On Triazoles XLIV [1]. Synthesis of New Ring Systems Containing Imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidine and Imidazo[1',2':2,3][1,2,4]triazolo[1,5-*a*]pyrimidine Skeleton

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Dedicated to Dr. János Császár on the occasion of his 70th birthday

Ring transformation of 2-cyanoimido-3-methyl-1,3-oxazolidine (**10**) yielded 5-amino-3-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1*H*-1,2,4-triazole (**6**) that was ring closed with different β-keto esters to 2-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1,2,4-triazolo[1,5-*a*]pyrimidinones (**4**). Cyclisation of derivatives **4** led to imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidines (**2**) and imidazo[1',2':2,3][1,2,4]triazolo[1,5-*a*]pyrimidines (**3**) representing 10 novel ring systems. Besides spectroscopical evidence of structure of derivatives **2** and **3** X-ray diffraction analysis of derivative **2b** was also performed.

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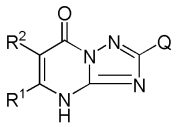
The antidepressant, sedative, spasmolytic and local anaesthetic activity of type **1** cycloalka- and heterocycloalka[*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5-ones [2-3] (Scheme 1) prompted us to add a further heterocyclic ring to the bi- or tricyclic heteroring systems of derivatives **1** originally present.

Scheme 1

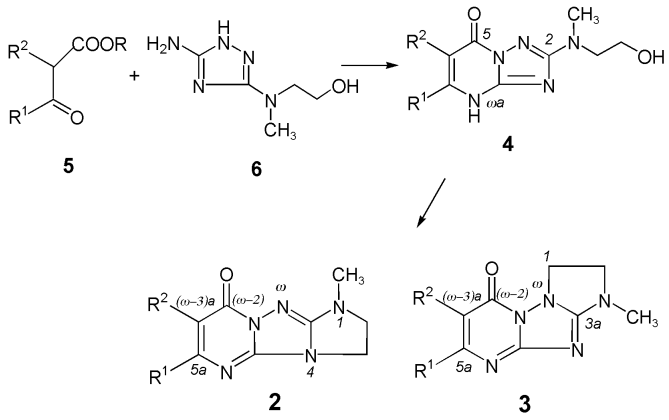


1, Q = SR' or NR'R'', **a:** $R^1 = CH_3$, $R^2 = H$
b: $R^1 + R^2 = -(CH_2)_3-$
c: $R^1 + R^2 = -(CH_2)_4-$
d: $R^1 + R^2 = -(CH_2)_3-S-$
e: $R^1 + R^2 = -CH_2-NBn-(CH_2)_2-$
f: $R^1 + R^2 = -(CH_2)_2-NBn-CH_2-$

Biological considerations led us to choose the imidazolidine ring as the further one condensed to **1**. Such compounds are derivatives **2** and **3** that were expected to form from intermediates **4** easily obtainable by the condensation of β-oxo-esters (**5**) with 5-amino-3-[*N*-(2-hydroxyethyl)-*N*-methyl]amino -1*H*-1,2,4-triazole (**6**) (Scheme 2).

Triazole **6** was prepared earlier [4] by treating the reaction mixture of dimethyl *N*-cyanoimidodithiocarbonate (**7**) and 2-(methylamino)ethanol (**8**) with hydrazine hydrate through the not isolated isothiourea derivative **9** (Scheme 3). However, the yield of this reaction was rather poor, 14 % only, and we needed a large quantity of **6** as starting material for the planned synthetical routes. In the hope of increasing the yield of the above reaction we tried to isolate the intermediate **9**, but during its isolation methanethiol was liberated and only the oxazolidine **10**

