On Triazoles **XVIII.** [1].
An Unexpected Rearrangement Observed During the Reaction of 5-Amino-1,2,4-triazoles with *N*-Heterocyclic *β*-Oxo-esters

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In the course of the synthesis of pyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **3c** representing a novel ring system an unexpected rearrangement of the intermediate enamines to yield **5** was observed. A mechanism of the formation of **5** was suggested. The isomeric pyrido[4,3-*e*]-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives **4c** containing also a new ring system were obtained, too. The structure of products obtained was proved with the help of their uv, cmr and X-ray spectra.

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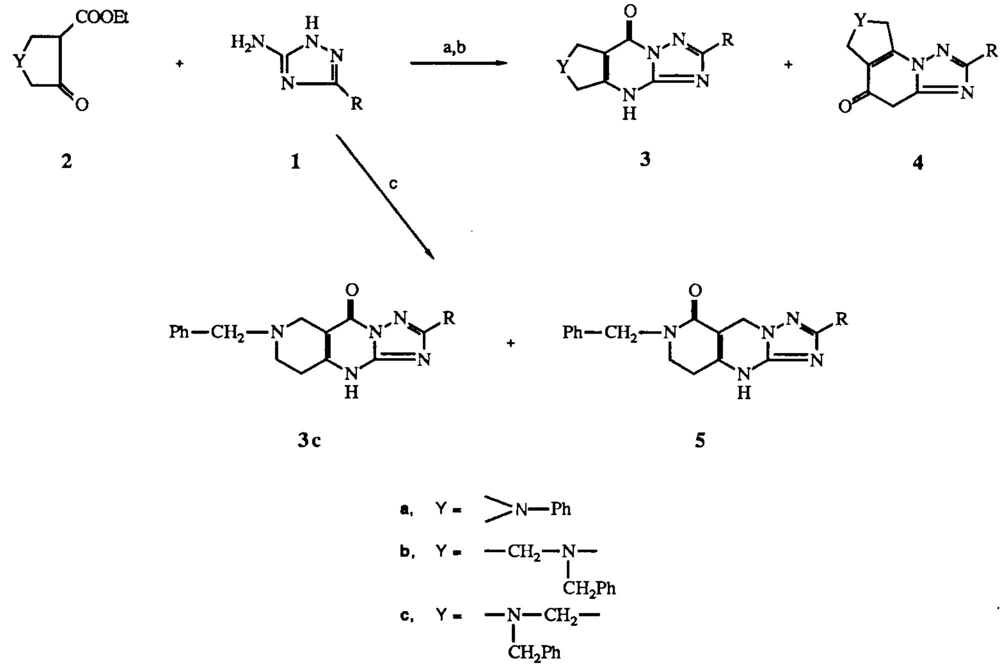
In the preceding paper of this series [1] we have studied the reaction of 5-amino-3-R-1*H*-1,2,4-triazoles (**1**) with two *N*-heterocyclic *β*-oxo-esters, namely the ethyl 4-oxo-1-phenyl-3-pyrrolidinecarboxylate (**2a**) to yield **3a** and the reaction of its 6-membered analogue, the ethyl 1-benzyl-3-oxo-4-piperidinecarboxylate hydrochloride (**2b**) to yield the mixture of the corresponding tricyclic isomers **3b** and **4b**, respectively (Scheme 1).

In hope to prepare the mixture of derivatives **3c** and **4c**, methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) was reacted with the corresponding derivatives **1**. Surprisingly, besides the expected derivatives **3c** the unexpected isomers **5** were obtained instead of the corresponding derivatives **4c**.

The structure of derivatives **3c** was proposed on the analogy of their uv spectra with those of derivatives **3a** and **3b**, respectively, as well as on the analogy of their cmr spectra with those of the corresponding bicyclic triazolopyrimidinones prepared earlier [2] as models for the structure elucidation of condensed-ring triazolopyrimidinone derivatives {compare *e.g.* the chemical shift of the triazole carbon atom 2 of **3c** (Y = -N(CH_2Ph)-CH_2-, R = methylthio; δ = 163.0 ppm) with that of the corresponding **3** type 7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (δ = 163.2 ppm, [2]) or that of the corresponding carbonyl carbon atom 5 of **3c** (Y = -N(CH_2Ph)-CH_2-, R = methylthio, δ = 154.1 ppm) with that of the corresponding **3** type 7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (δ = 154.9 ppm, [2]), respectively (see also the cmr rule elaborated [2])}.

On the other hand, the uv and the cmr data of derivatives **5** corresponded neither to the uv and cmr data

Scheme 1

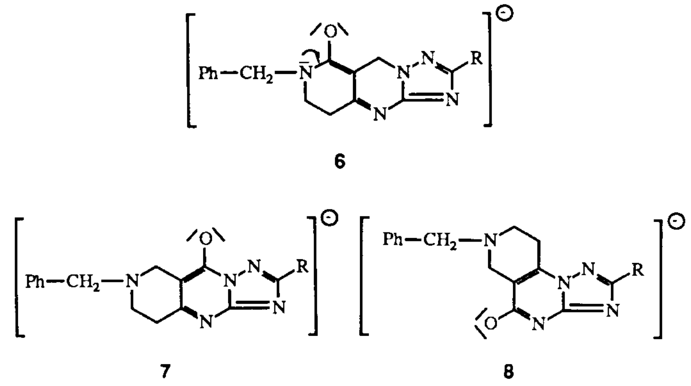


of derivatives **4** nor to any of the four possible bicyclic triazolo[1,5-*a*]pyrimidinone isomers prepared previously [2]. The most visible difference between the spectra of derivatives **5** and those of the model compounds was a strong bathochromic shift of the highest maxima observed in the spectra of derivatives **5** taken in alkaline solution as compared with that observed in their uv spectra taken in neutral solution accompanied with the increase of the specific absorbance. This fact could not be explained by any of the four possible 1,2,4-triazolopyrimidinone structures deduced from the different type condensations of **1** and **2**.

The X-ray spectra of derivative **21** [R = SCH_3, R^1 = 2-piperidinoethyl (see its preparation on Scheme 9)] were recorded pointing out to its quite unexpected 7-benzyl-2-methylthio-10-(2-piperidinoethyl)-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one structure.

