9) 279 (8.9)	234 (24.0) 278 (10.1)	289 (9.4)
3/27	1681	4.41 d 7.2–7.4 m		2.36 s	163.3	152.0	105.5	147.1	149.2	18.4 46.1 126.5 127.4 128.4 140.3	230 (28.7) 280 (8.3)	230 (29.2) 279 (9.5)	289 (8.2)

Table 2 (continued)

Compound no.	IR [cm^{-1}] ν(C=O)	^{1}H-NMR [δ, ppm] (*DMSO-d_6*) Substituent at			^{13}C-NMR [δ, ppm] (*DMSO-d_6*)					Other char. bands	UV λ_{max} [nm] ($\varepsilon \cdot 10^{-3}$)		
		C-2 (3)	C-6	C-7 (5)	C-2	C-5	C-6	C-7	C-8 a		*Et*OH	10% *Et*OH + 90% 0.1 *N* HCl	10% *Et*OH + 90% 0.1 *N* NaOH
4/1	1 680 1 725	2.53 s	1.10 t 1.27 d 3.84 q 4.02 m	2.48 s	161.8	142.8	116.2	159.1	148.6	13.2 13.3 13.6 14.4 36.2 59.7 172.2	205 (25.8) 291 (11.6)	206 (28.8) 289 (12.5)	222 (27.9) 288 (9.2)
4/2	1 680 1 745	3.34 t 3.68 t	1.25 t 1.55 d 3.65 q 4.05 m	2.45 s	164.2	143.3	114.4	159.3	147.9	13.5 13.6 14.8 36.2 45.7 59.8 65.3 172.5	205 (29.8) 220sh(12.6) 310 (10.7)	205 (31.5) 222 sh (12.3) 308 (10.9)	222 (27.4) 298 (9.2)

the mixture was refluxed with stirring for 2 h. After cooling the crystals precipitated were filtered off, washed with water and recrystallized from an appropriate solvent to yield the corresponding derivative **3** (Table 1, for spectral data see Table 2).

The mother liquors were diluted with water, extracted twice with chloroform, the chloroform layers were washed with water, dried and evaporated *in vacuo* to dryness. The residue was chromatographed on a silica-gel column (eluent a 1 : 2 mixture of benzene and ethyl acetate) to yield **4**, which was recrystallized from an appropriate solvent (Table 1, for spectral data see Table 2).

Method B. To a solution of 0.01 mol of the appropriate triazole **1** [4, 5] in 5 ml of acetic acid 0.012 mol of the appropriate derivative **2** was added and the mixture was refluxed with stirring for 2 h. After cooling 10 ml of water was added to the reaction mixture, the crystals precipitated were filtered off and recrystallized from an appropriate solvent to yield the corresponding derivative **3** (Table 1, for spectral data see Table 2).

Method C. To a solution of 0.01 mol of the appropriate triazole **1** [4, 5] in 5 ml of acetic acid 0.012 mol of the appropriate derivative **2** was added and the mixture was refluxed with stirring for 2 h. After cooling 10 ml of water was added to the reaction mixture, the product was extracted twice with chloroform, the combined chloroform layers were washed with water, dried and evaporated *in vacuo* to dryness. The residue was recrystallized from an appropriate solvent to yield **3** (Table 1, for spectral data see Table 2).

Method D. To a solution of 0.01 mol of the appropriate triazole **1** [4, 5] in 5 ml of acetic acid 0.012 mol of the appropriate derivative **2** was added and the mixture was refluxed with stirring for 2 h. The solution obtained was evaporated *in vacuo* to dryness, the residue was trituated with 2-propanol, the crystals precipitated were collected and recrystallized from an appropriate solvent to yield **3** (Table 1, for spectral data see Table 2).

General Method for the Formation of the Sodium Salts of Derivatives **3** (**3**; Na)

1 g of the crude derivatives **3** was dissolved in 5–10 ml of hot 10% sodium hyroxide solution, filtered and let to crystallize. After cooling the crystals precipitated were collected, washed with cold water and dried to yield the corresponding sodium salt (**3**; Na) (Table 1).

Ethyl 4-Oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = *methyl*, R^2 = *1-ethoxycarbonylethyl*, R^3 = *ethyl*)

A mixture of 48.8 (0.375 mol) of ethyl acetoacetate, 67.9 g (0.375 mol) of ethyl 2-bromo-propionate, 69.0 g (0.5 mol) of powdered anhydrous potassium carbonate, 2.0 g of tetrabutylammonium hydrogen sulfate and 450 ml of dry toluene was refluxed with stirring for 18 h. After cooling the unsoluble salts were filtered off, the toluene layer was washed twice with water, dried over sodium sulfate and evaporated *in vacuo* to dryness. The residue was fractionated under high vacuum to yield 74.6 g (86%) of ethyl 4-oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl), b.p. 92°C/0.3 mm Hg; Lit. [6], b.p. 145–147°C/14 mm Hg.