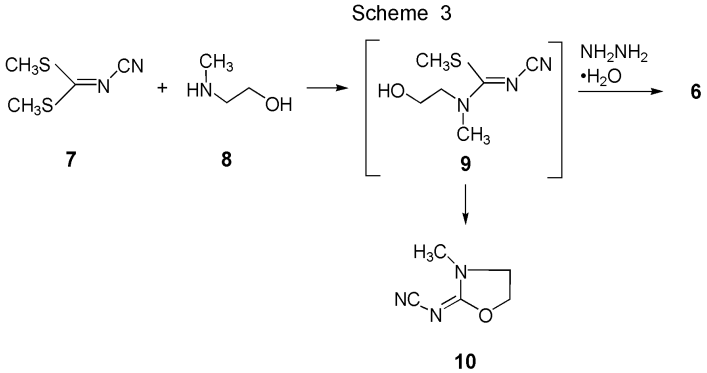
Scheme 2



5 **6** **4** **2** **3**

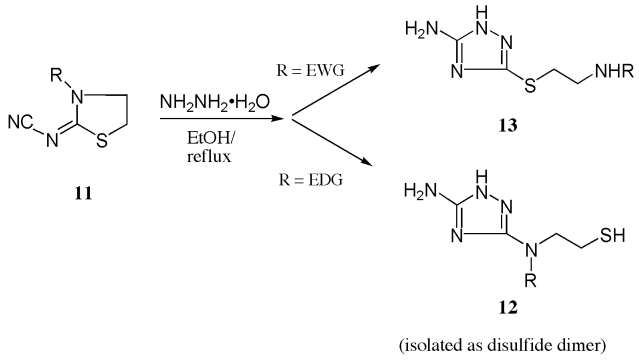
was obtained with excellent yield (Scheme 3). The same result was achieved when the reaction of **7** and **8** was carried out analogously to Ref. [5] in ether at room temperature for 36 hours.

Scheme 3



7 **8** **9** **6** **10**

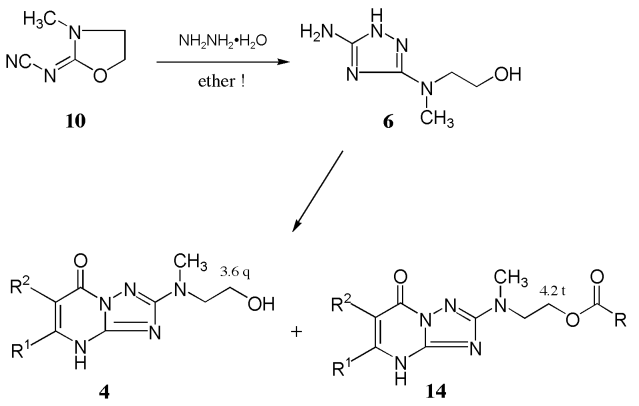
Scheme 4



It was known from the literature [6] that heating of 2-cyanoimino-3-R-thiazolidine derivatives (**11**) with hydrazine hydrate in ethanol led to ring transformation to yield in case of R = electron donating group (EDG) the corresponding 3,5-diamino-1,2,4-triazole derivatives (**12**) (Scheme 4) isolated as disulfide dimers, while in case of R = electron withdrawing group (EWG) to the corresponding 5-amino-3-alkylthio-1,2,4-triazoles (**13**).

Based on the above analogy ring transformation of **10** with hydrazine hydrate was attempted (Scheme 5). Interestingly, when performing the reaction at conditions described in Ref. [6], *i.e.* in hot ethanol only red tars were obtained. On the other hand, the heterogeneous reaction in ether at room temperature afforded 62 % of the desired **6**.

Scheme 5

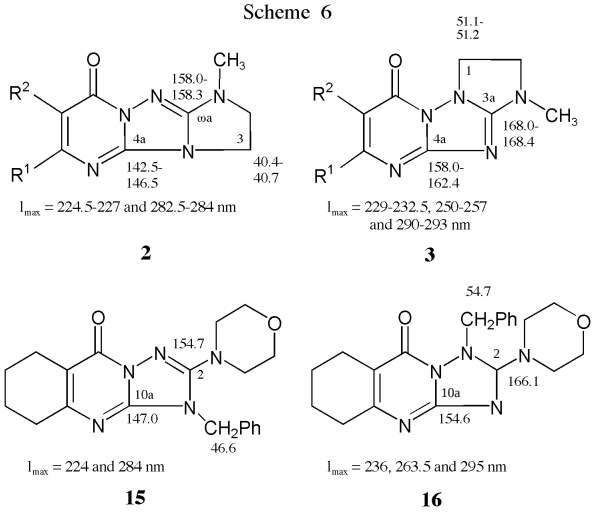


Having in hand a good synthetical route for the preparation of **6** its ring closure with different β-oxo-esters (**5**) was attempted (Scheme 2). As the required 1,2,4-triazolo[1,5-*a*]pyrimidine-5-one isomers were previously formed preferentially in acidic media [7-10], the reactions were performed in hot acetic acid as solvent (Method A), but the use of the corresponding β-oxo-ester (**5**) as solvent was also attempted (Method B). However, at both reaction conditions the hydroxyl group of derivatives **4** was partly acylated to yield a mixture of **4** and **14** (R = methyl and cyclopentanon-2-yl, respectively) (Scheme 5). Derivatives **14** (R = methyl and cyclopentanon-2-yl, respectively) were isolated and their structure proved spectroscopically. Luckily a simple work up of the mixtures of **4** and **14** with diluted sodium hydroxide solution or their reesterification with *n*-butanol led to pure derivatives **4** in good yield (Table I, for their nmr data see Table II).