The 6-one structure of derivatives **5** explains the unexpected behaviour of their uv spectra taken in alkaline media as the free electron pair of the piperidino nitrogen atom in the ions **6** derived from derivatives **5** is conjugated with a system of the linearily conjugated double bonds while the ions derived from all other possible isomers (see *e.g.* the ions **7** and **8** derived from **3c** and **4c**, respectively) have rather aromatic character (Scheme 2).

Scheme 2



The formation of the unexpected derivatives **5** can be explained by the route "B" or "C" shown on Scheme 3. Thus the first step of the reaction of **2c** with **1** is the formation of the Schiff base **9x** which can be stabilised in the enamino tautomeric form **9y** containing an intramolecular chelate moiety. If the formation of **9** is followed by the elimination of methanol from the methoxycarbonyl and the triazole NH groups the expected derivative **3c** is formed (Route "A").

On the other hand, if the formation of **9** (**9y**) is followed by an electron shift - Route "B" shown on Scheme 3, brought about by the positive charge of the piperidinium nitrogen atom and enhanced by the enamino moiety present in the molecule, an intermediate **10** is formed which forms **11** after rotation around the newly formed single C-C bond. The intermediate **11** may be stabilized either by loss of a methanol molecule leading to the formation of intermediate **12**, followed by an intramolecular nucleophilic attack of the N-1 nitrogen atom of the triazole ring to yield **5** (Route B1), or by a nucleophilic attack of the triazole N-1 nitrogen atom to yield **13**, followed by the ring closure of the piperidone ring leading again to **5** (Route B2).

Finally, the formation of derivatives **5** can be explained also by Route "C". In this case the loan electron pair of the triazole N-1 nitrogen atom of the enamine **9y** starts the reaction by a nucleophilic attack against the "allylic" carbon atom 2 of the Δ^3-piperideine ring. The Δ^3-piperideine ring is opened to form (after loss of a molecule of hydrochloric acid) **13** which undergoes intramolecular condensation accompanied with a loss of a molecule of methanol to form **5**.

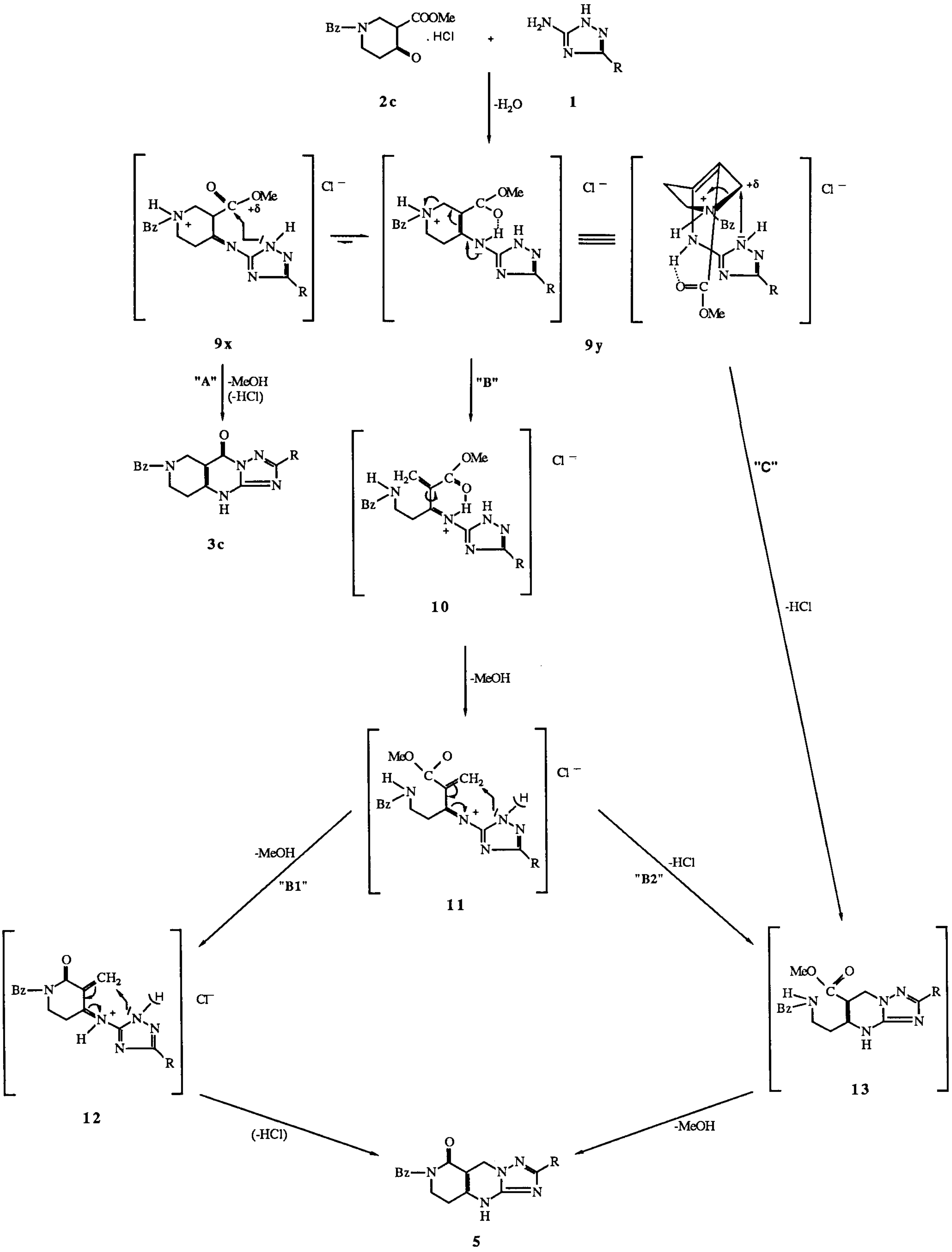
However, there was no *a priori* evidence that the formation of **3c** really proceeded through a Schiff's base **9** as the above reaction could also start with the formation of a **15** (R′ = NH_2) type amide (Scheme 4) that could also undergo ring closure to form **3c**. To exclude this possibility the 5-deamino derivatives of **1**, namely the derivatives **14a-c** (R = H, Br and Cl, respectively, R′ = H) which could not form Schiff bases were refluxed in acetic acid with **2c**. No formation of the corresponding amides **15o-q** (R = H, Br and Cl, respectively, R′ = H) was detected excluding the possibility of this reaction route (Scheme 4).