Ethyl 4-Oxo-3-ethoxycarbonyl-valerate (**2**, R^1 = *methyl*, R^2 = *1-ethoxycarbonylmethyl*, R^3 = *ethyl*)

Prepared as ethyl 4-oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl) using instead of ethyl 2-bromopropionate ethyl 2-bromoacetate. Yield 69.5%, b.p. 86°C/0.2 mm Hg; Lit. [7], b.p. 133–134 °C/8 mm Hg.

6-(1-Ethoxycarbonylethyl)-5-methyl-2-methylthio-1,2,4-triazolo[1,5-a]pyrimidin-7(8H)-one (**4/1**, R^1 = *methyl*, R^2 = *1-ethoxycarbonylethyl*, Q = *methylthio*) *and 5,6-Dihydro-6,8-dimethyl-7-ethoxycarbonyl-3-methylthio-1,2,4-triazolo[4,3-a]-1,3-diazepin-5(9H)-one* (**7**)

A mixture of 3.90 g (0.03 mol) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1**, Q = methylthio) [4], 7.13 g (0.031 mol) of ethyl 4-oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl) and 15 ml of dimethylformamide was refluxed for 24 h. The solution obtained was poured to 100 ml of water, extracted twice with chloroform, the combined chloroform layers were washed with water, dried and evaporated *in vacuo* to dryness. The residue (10.0 g) was chromatographed on a silica gel column (eluent a 1 : 2 mixture of benzene and ethyl acetate) to yield 2.5 g (25%) of **7**, which after recrystallization from 2-propanol melted at 110–111°C. IR: 2.15 d (J = 1 Hz, CCH_3), 2.56 s (SCH_3), 4.32 m (CH_2CH_3), 4.86 m (CH), 13.6 b (NH); ^{13}C NMR 2.15 d (J = 1 Hz, CCH_3), 2.56 s (SCH_3), 4.32 m (CH_2CH_3), 4.86 m (CH), 13.6 b (NH); ^{13}C NMR (*DMSO-d*$_6$): 10.4 ($CHCH_3$), 13.6 (CH_2CH_3), 13.8 (SCH_3), 17.1 (CCH_3), 56.9 (CH_2), 61.1 (CH-6), 140.1 (C-7), 143.7 (C-3), 147.3 (C-9a), 157.6 (C-5), 162.2 (C-8), 167.6 (COO*Et*); UV: (*Et*OH): λ_{max} (17.3), 288 (4.8); (10% *Et*OH + 90% 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon \cdot 10^{-3}$): 232 (11.1), 292 (3.7); (17.3), 288 (4.8); (10% *Et*OH + 90% 0.1 *N* sodium hydroxide): λ_{max} ($\varepsilon \cdot 10^{-3}$): 232 (11.1), 292 (3.7); MS: M^+ = 296.

Continuing the chromatography 4.05 g (41%) of **4/1** was obtained, which after recrystallization from 2-propanol melted 193–194°C (Tables 1 and 2).

6-(1-Ethoxycarbonylethyl)-7-methyl-2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-5(8H)-one (**3/23**, R^1 = *methyl*, R^2 = *1-ethoxycarbonylethyl*, Q = *morpholino*) *and 6-(1-Ethoxycarbonylethyl)-5-methyl-2-morpholino-1,2,4-triazolo[1,5-a]pyrimidin-7(8H)-one* (**4/2**, R^1 = *methyl*, R^2 = *1-ethoxycarbonylethyl*, Q = *morpholino*)

A mixture of 5.08 g (0.03 mol) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1**, Q = morpholino) [5]) 7.13 g (0.031 mol) of ethyl 4-oxo-3-ethoxycarbonyl-2-methyl-valerate (**2**, R^1 = methyl, R^2 = 1-ethoxycarbonylethyl, R^3 = ethyl) and 20 ml of dimethylformamide was refluxed for 24 h. The solution obtained was poured to 100 ml of water, extracted twice with chloroform, the combined chloroform layers were washed with water, dried and evaporated *in vacuo* to dryness. The residue (9.0 g) was chromatographed on a silica gel column (eluent a 3 : 1 mixture of benzene and ethanol) to yield 2.4 g (24%) of **4/2**, which after recrystallization from 2-propanol melted at 150–152°C (Tables 1 and 2). Continuing the chromatography 3.6 g (36%) of **3/23** was obtained, which after recrystallization from methanol melted at 253–256°C (Tables 1 and 2).

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References

[1] For Part XVIII see: Reiter J., Rivó E. (1989) J. Heterocycl. Chem. **26**: 971
[2] Presented on the Annual Conference of the Hungarian Chemical Society. Kaposvár, 1989
[3] Reiter J., Pongó L., Dvortsák P. (1987) Tetrahedron **43**: 2497
[4] Reiter J., Somorai T., Jerkovich Gy., Dvortsák P. (1982) J. Heterocycl. Chem. **19**: 1157
[5] Reiter J., Pongó L., Somorai T., Dvortsák P. (1986) J. Heterocycl. Chem. **23**: 401
[6] Beilsteins Handbuch der Organischen Chemie (1921) Vol. 3. Springer, Berlin, S. 811
[7] Beilsteins Handbuch der Organischen Chemie (1921) Vol. 3, Springer, Berlin, S. 801

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