The ring closure of derivatives **4** to the mixture of isomeric compounds **2** and **3** (Scheme 2) was performed analogously to the ring closure of some azasteroids [11] by heating them in polyphosphoric acid (PPA) at 120-130°. Work up of the reaction mixture led to 60-79 % of derivatives **2** and 4-6 % of derivatives **3** (Tables III and V, for their nmr data see Tables IV and VI, respectively). The assignment of the nmr signals being in full accordance with the structure of derivatives **2** and **3** was confirmed by 2D-nmr.

The structure of derivatives **2** and **3** was also corroborated by the analogy of their cmr and uv spectra with those of isomeric compounds **15** and **16** (Scheme 6) prepared earlier [12]. Thus the chemical shifts of carbon atoms 4a and ωa of derivatives **2** were analogous with the chemical shifts of the corresponding carbon atoms 10a and 2, respectively, of derivative **15** (Scheme 6). On the other hand the chemical shifts of carbon atoms 3a and 4a of derivatives **3** were analogous with those of the corresponding carbon atoms 2 and 10a, respectively, of derivative **16** (Scheme 6).

Scheme 6



Interestingly, the *N*-methylene carbon atoms 3 of derivatives **2** were strongly shifted upfield compared with those of the corresponding carbon atoms 1 of derivatives **3**. This observation is analogous to those of the *N*-benzyl methylenes of derivatives **15** as compared with the *N*-benzyl methylenes of derivatives **16** (Scheme 6). This fact further corroborates the structure of derivatives **2** and **3**.

In the uv spectra the two maxima of derivatives **2** were analogous to those of derivative **15**, while the three maxima of derivatives **3** were analogous to those of derivative **16**, respectively (Scheme 6).

Table I

Compound	R^1	R^2	Method	Reaction Time (hours)	Yield (%)	Mp (°C) (Cryst from)	Molecular Formula (MW)	ms (M^+)	Analysis Calcd / Found C	H	N	S	ir. ν (cm^{-1})	uv (EtOH) λ_{max}(ε .10^{-3})
4a	Me	H	B	2.5	74	235-241 (CH_3CN/EtOH)	$C_9H_{13}N_5O_2$ 223.23	EI 223	48.42 48.36	5.87 5.99	31.37 31.18		1694 1674 1587	230 (23.4) 276 (9.1)
4b •1/2 H_2O	-$(CH_2)_3$-		A B	1.5 2.5	77 42	250-259 (dec) (CH_3CN/EtOH)	$C_{11}H_{15}N_5O_2$ •1/2H_2O 258.28	EI 249	51.15 51.16	6.25 6.24	27.12 26.86		1653 1577	232.5 (28.1) 279 (13.0)
4c	-$(CH_2)_4$-		A B	1 1	70 74	250-258 (dec) (CH_3CN/EtOH)	$C_{12}H_{17}N_5O_2$ 263.30	EI 263	54.74 54.96	6.51 6.38	26.60 26.63		1654 1577	232.5 (28.4) 279.5 (12.3)
4d	-$(CH_2)_3$-S-		A	0.5	88	281-293 (dec) (EtOH/H_2O)	$C_{11}H_{15}N_5O_2S$ 281.34	EI 281	46.96 47.02	5.37 5.51	24.89 24.76	11.40 11.37	1656 1641 1585	257.5 (28.8) 304.5 (8.1)
4e	-CH_2-NBn-$(CH_2)_2$-		A	12	69	213-230 (dec) (CH_3CN/EtOH)	$C_{18}H_{22}N_6O_2$ 354.42	EI 354	61.00 60.92	6.26 6.44	23.71 23.69		1674 1609 1590	233.5 (30.5) 281.5 (10.1)

Table II

nmr (DMSO-d_6)

Compound	OH bs	OCH_2	NCH_2	NMe	2	5 (CO)	5a	(ω-1)a	ωa	NH bs	$R^1 + R^2$		
4a	4.7	3.58 t 58.8	3.44 t 52.3	3.02 s 36.5	164.6	155.5	5.64 s 98.7 (CH-6)	150.7	148.8	12.8	2.22 s 18.5 (7-Me)		
4b •1/2 H_2O	4.7	3.60 t 58.8	3.45 t 52.3	3.03 s 36.5	164.4	154.2	110.1	152.0	150.9	12.9	2.85 t 31.3 (CH_2-8)	2.05 qi 21.7 (CH_2-7)	2.63 t 27.1 (CH_2-6)
4c	4.7	3.60 t 58.8	3.45 t 52.3	3.03 s 36.5	164.4	155.8	106.0	145.0	149.7	12.5	2.54 t 26.3 (CH_2-9)	1.70 m (4H) 21.4 (CH_2-8)	21.2 (CH_2-7) 2.34 t 21.5 (CH_2-6)
4d	4.65	3.59 t 58.7	3.45 t 52.3	3.03 s 36.4	164.4	153.2	103.7	140.3	149.1	12.8	2.67 t 26.1* (CH_2-9)	2.04 m 21.9 (CH_2-8)	2.90 m 25.3* (CH_2-7)
4e	4.6	3.58 t 58.7	3.44 t 52.3	3.02 s 36.4	164.4	155.6	104.2	143.2	149.9	12.55	3.38 s 51.5 (CH_2-9) 3.67 s 60.9 ($PhCH_2$)	2.69 t 49.1 (CH_2-7) 7.25-7.40 m (5H) 138.0 (*s*); 129.1 (*m*);	2.44 t 21.7 (CH_2-6) 127.5 (*p*) 128.6 (*o*)