To verify the proposed mechanism "B" or "C" of the formation of derivatives **5** an attempt was made to isolate the intermediate Schiff's base **9** (Scheme 3). However, **2c** did not react with **1** under mild conditions. On the other hand, the intermediate **9** proved to be too reactive and only **5** could be isolated from the reaction mixture at elevated temperature.

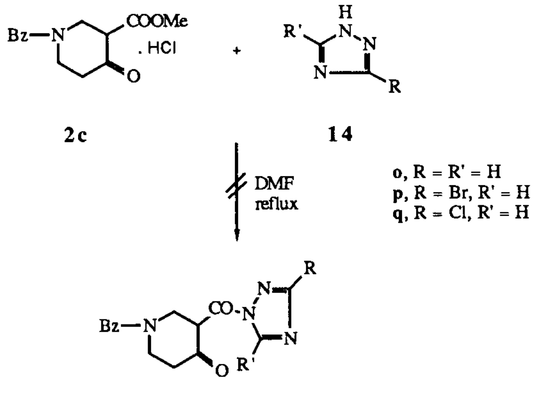
To prevent the further transformation of the intermediate Schiff's base 5-amino-2-methyl-3-morpholino-2*H*-1,2,4-triazole (**16**), which was not able to undergo ring closure to yield either a type **3c** or a type **5** product, was reacted with **2c** (Scheme 5). As expected, in this reaction the corresponding Schiff's base **17** was obtained appearing in the enamino tautomeric form stabilized by an intramolecular chelate ring.

Once the intermediate Schiff base is formed in the reaction three concurrent procedures may follow it: one leading to **3c** type products (Route "A") and those leading to type **5** products (Routes "B" and "C", Scheme 3). Route "A" does not require either the protonated nitrogen atom of the piperidinium ring or the enamino form **9y**, it may proceed simply from any of the tautomeric forms **9x** or **9y**. On the other hand, Routes "B" and "C" require both the formation of the enamino tautomeric

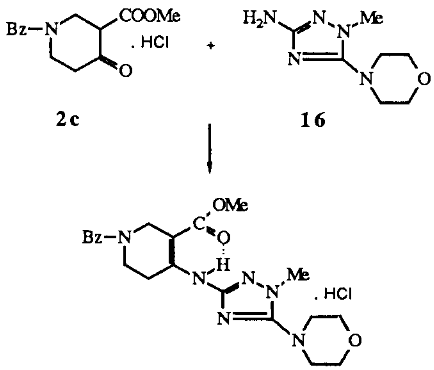
Scheme 3


2c
1
-H₂O
Cl⁻
9x
9y
"A"
-MeOH
(-HCl)
"B"
"C"
3c
10
-MeOH
-HCl
11
-MeOH
"B1"
-HCl
"B2"
12
13
(-HCl)
-MeOH
5

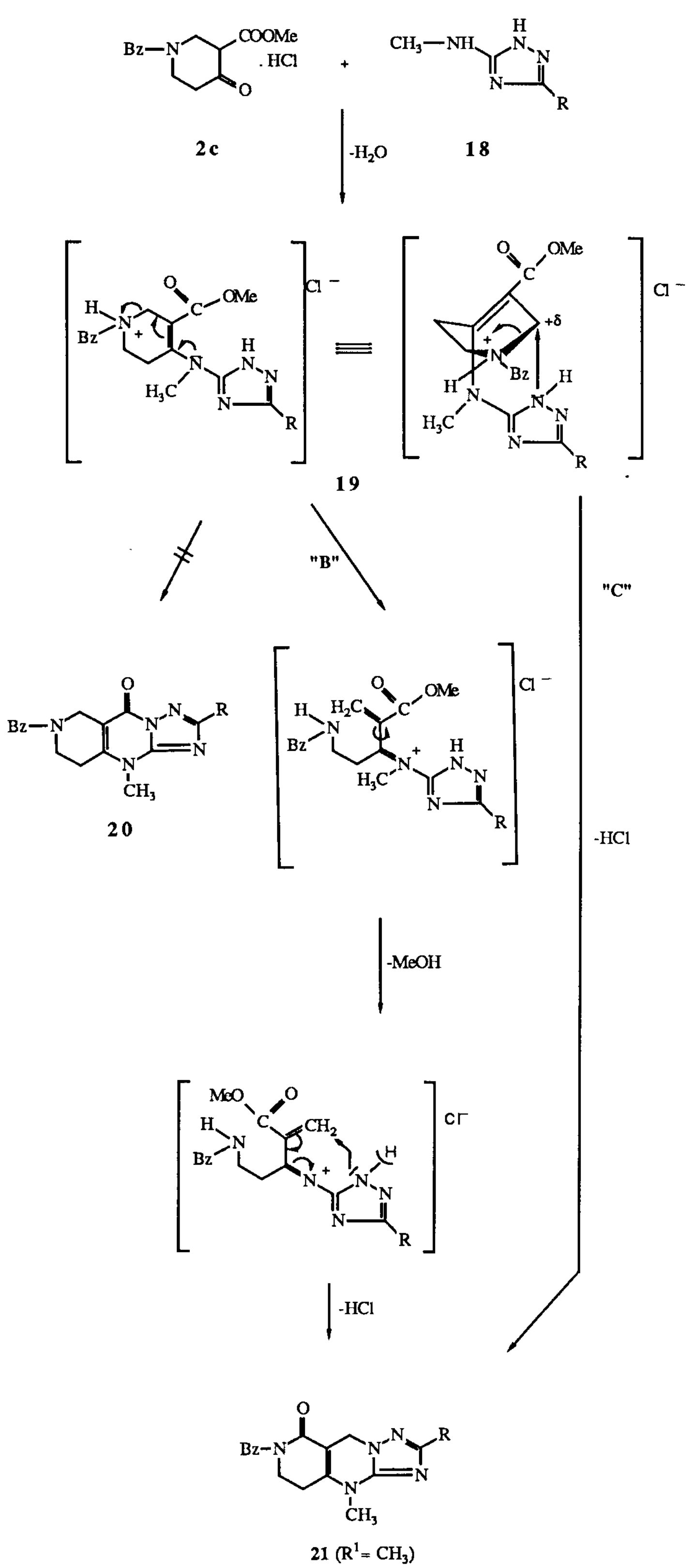
Scheme 4



Scheme 5



Scheme 6

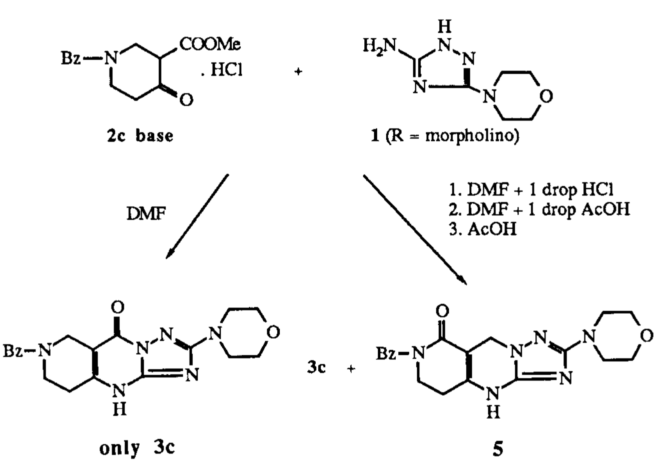


form **9y** and the electron withdrawing effect of the protonated piperidinium nitrogen atom. Consequently, the more stable the enamino form **9y** is, the more of type **5** products will be formed.

To bring about the complete formation of the enamino form **9y**, **2c** was reacted with 5-methylamino-3-methylthio-1*H*-1,2,4-triazole (**18**) (Scheme 6) which was not able to form the **9x** type "classical" Schiff base because of the 5-methylamino moiety. As expected, in this reaction the formation of a **3c** type derivative **20** was not observed, and only **21** (R^1 = CH_3) was formed.

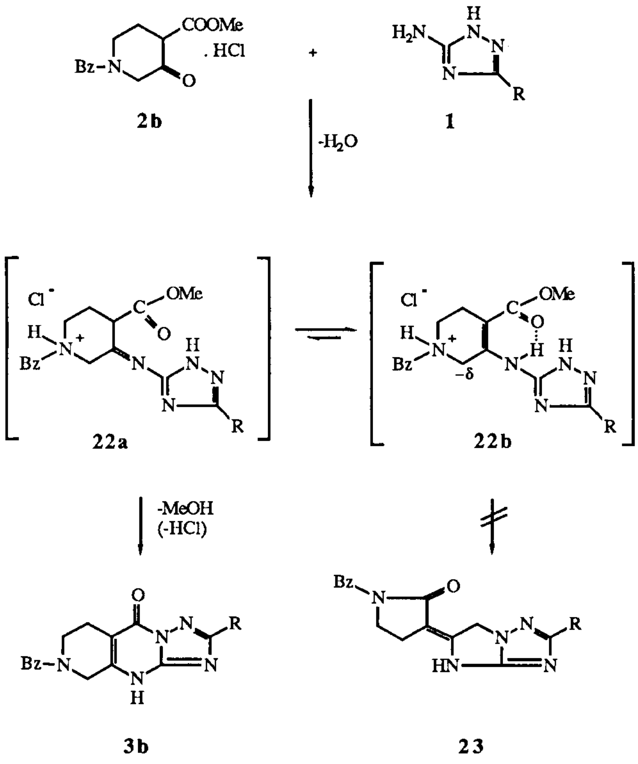
Next, the presence of the positive charged Δ^3-piperideine nitrogen atom of **9y** as a basic requirement of the above reaction leading to **5** had to be proved. For this purpose the reaction of **1** (R = morpholino) and **2c** that led previously to the mixture of **3c** and **5** (Scheme 1) was repeated under conditions excluding the presence of the positively charged Δ^3-piperideine nitrogen atom, *i.e.* with **2c-base** in dimethylformamide as solvent (Scheme 7). As expected, only **3c** was formed. On the other hand, if the reaction of **1** (R = morpholino) and **2c-base** provided in dimethylformamide or ethanol was run in the presence of a drop of hydrochloric or acetic acid, or in acetic acid as the solvent, the formation of **5** was observed again proving unambiguously the necessity of the positively charged Δ^3-piperideine nitrogen atom being the most probable driving force of the above reaction. However, at present we have no data whether the reaction proceeds *via* Route "B" ("B1", "B2") or "C".

Scheme 7



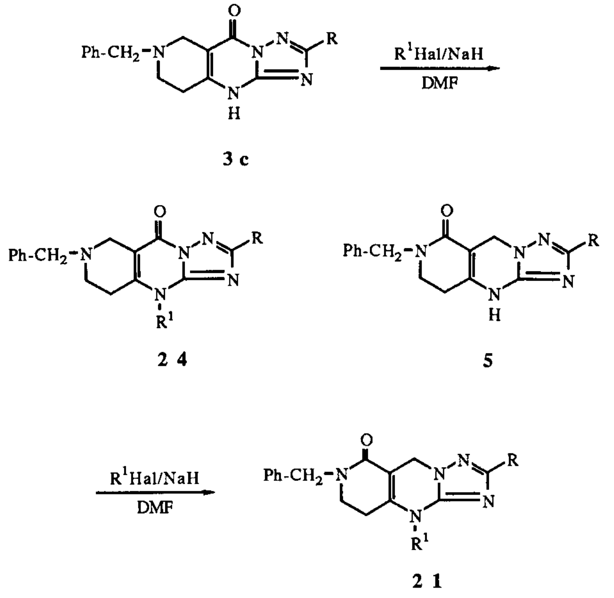
The proposed mechanism of the formation of the **5** type derivatives (Routes "B" or "C", Scheme 3) gave also the answer why the rearranged derivatives **23** (Scheme 8) corresponding to the **5** type compounds did not form in the reaction of the isomeric **2b** and **1** reported previously [1]. The intermediate enamine **22b** of this reaction had a negative charge in the position 2 of the Δ^3-piperideine ring as a consequence of the -I effect of the ester carbonyl group. Consequently the electron shift required for Route "B" or the nucleophilic attack of the triazole nitrogen atom 1 against the piperidinium carbon atom 2 required for Route "C" was impossible in this case.