The only exceptions from the above uv rules were shown by the sulfur containing derivatives **2** [$R^1 + R^2$ = -$(CH_2)_3$-S-] and **3** [$R^1 + R^2$ = -$(CH_2)_3$-S-] having a sulfur atom attached to the imidazo-triazolo-pyrimidinone chromophore causing a batochromic shift of the spectra. Such a batochromic shift was observed previously in the analogous sulfur-containing derivatives [7,13]. However, the cmr spectra characterised also these derivatives unequivocally.

To corroborate the decisions made on the basis of the cmr and uv spectra X-ray diffraction analysis of **2b** [$R^1 + R^2$ = -$(CH_2)_3$-] was also performed (Figure 1) being in full accordance with that of expected [14].

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 882 spectrophotometer. The ultraviolet spectra were obtained by using a Varian Cary 1E UV-VIS instrument. The pmr and the cmr measurements were performed on Bruker WM-250 and Varian Unity Inova 400

Table III

Compound	R^1	R^2	Reaction Time (hours)	Yield (%)	mp (°C) (Cryst. from)	Molecular Formula (MW)	ms (M^+)	Analysis Calcd/Found C	H	N	S	ir ν (cm^{-1})	uv (EtOH) $\lambda_{max}(\varepsilon.10^{-3})$
2a	Me	H	2	65	305-307 (EtOH/H_2O)	$C_9H_{11}N_5O$ 205.22	EI 205 (100%)	52.68 52.75	5.40 5.56	34.13 34.04		1690 1656 1596	224.5 (32.8) 282.5 (9.2)
2b	-(CH_2)$_3$-		6	71	307-309 (EtOH/H_2O)	$C_{11}H_{13}N_5O$ 231.26	EI 231 (100%)	57.13 57.05	5.67 5.80	30.28 30.18		1690 1647 1595	227.5 (35.6) 283.5 (9.8)
2c	-(CH_2)$_4$-		4	69	297-300 (dec) (EtOH/H_2O)	$C_{12}H_{15}N_5O$ 245.29	EI 245 (75%)	58.76 58.82	6.16 6.34	28.55 28.48		1690 1639 1595	226.5 (33.3) 283.5 (9.8)
2d	-(CH_2)$_3$-S-		7	79	328-333 (dec) (EtOH/H_2O)	$C_{11}H_{13}N_5OS$ 263.32	EI 263 (100%)	50.18 50.23	4.98 5.12	26.60 26.51	12.18 12.07	1671 1650 1612	246.5 (19.0) 263.5 (sh) 317 (8.1)
2e	-CH_2-NBn-(CH_2)$_2$-		12	60	220-240 (dec) (EtOH/H_2O)	$C_{18}H_{20}N_6O$ 336.40	EI 336 (25%)	64.27 64.18	5.99 6.11	24.98 25.03		1672 1650 1610	227 (36.9) 284 (9.8)

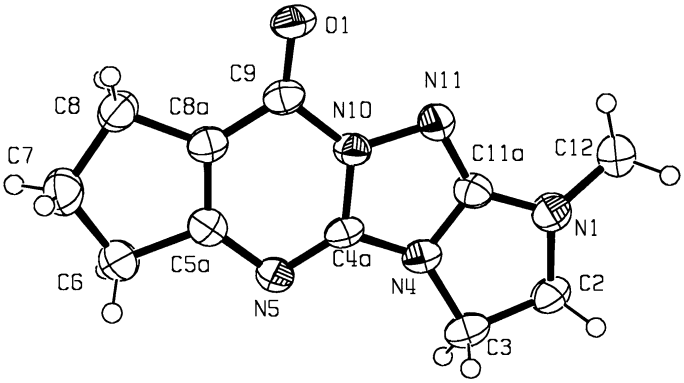


Figure 1. Perspective view of **2b** [$R^1 + R^2$ = -$(CH_2)_3$-]. Atomic thermal ellipsoids are on 50% probability level.

(400 MHz) instruments. To confirm the assignments in some cases standard Varian HSQC and HMBC 2D-nmr programs were used. The ms spectra were recorded on a Kratos MS25RFA instrument using direct inlet probe in EI or CI mode, as well as on a VG Quattro instrument (APCI or ES). The dry column flash chromatographies were performed according to [15].