Scheme 8



The alkylation of the sodium salts of derivatives **3c** and **5** (prepared with sodium hydride in dimethylformamide) led to the corresponding 10-alkylated derivatives **24** and **21**, respectively (Scheme 9). The position of the R^1 groups was unequivocally proved with the help of the gated cmr spectra on the basis of the changed multiplicity of the carbon atoms 9a and 10a in **24** and **21** as compared with those of the corresponding carbon atoms of **3c** and **5**, respectively. The analogy of the uv spectra of derivatives **3c** and **5** with those of their alkylated derivatives **24** and **21**, respectively, gave an unequivocal proof of the dominant tautomeric structures of derivatives **3c** and **5**, respectively, in ethanolic solution shown on Scheme 1.

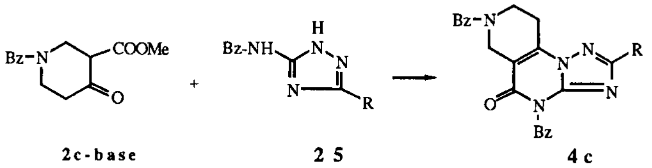
Scheme 9



As the isomers **4c** were not formed in direct synthesis (Scheme 1) they were prepared by the reaction of **2c-base** with 5-benzylamino-3-R-1*H*-1,2,4-triazole derivatives **25** (Scheme 10). The structure of compounds obtained was proved again with the help of the identity of their uv spectra with those of **4b** and the corresponding **4** type 5-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-7(8*H*)-one as well as using the cmr rule [2] {δ C-2 **4c** (R = morpholino) = 164.4 ppm, δ C-2 5-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-7(8*H*)-one = 162.8 ppm, δ C=O **4c** (R = morpholino) = 158.0 ppm and δ C=O 5-methyl-

2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-7(8*H*)-one = 160.6 ppm, respectively}.

Scheme 10



The pyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidine and the pyrido[4,3-*e*]-1,2,4-triazolo[1,5-*a*]pyrimidine ring systems of derivatives 3c and 4c, respectively, represent two new ring systems not described previously.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are uncorrected. The infrared spectra were obtained as potassium bromide pellets using Bruker IFS 113-V spectrophotometer. The ultraviolet spectra were obtained by a Pye Unicam SP 8-150 and a Perkin-Elmer 555 instrument. The pmr and the cmr measurements were performed using a Bruker WM-250 and Bruker WP-80 SY instruments. The X-ray measurements were performed using an Enraf-Nonius diffractometer. All tlc determinations were carried out on Kieselgel GF_{254} (Merck) plates using a 12:6:1:1 (v/v/v/v) mixture of acetone, chloroform, methanol and water as eluent. The spots were detected by uv.

7-Benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) and 7-Benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino).

A mixture of 50.8 g (0.3 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1**, R = morpholino) [3], 85.1 g (0.3 mole) of metlhyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) [4] and 175 ml of acetic acid was refluxed with stirring for 6 hours. After cooling 400 ml of concentrated ammonium hydroxide solution was slowly added to the reaction mixture, the crystals precipitated were filtered off, washed with 200 ml of water and dried. The dry crystals were refluxed with 500 ml of methanol for 15 minutes, filtered while hot, washed with methanol, then dissolved in hot dimethylformamide and precipitated again with acetonitrile. 78.8 g (72%) of 7-benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) was obtained, mp 291-293°; ir: ν C=O = 1655 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.46 (t, 2H, CH_2-9), 2.76 (t, 2H, CH_2-8), 3.40 (s, 2H, CH_2-6), 3.42 (t, 4H, NCH_2), 3.68 (s, 2H, CH_2Ph), 3.70 (t, 4H, OCH_2), 7.3-7.4 (m, 5H, ArH), 10.0 (bs, 1H, NH); cmr (DMSO-d_6): δ ppm 24.8 (C-9), 46.6 (NCH_2), 46.8 (C-8), 48.8 (NCH_2), 63.0 (C-6), 66.4 (OCH_2), 104.4 (C-5a), 127.0 (*p*-C-Ph), 130.7 (*o*-C-Ph), 131.3 (*p*-C-Ph), 136.7 (*s*-C-Ph), 146.9 (C-9a), 150.2 (C-10a), 153.4 (C=O), 163.1 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (25.3), 232 (34.2), 276 (11.0); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 201 (20.6), 232 (25.9), 276 (8.6); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 232 (36.1), 284 (10.5).

Anal. Calcd. for $C_{19}H_{22}N_6O_2$ (MW. 366.43): C, 62.28; H, 6.05; N, 22.94. Found: C, 62.21; H, 5.99; N, 22.89.

After cooling the crystals precipitated from the methanolic solution were filtered off, dissolved in a small amount of hot dimethylformamide and acetonitrile was added to the still hot solution. After cooling the crystals precipitated were filtered off to yield 6.6 g (6%) of 7-benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino), mp 252-254°; ir: ν C=O = 1664 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.48 (t, 2H, CH_2-9), 3.50 (s, 2H, CH_2-8), 3.50 (t, 4H, NCH_2), 3.74 (t, 4H, OCH_2), 4.63 (s, 2H, CH_2Ph), 4.68 (s, 2H, CH_2-5), 7.2-7.4 (m, 5H, ArH), 9.4 (bs, 1H, NH); cmr (DMSO-d_6): δ ppm 24.1 (C-9), 41.5* (C-5), 43.2* (C-8), 45.4 (NCH_2), 48.0 (NCH_2), 64.6 (OCH_2), 95.8 (C-5a), 125.8 (*p*-C-Ph), 126.3 (*o*-C-Ph), 127.0 (*m*-C-Ph), 135.7 (*s*-C-Ph), 139.5 (C-9a), 144.4 (C-10a), 163.0 (C-2), 166.7 (C-6); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 234 (22.1), 238 sh (7.4), 313 (7.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (13.1), 234 sh (5.0), 312 (5.1); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 235 (13.7), 359 (17.5).

Anal. Calcd. for $C_{19}H_{22}N_6O_2$ (MW. 366.43): C, 62.28; H, 6.05; N, 22.94. Found: C, 62.19; H, 6.11; N, 23.02.

7-Benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) - from **1** (R = morpholino) and **2c-base**.

A solution of 1.69 g (0.01 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1**, R = morpholino) [3] and 2.47 g (0.01 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (**2c-base**, prepared from the corresponding hydrochloride [4] by dissolving it in a small amount of water, made alkaline with sodium hydroxide, extracting with chloroform, washing the chloroform layer with water, drying and evaporating *in vacuo* to dryness) in 10 ml of dimethylformamide was refluxed for 8 hours. Tlc of the reaction mixture showed the spot of **3c** (R = morpholino), but the formation of **5** (R = morpholino) could not be detected. After cooling the solution was made alkaline with 5 ml of concentrated ammonium hydroxide and evaporated *in vacuo* to dryness. The residue was recrystallized by dissolving it in hot dimethylformamide and precipitating with acetonitrile to yield 2.24 g (61%) of **3c** (R = morpholino), mp 291-293°. The product is identical (mixed mp, ir) with that of **3c** (R = morpholino) obtained above.

7-Benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) and 7-Benzyl-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino) from **1** (R = morpholino), **2c-base** and two drops of acetic acid.

A mixture of 1.69 g (0.01 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1**, R = morpholino) [3], 2.47 g (0.01 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (**2c-base**, prepared as above), 10 ml of dimethylformamide and 2 drops of acetic acid was refluxed for 8 hours. Tlc of the reaction mixture showed the spots of both, **3c** (R = morpholino) and **5** (R = morpholino). After cooling the solution was made alkaline with 5 ml of concentrated ammonium hydroxide and evaporated *in vacuo* to dryness. The residue was dissolved in hot dimethylformamide and acetonitrile was added to the still hot solution. After cooling the crystals precipitated were filtered off to yield 2.49 g (68%) of **3c** (R = morpholino), mp 291-293°. The product is identical (mixed mp, ir) with that of **3c** (R = morpholino) obtained above.

The mother liquor was evaporated *in vacuo* to dryness and the residue was recrystallized from dioxane to yield 0.59 g (16%) of **5** (R = morpholino), mp 252-254°. The product is identical (mixed mp, ir) with that of **5** (R = morpholino) obtained above.

7-Benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) and 7-Benzyl-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino) From **1** (R = morpholino), **2c-base** and Two Drops of Hydrochloric Acid.

The same procedure was used as above but two drops of hydrochloric acid were added instead of two drops of acetic acid to the reaction mixture; yield 2.12 g (58%) of **3c** (R = morpholino), mp 292-294° and 0.66 g (18%) of **5** (R = morpholino), mp 251-254°.

7-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = methylthio) and 7-Benzyl-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = methylthio).

A mixture of 39.1 g (0.03 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1**, R = methylthio) [5], 85.1 g (0.3 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) [4] and 125 ml of acetic acid was refluxed for 5.5 hours. After cooling 350 ml of concentrated ammonium hydroxide solution was slowly added to the reaction mixture, the crystals precipitated were filtered off, washed with 200 ml of water and dried. The dry crystals were refluxed with 300 ml of methanol for 15 minutes, filtered while hot, washed with methanol, then dissolved hot in dimethylformamide and precipitated again with acetonitrile. 53.6 g (54%) of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = methylthio) was obtained, mp 245-247°; ir: ν C=O = 1650 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.50 (t, 2H, CH$_2$-9), 2.57 (s, 3H, SCH$_3$), 2.76 (t, 2H, CH$_2$-8), 3.32 (s, 2H, CH$_2$-6), 3.75 (s, 2H, CH$_2$Ph), 7.3-7.4 (m, 5H, ArH); cmr (DMSO-d$_6$): δ ppm 13.3 (SCH$_3$), 26.7 (C-9), 48.0* (C-8), 48.2* (CH$_2$Ph), 60.9 (C-6), 104.0 (C-5a), 127.0 (*p*-C-Ph), 127.2 (*o*-C-Ph), 128.7 (*m*-C-Ph), 137.5 (*s*-C-Ph), 146.1 (C-9a), 151.0 (C-10a), 154.1 (C=O), 163.0 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 201 (16.1), 233 (20.3), 277 (6.6); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 200 (10.4), 230 (13.1), 278 (5.6); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 234 (34.2), 284 (11.4).

Anal. Calcd. for $C_{16}H_{17}N_5OS$ (MW. 327.41): C, 58.70; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.81; H, 5.18; N, 21.47; S, 9.87.

After cooling the crystals precipitated from the methanolic solution were filtered off, dissolved in a small amount of hot dimethylformamide and acetonitrile was added to the still hot solution. After cooling the precipitated crystals were filtered off to yield 28.1 g (29%) of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = methylthio), mp 236-238°; ir: ν C=O = 1680 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.51 (s, 3H, SCH$_3$), 2.72 (t, 2H, CH$_2$-9), 3.40 (t, 2H, CH$_2$-8), 4.64 (s, 2H, CH$_2$Ph), 5.00 (s, 2H, CH$_2$-5), 7.2-7.4 (m, 5H, ArH); cmr (DMSO-d$_6$): δ ppm 13.6 (SCH$_3$), 24.9 (C-9), 43.8* (C-5), 44.8* (C-8), 48.9 (Ph-CH$_2$), 94.9 (C-5a), 126.9 (*p*-C-Ph), 127.6 (*o*-C-Ph), 128.4 (*m*-C-Ph), 137.9 (*s*-C-Ph), 142.9 (C-9a), 148.1 (C-10a), 158.3 (C-2), 164.1 (C-6); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (17.3), 245 sh (5.7), 307 (7.5); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 200 (14.9), 235 (5.4), 308 (7.0); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 238 sh (9.1), 357 (18.7).

Anal. Calcd. for $C_{16}H_{17}N_5OS$ (MW. 327.41): C, 58.70; H, 5.23; N, 21.39; S, 9.79. Found: C, 58.61; H, 5.32; N, 21.49; S, 9.70.

Attempted Preparation of **15o-q** (R = H, Br and Cl, R' = H).

A mixture of 2.07 g (0.03 mole) of 1,2,4-triazole (**14**, R = R' = H) [6], 8.51 g (0.03 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) [4] and 25 ml of acetic acid was refluxed for 16 hours. After cooling the precipitated crystals were filtered off and washed with diethyl ether to yield 0.44 g (21%) of the starting 1,2,4-triazole (**14**, R = R' = H), mp 114-116°. The mother liquor was evaporated *in vacuo* to dryness and the residue was recrystallized from 2-propanol to yield a further 1.61 g (78%) crop of the starting 1,2,4-triazole (**14**, R = R' = H), mp 114-116°.