2-Cyanoimido-3-methyl-1,3-oxazolidine (**10**).

To a solution of 29.25 g (0.2 mole) of dimethyl *N*-cyanoimidodithiocarbonate (**7**) [16] in 400 ml of diethyl ether a solution of 15.2 g (0.2 mole) of 2-(methylamino)ethanol (**8**) (Aldrich) in 80 ml of diethyl ether was added dropwise with stirring at room temperature over a period of 2 hours (the methanethiol liberated during the reaction was trapped with a sodium hydroxide solution). The reaction mixture was stirred at room temperature for 36 hours. During stirring the white oily product separated and crystallised. This was filtered off and washed with diethyl ether to yield 24.5 g (98 %) of 2-cyanoimido-3-methyl-1,3-oxazolidine (**10**) as a slightly hygroscopic powder, mp 60-62°. ir: ν (CN) = 2193 cm^{-1}; pmr (deuteriochloroform): δ, ppm, 2.99 (s, 3H, CH_3), 3.81 (m, 2H, NCH_2), 4.62 (m, 2H, OCH_2); cmr (deuteriochloroform): δ, ppm, 31.4 (CH_3), 48.3 (NCH_2), 66.1 (OCH_2), 115.4 (CN), 163.2 (C=N). ms (APCI): $(M + 1)^+$ = 126.

5-Amino-3-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1*H*-1,2,4-triazole (**6**).

To a suspension of 25.02 g (0.2 mole) of 2-cyanoimido-3-methyl-1,3-oxazolidine (**10**) in 150 ml of diethyl ether 10.51 g (10.2 ml, 0.21 mole) of 100 % hydrazine hydrate was added with stirring at room temperature. The exothermicity kept the ether refluxing for 1 hour. The mixture was stirred for further 24 hours at room temperature. The red reaction mixture obtained was decanted, the solid residue washed with 50 ml of ether and stirred at 5° for 30 minutes with 30 ml of 2-propanol. The crystalline product was isolated by filtration and washed with cold 2-propanol and diethyl ether to yield 19.5 g (62 %) of tlc pure material, mp 148-151°. An analytical sample was recrystallised from a 1:1 mixture of ethanol and acetonitrile, mp 150-152° (Lit. [4] mp 147-149°); pmr (DMSO-d_6): δ, ppm, 2.84 (s, 3H, CH_3), 3.26 (t, 2H, NCH_2), 3.52 (q, 2H, OCH_2), 4.68 (t, 1H, OH), 5.6 (bs, 2H, NH_2), 10.8 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm, 36.8 (CH_3), 53.0 (NCH_2), 59.2 (OCH_2), 157 and 162.5 (broad peaks, triazole C-3 and C-5). ms (ES): $(M + 1)^+$ = 158.

General Method for the Synthesis of 2-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1,2,4-triazolo[1,5-*a*]pyrimidin-5-ones (**4**) – Method A.

To a solution of 5.50 g (0.035 mole) of 5-amino-3-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1*H*-1,2,4-triazole (**6**) in 10 ml of acetic acid 0.04 mole of the corresponding β-oxo-ester **5** was added and the mixture heated with stirring at 130° (oil bath) for 0.5-12 hours (Table I). After cooling the crystals that precipitated while hot were isolated by filtration and washed with acetic acid and ethanol to yield the corresponding derivatives **4** contaminated with a small amount of the corresponding *O*-acetyl derivatives **14** (R = methyl). This was placed into a 5 % aqueous solution of sodium hydroxide and stirred at room temperature for 30 minutes. The pH of the solution was adjusted with concentrated hydrochloric acid to 6, the crystals that precipitated were isolated by filtration and washed with water and acetonitrile to yield the title products **4** (Tables I and II).

Table IV

nmr (deuteriochloroform)

Compound	N-Me (s)	2 (m)	3 (m)	4a	5a	(ω-3)a	ω-2 (CO)	ωa	$R^1 + R^2$		
2a [a]	3.05	4.06	4.23			6.01s			2.28 s		
	32.6	55.2	40.6	146.0	161.7 (C-6)	103.7 (CH-7)	156.8	158.0	23.8 (6-Me)		
2b	3.06	4.04	4.21						2.88 t	2.10 m	2.84 t
	32.7	55.2	40.6	146.5	166.3	115.5 (C-8a)	155.2	158.2	34.8 (CH_2-6)	22.1 (CH_2-7)	27.3 (CH_2-8)
2c [a]	3.04	4.03	4.19						2.60 t	1.75 m (4H)	2.60 t
	32.8	55.4	40.6	144.2	157.8	112.8 (C-9a)	157.3	158.3	32.1 (CH_2-6)	22.6 (CH_2-7) 22.2 (CH_2-8)	22.65 (CH_2-9)
2d	3.04	4.08	4.23						2.74 t	2.19 m	2.96 m
	32.1	55.0	40.7	142.5	151.3	110.3 (C-9a)	154.1	158.3	31.0 (CH_2-6)	22.9 (CH_2-7)	26.0 (CH_2-8)
2e [a]	3.03	4.01	4.15						3.43 s	2.74 s (4H)	
	32.6	55.2	40.4	144.5	155.3	110.4 (C-9a)	156.6	158.0	57.0 (CH_2-6)	49.8 (CH_2-8)	22.8 (CH_2-9)
									N-CH_2Ph: 3.70 s	7.25-7.40 m (5H)	
									62.3 (Ph*C*H_2)	137.6 (*s*); 127.2 (*p*) 129.1 (*m*); 128.3 (*o*)	