Similarly, using 4.44 g (0.03 mole) of 3-bromo-1,2,4-triazole (**14**, R = Br, R' = H) [7], or 3.11 g (0.03 mole) of 3-chloro-1,2,4-triazole (**14**, R = Cl, R' = H) [7] instead of 1,2,4-triazole (**14**, R = R' = H) in the above reaction the starting materials were recovered again in yields of 98% and 97%, respectively.

Methyl 1-Benzyl-4-(2-methyl-3-morpholino-1,2,4-triazol-5-yl)-amino-1,2,5,6-tetrahydro-3-piperidinecarboxylate Hydrochloride (**17**).

A mixture of 1.75 g (0.01 mole) of 5-amino-2-methyl-3-morpholino-2*H*-1,2,4-triazole (**16**) [3], 2.84 g (0.01 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) [4] and 2 ml of acetic acid was stirred at 40-50° for 30 hours. The solution obtained was evaporated *in vacuo* to dryness, the residue was triturated with ethyl acetate, the precipitated crystals were filtered off and recrystallized from a mixture of dimethylformamide and acetonitrile to yield 1.59 g (39%) of the title product, mp 209-211°; ir: ν C=O = 1664 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.51 (t, 2H, piper. CH$_2$-5), 3.11 (t, 2H, piper. CH$_2$-6), 3.37 (t, 4H, NCH$_2$), 3.58 (s, 3H, NCH$_3$), 3.65 (s, 3H, OCH$_3$), 3.73 (t, 4H, OCH$_2$), 3.75 (s, 2H, piper. CH$_2$-2), 4.40 (s, 2H, CH$_2$Ph), 7.45-7.7 (m, 5H, ArH), 11.6 (bs, 1H, NH); cmr (DMSO-d$_6$): δ ppm 24.8 (piper. CH$_2$-5), 35.0 (NCH$_3$), 46.5* (NCH$_2$), 47.0* (PhCH$_2$), 49.4 and 51.3 (piper. CH$_2$-2 and 6), 58.0 (OCH$_3$), 65.5 (OCH$_2$), 87.7 (piper. C-3), 128.5 (*m*-C-Ph), 129.4 (*o*-C-Ph), 129.8 (*p*-C-Ph), 131.2 (*s*-C-Ph), 151.6 (piper. C-4), 157.0 (triazole C-3), 165.0 (triazole C-5), 167.2 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (17.9), 228 sh (7.6), 303 (15.1).

Anal. Calcd. for $C_{21}H_{29}ClN_6O_3$ (MW. 448.96): C, 56.18; H, 6.51; N, 18.72; Cl, 7.90. Found: C, 56.26; H, 6.44; N, 18.83; Cl, 7.81.

7,10-Dibenzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24a**, R = morpholino, R^1 = benzyl).

To a mixture of 11.0 g (0.03 mole) of 7-benzyl-2-morpholino-6,7,8,9-tetrahydro[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino) and 50 ml of dry dimethylformamide 0.84 g (0.035 mole) of sodium hydride (80% suspension in paraffin oil) was added and the mixture was heated with stirring for 3 hours. After cooling 4.43 g (4.03 ml, 0.035 mole) of benzyl chloride was added to the reaction mixture and refluxed with stirring for 16 hours. After cooling the precipitated crystals were filtered off, the filtrate was diluted with 100 ml of water and extracted 5 times with 50 ml portions of chloroform. The combined chloroform extracts were dried over sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The crystalline residue was recrystallized from acetonitrile to yield 8.63 g (63%) of the title product, mp 185-187°; ir: ν C=O = 1674 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.53 (t, 2H, CH_2-9), 2.72 (t, 2H, CH_2-8), 3.40 (s, 2H, CH_2-6), 3.40 (t, 4H, NCH_2), 3.70 (s, 2H, CH_2Ph), 3.70 (m, 4H, OCH_2), 5.46 (s, 2H, CH_2Ph-10), 7.2-7.4 (m, 10H, ArH); cmr (DMSO-d$_6$): δ ppm 25.3 (C-9), 45.6 (NCH_2), 48.0* (C-8), 48.6 (CH_2Ph), 49.0* (NCH_2), 60.8 (C-6), 65.4 (OCH_2), 106.8 (C-5a), 126.2 and 126.8 (*o*-C-Ph), 127.5 and 127.9 (*p*-C-Ph), 128.0 and 128.9 (*m*-C-Ph), 135.2 and 137.7 (*s*-C-Ph), 144.8 (C-9a), 151.3 (C-10a), 153.4 (C=O), 163.8 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (36.0), 236 (35.3), 283 (13.7); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (13.7), 237 (13.2), 281 (7.1); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 232 (19.9), 280 (10.3).

Anal. Calcd. for $C_{26}H_{28}N_6O_2$ (MW. 456.55): C, 68.40; H, 6.18; N, 18.41. Found: C, 68.32; H, 6.23; N, 18.51.

7-Benzyl-2-morpholino-10-(2-piperidinoethyl)-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24b**, R = morpholino, R^1 = 2-piperidinoethyl).

Prepared as **24a** (R = morpholino, R^1 = benzyl) using 6.64 g (0.045 mole) of 2-piperidinoethyl chloride in the form of a 17.3% solution in xylene instead of benzyl chloride, yield 9.84 g (67%), mp 193-195° (chloroform); ir: ν C=O = 1665 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.6 (m, 6H, piperidine $CH_2CH_2CH_2$), 2.40 (t, 4H, piperidine NCH_2), 2.64 (t, 2H, CH_2-9), 2.73 (t, 2H, CH_2-8), 2.85 (t, 2H, NCH_2), 3.60 (s, 2H, CH_2-6), 3.60 (m, 4H, NCH_2), 3.72 (s, 2H, CH_2Ph), 3.80 (t, 4H, OCH_2), 4.17 (t, 2H, NCH_2), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform, α-coupling only): δ ppm 24.1 (t, piper. C-4), 26.5* (t, C-9), 26.7* (t, piper. C-3), 44.7 (t, NCH_2), 46.2 (t, C-8), 48.2 (t, CH_2Ph), 50.2 (t, NCH_2), 55.2 (t, NCH_2), 56.7 (t, piper. C-2), 61.9 (t, C-6), 66.5 (t, OCH_2), 107.9 (s, C-5a), 127.3 (d, *p*-C-Ph), 128.4 (d, *o*-C-Ph), 129.0 (d, *m*-C-Ph), 137.8 (s, *s*-C-Ph), 144.3 (s, C-9a), 150.9 (s, C-10a), 154.4 (s, C=O), 164.7 (s, C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 201 (25.3), 237 (25.6), 279 (11.5); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 200 (20.1), 236 (18.3), 278 (9.8); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (19.3), 280 (10.5).