[a] Assignment corroborated by 2D method.

Table V

Compound	R^1	R^2	Reaction Time (hours)	Yield (%)	mp (°C) (Cryst from)	Molecular Formula (MW)	ms (M^+)	Analysis Calcd /Found C	H	N	S	ir ν (cm^{-1})	uv (EtOH) λ_{max}(ε.10^{-3})
3a	Me	H	2	5	158-162 (ether)	$C_9H_{11}N_5O$ 205.22	EI 205 (100%)	52.68 52.55	5.40 5.55	34.13 34.11		1665 1563 1522	230 (24.0) 250 (10.5) 290 (7.7)
3b	-$(CH_2)_3$-		6	5	188-189.5 (ether)	$C_{11}H_{13}N_5O$ 231.26	EI 231 (100%)	57.13 57.25	5.67 5.72	30.28 30.24		1668 1564 1530	232.5 (25.4) 257 (12.8) 293 (8.4)
3c	-$(CH_2)_4$-		4	6	208-210 (ether)	$C_{12}H_{15}N_5O$ 245.29	EI 245 (100%)	58.76 58.65	6.16 6.24	28.55 28.61		1650 1563 1533	231 (26.0) 257 (14.3) 291.5 (8.8)
3d	-$(CH_2)_3$-S-		7	6	223-228 (dec) (EtOAc)	$C_{11}H_{13}N_5OS$ 263.32	EI 263 (100%)	50.18 50.31	4.98 5.09	26.60 26.48	12.18 12.11	1651 1564	229 (16.7) 279.5 (11.3) 326.5 (8.6)
3e	-CH_2-NBn-$(CH_2)_2$-		12	4	190-200 (dec) (ether)	$C_{18}H_{20}N_6O$ 336.40	EI 336 (27 %)	64.27 64.33	5.99 6.09	24.98 25.06		1656 1582 1544	232 (27.0) 252 (14.6) 292.5 (8.5)

Isolation of 2-[*N*-(2-Acetoxyethyl)-*N*-methyl]amino-8-benzyl-6,7,8,9-tetrahydropyrido[3,4-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one.

14e (R = methyl) from the Mixture of **4e** and **14e** (R = methyl).

A small amount of the mixture of **4e** and **14e** (R = methyl) was chromatographed on a Kieselgel 60 H column (eluent a 50:1 mixture of dichloromethane and methanol) to yield 2-[*N*-(2-acetoxyethyl)-*N*-methyl]amino-8-benzyl-6,7,8,9-tetrahydropyrido[3,4-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one **14e** (R = methyl), mp 190-205° (dec) (ethyl acetate). ir: ν (C=O) = 1743 cm^{-1} (ester) and 1672 cm^{-1} (amide); uv (EtOH): λ_{max}, nm (ε.10^{-3}): 280.5 (12.1) and 233 (32.6); ms (EI): M^+ = 396; pmr (DMSO-d_6): δ, ppm, 1.96 (s, 3H, CH_3), 2.44 (t, 2H, CH_2-6), 2.69 (t, 2H, CH_2-7), 3.02 (s, 3H, NCH_3), 3.38 (t, 2H, CH_2-9), 3.63 (t, 2H, NCH_2), 3.68 (s, 2H, $PhCH_2$), 4.21 (t, 2H, OCH_2), 7.25-7.40 (m, 5H, PhH), 12.6 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm, 20.8 (CH_3), 21.7 (CH_2-6), 36.1 (NCH_3), 48.6 (NCH_2), 49.1 (CH_2-7), 51.5 (CH_2-9), 60.8 ($PhCH_2$), 61.5 (OCH_2), 104.2 (C-5a), 127.3 (PhC-4'), 128.4 (PhC-2',6'), 128.9 (PhC-3',5'), 137.9 (PhC-1'), 143.1 (C-9a), 149.8 (C-10a), 155.5 (C-5), 170.4 (C=O, ester).

Anal. Calcd. for $C_{20}H_{24}N_6O_3$ (MW = 396.44): C, 60.59; H, 6.10; N, 21.20. Found: C, 60.38; H, 6.12; N, 21.01.

Synthesis of 2-[*N*-(2-Hydroxyethyl)-*N*-methyl]amino-cyclopenta[*d*]-6,7-dihydro-8*H*-1,2,4-triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**4b**) – Method B.

A mixture of 0.943 g (0.006 mole) of 5-amino-3-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-1*H*-1,2,4-triazole (**6**) and 3.75 g (0.024 mole) of ethyl 2-oxocyclopentanecarboxylate (4.0 g, 95 %

Table VI

nmr (deuteriochloroform)

Compound	N-Me (s)	1 (m)	2 (m)	4a	5a	(ω-3)a	ω-2	3a (CO)	$R^1 + R^2$		
3a [a]	3.18	4.25	4.00			5.90 s			2.31 s		
	32.0	51.1	52.7	161.7	165.7 (C-6)	102.5 (CH-7)	157.0	168.3	24.4 (6-Me)		
3b	3.17	4.26	3.97						2.86 t	2.08 m	2.81 t
	32.0	51.1	52.6	162.4	170.7	114.4 (C-8a)	155.2	168.3	35.2 (CH_2-6)	21.9 (CH_2-7)	26.8 (CH_2-8)
3c [a]	3.16	4.21	3.97						2.66 t	1.75 m (4H)	2.54 t
	32.2	51.2	52.8	159.4	161.7	111.9 (C-9a)	157.4	168.4	32.5 (CH_2-6)	22.1 22.15 (CH_2-7) (CH_2-8)	22.6 (CH_2-9)
3d	3.17	4.25	4.00						2.78 t	2.17 m	2.95 m
	32.0*	51.1	52.7	158.0	155.9	109.2 (C-9a)	154.3	168.0	31.9* (CH_2-6)	23.2 (CH_2-7)	26.2 (CH_2-8)
3e [a]	3.15	4.20	3.96						3.51 s	2.7 m (4H)	
	32.0	51.1	52.7	159.2	160.0	109.7 (C-9a)	156.9	168.2	57.6 (CH_2-6)	49.4 (CH_2-8)	22.3 (CH_2-9)
									N-CH_2Ph:		
									3.71 s	7.25-7.40 m (5H)	
									62.1 (PhCH_2)	137.7 (*s*); 127.1 (*p*) 129.1 (*m*); 128.3 (*o*)	

[a] Assignment corroborated by 2D method.

Fluka) was heated at 120-125° (oil bath) with stirring for 2.5 hours. The hot suspension obtained was diluted with 6 ml of acetonitrile, the crystals that precipitated while hot were isolated by filtration and washed with acetonitrile and ether to yield 0.88 g of a mixture of derivatives **4b** and **14b (**R = cyclopentanon-2-yl). To this mixture 10 ml of *n*-butanol was added and stirred at 100° overnight. The reaction mixture obtained was evaporated *in vacuo* to dryness, the residue was triturated with acetonitrile and the crystals obtained isolated by filtration and washed with acetonitrile and ether to yield 0.63 g (42 %) of 2-[*N*-(2-hydroxyethyl)-*N*-methyl]amino-cyclopenta[*d*]-6,7-dihydro-8*H*-1,2,4-triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**4b**) that after recrystallisation from a mixture of 30 ml of acetonitrile and 12 ml of ethanol decomposed at 250-259°. For its analytical and spectral data see Tables I and II.

Isolation of 2-[*N*-(Cyclopentanon-2-yl-carbonyloxyethyl)-*N*-methyl]amino-cyclopenta[*d*]-6,7-dihydro-8*H*-1,2,4-triazolo[1,5-*a*]-pyrimidin-5(9*H*)-one (**14b**, R = cyclopentanon-2-yl) from the Mixture of **4b** and **14b** (R = cyclopentanon-2-yl).

The mixture of derivatives **4b** and **14b** (R = cyclopentanon-2-yl) (1.05 g) obtained according to the previous experiment was chromatographed on a Kieselgel 60 H column (eluent dichloromethane and different mixtures of dichloromethane and acetonitrile up to 4:1) to yield 0.49 g of 2-[*N*-(cyclopentanon-2-yl-carbonyloxyethyl)-*N*-methyl]amino-cyclopenta[*d*]-6,7-dihydro-8*H*-1,2,4-triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**14b**, R = cyclopentanon-2-yl) that after recrystallisation from acetonitrile decomposed at 240-244°. ir: ν (C=O) = 1758, 1722, 1649 cm^{-1}; uv (EtOH): λ_{max}, nm ($\varepsilon.10^{-3}$): 279 (14.2) and 232.5 (29.7); ms (EI): M^+ = 359; pmr (DMSO-d_6): δ, ppm 1.75 (m, 1H, cylopentane-4'-α), 1.90 (m, 1H, cylopentane-4'-β), 2.0 (m, 1H, cylopentane-3'-α), 2.05 (m, 2H, CH_2-7), 2.15 (m, 1H, cylopentane-3'-β), 2.2 (m, 2H, cyclopentane-5'), 2.64 (t, 2H, CH_2-6), 2.86 (t, 2H, CH_2-8), 3.01 (s, 3H, NCH_3), 3.27 (t, 1H, cyclopentane-CH), 3.65 (t, 2H, NCH_2), 4.26 (t, 2H, OCH_2), 13.0 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 20.5 (cylopentane-CH_2-4'), 21.7 (CH_2-7), 27.0 (cylopentane-CH_2-3'), 27.1 (CH_2-6), 31.3 (CH_2-8), 36.1 (NCH_3), 37.7 (cylopentane-CH_2-5'), 48.6 (NCH_2), 54.4 (cylopentane-CH), 62.4 (OCH_2), 110.1 (C-5a), 151.0 (C-9a), 152.2 (C-8a), 154.2 (C-5), 169.4 (C=O, ester), 212.4 (CO, ketone).

Anal. Calcd. for $C_{17}H_{21}N_5O_4$ (MW = 359.38): C, 56.81; H, 5.89; N, 19.49. Found: C, 56.74; H, 5.87; N, 19.34.

Continuing the chromatography with a 19:1 mixture of dichloromethane and methanol 0.40 g of **4b** was obtained, mp 250-258° (dec). For its analytical and spectral data see Tables I and II.

General Method for the Synthesis of Imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidine (**2**) and Imidazo[1',2':2,3][1,2,4]triazolo[1,5-*a*]pyrimidine (**3**) Derivatives.

A mixture of 0.029 mole of the corresponding derivative **4** with 54 g of polyphosphoric acid (Fluka) was strirred at 130° (oil bath) for 2-12 hours (Table III). The honey-like brown solution obtained was dissolved in 3 x 100 ml of water keeping the temperature of the mixture continuously below 50°. The pH of the intensively stirred solution was adjusted by addition of 60 g of sodium hydrogen carbonate to 5 (in small portions; the intensive foaming could be ceased by addition of a few drops of ether). To the cold suspension obtained 30 ml of concentrated ammonium hydroxide was added dropwise over a period of a few minutes to yield a suspension of pH = 11. The product that pecipitated was filtered off and washed with diluted aqueous ammonium hydroxide solution to yield the raw derivative **2**. This was dry column flash chromatographed on a short Kieselgel 60 H column [eluent: chloroform and different mixtures of chloroform and methanol (up to 5 %)] and after evaporation of the appropriate fractions *in*

vacuo the residue was recrystallised from aqueous ethanol (Tables III and IV).

The original aqueous mother liquor (pH = 11) was extracted with 3 x 40 ml portions of chloroform, the combined organic layers were dried over sodium sulfate, evaporated to dryness and dry column flash chromatographed on a short Kieselgel 60 H column (eluents different mixtures of ethyl acetate and acetonitrile). The tlc pure **3** obtained was triturated with an appropriate solvent (Tables V and VI) and filtered.

Crystal structure analysis of **2b** {1-Methyl-2,3,6,7-tetrahydro-8*H*-cyclopenta[*d*]-imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidin-9(1*H*)-one} [14].

The X-ray diffraction was performed according to the following parameters: $C_{11}H_{13}N_5O$, Fwt.: 231.26, orthorhombic, space group *P n a 2*$_1$, a = 7.743(1) Å, b = 9.074(1) Å, c = 15.023(2) Å, V = 1055.5(2) Å^3, T = 293(2)K, Z = 4, F(000) = 488, Dx =1.455Mg/m^3, μ = 0.100mm^{-1}, crystal size: 0.20 x 0.20 x 0.10 mm. Intensities of 2728 reflections (2547 unique [R(int) = 0.0037]; 1511 observed with I >2σ(I)) were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71070Å) at 293(2)K in the range 2.62° ≤ θ ≤ 27.99° using ω-2θ scans. A psi-scan absorption correction was applied to the data. The structure was solved by direct methods and refined in anisotropic mode by full-matrix least-squares on F^2 for all non-hydrogen atoms to R1 = 0.0406 and wR2 = 0.1075 for observed and R1 =0.0906 and wR2 = 0.1256 for all intensity data (goodness-of-fit = 0.743; the maximum shift/esd 0.000; extinction coefficient = 0.0046(18)). Number of parameters = 156. The maximum and minimum residual electron density in the final difference map was 0.178 and -0.168e/Å^3. Hydrogen atomic positions were located from assumed geometries but were not refined.

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