Anal. Calcd. for $C_{26}H_{35}N_7O_2$ (MW. 477.61): C, 65.38; H, 7.39; N, 20.53. Found: C, 65.21; H, 7.28; N, 20.50.

7-Benzyl-10-(1-dimethylamino-2-propyl)-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24c**, R = morpholino, R^1 = 1-dimethylamino-2-propyl).

Prepared as **24a** (R = morpholino, R^1 = benzyl) using 5.47 g (0.045 mole) of 1-dimethylamino-2-propyl chloride in the form of a 38.8% solution in xylene instead of benzyl chloride, yield 3.66 g (27%), mp 165-167° (acetonitrile); ir: ν C=O = 1672 cm^{-1}; pmr (deuteriochloroform): δ ppm 0.90 (d, 3H, CCH_3), 2.16 (s, 6H, $N(CH_3)_2$), 2.50 (d, 2H, CH_2), 2.72 (b, 2H, CH_2-9), 2.88 (b, 2H, CH_2-8), 3.35 (s, 2H, CH_2-6), 3.40 (t, 4H, NCH_2), 3.70 (s, 2H, CH_2Ph), 3.70 (t, 4H, OCH_2), 4.20 (m, 1H, CH), 7.3-7.4 (m, 5H, ArH); cmr (DMSO-d$_6$): δ ppm 9.8 (CCH_3), 25.6 (C-9), 40.5 [$N(CH_3)_2$], 45.9 (NCH_2), 48.4 (CH_2Ph), 48.6* (C-8), 49.0* (NCH_2), 57.4 (CH), 61.2 (C-6), 65.7 (OCH_2), 106.3 (C-5a), 127.2 (*o*-C-Ph), 128.3 (*p*-C-Ph), 128.9 (*m*-C-Ph), 138.0 (*s*-C-Ph), 145.6 (C-9a), 151.2 (C-10a), 153.7 (C=O), 164.0 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 205 (24.5), 236 (30.1), 283 (13.2); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 206 (21.7), 232 (27.2), 280 (11.0); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 236 (29.2), 282 (12.4).

Anal. Calcd. for $C_{24}H_{33}N_7O_2$ (MW. 451.58): C, 63.84; H, 7.37; N, 21.71. Found: C, 63.79; H, 7.30; N, 21.82.

7-Benzyl-10-(3-dimethylaminopropyl)-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24d**, R = morpholino, R^1 = 3-dimethylaminopropyl).

Prepared as **24a** (R = morpholino, R^1 = benzyl) using 5.47 g (0.045 mole) of 3-dimethylaminopropyl chloride in the form of a 17% solution in xylene instead of benzyl chloride, yield 9.21 g (68%), mp 95-97° (acetonitrile); ir: ν C=O = 1660 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.9 (m, 2H, CCH_2C), 2.21 (s, 6H, $N(CH_3)_2$), 2.30 (t, 2H, NCH_2), 2.70 (t, 2H, CH_2-9), 2.80 (t, 2H, CH_2-8), 3.60 (s, 2H, CH_2-6), 3.61 (b, 4H, NCH_2), 3.75 (s, 2H, CH_2Ph), 3.80 (b, 4H, OCH_2), 4.14 (t, 2H, NCH_2), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 26.1* (C-9), 26.2* ($C\mathit{C}H_2C$), 44.7 (NCH_2), 45.1 [$N(\mathit{C}H_3)_2$], 46.1 and 46.2 (NCH_2), 48.2* (C-8), 49.9* (CH_2Ph), 61.7 (C-6), 66.3 (OCH_2), 107.9 (C-5a), 127.1 (*p*-C-Ph), 128.0 (*o*-C-Ph), 128.6 (*m*-C-Ph), 137.4 (*s*-C-Ph), 143.7 (C-9a), 150.8 (C-10a), 154.2 (C=O), 164.8 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (22.4), 235 (29.3), 281 (10.2); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (19.6), 233 (26.2), 280 (9.9); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (32.5), 281 (12.2).

Anal. Calcd. for $C_{24}H_{33}N_7O_2$ (MW. 451.58): C, 63.84; H, 7.37; N, 21.71. Found: C, 63.77; H, 7.46; N, 21.78.

7,10-Dibenzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24e**, R = methylthio, R^1 = benzyl).

Prepared as **24a** (R = morpholino, R^1 = benzyl) using instead of **3c** (R = morpholino) 9.82 g (0.03 mole) of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = methylthio), yield 8.39 g (67%), mp 223-224°; ir: ν C=O = 1676 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.53 (t, 2H, CH_2-9), 2.61 (s, 3H, SCH_3), 2.71 (t, 2H, CH_2-8), 3.32 (s, 2H, CH_2-6), 3.68 (s, 2H, CH_2Ph-7), 5.49 (s, 2H, CH_2Ph-10), 7.2-7.4 (m, 10H, ArH); cmr (DMSO-d$_6$): δ ppm 13.2 (SCH_3), 25.5 (C-9), 47.9 (C-8), 48.6* (CH_2Ph-7), 49.3* (CH_2Ph-10), 60.7 (C-6), 106.9 (C-5a), 126.2 (two peaks, *o*-C-Ph), 126.9 and 127.5 (*p*-C-Ph), 128.6 (two peaks, *m*-C-Ph), 135.2 and 135.6 (*s*-C-Ph), 146.2 (C-9a), 152.1 (C-10a), 152.5 (C=O), 163.0 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (30.4), 238 (28.9), 282 (11.9); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (17.3), 238 (17.1), 279 (8.0); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (15.1), 283 (9.9).

Anal. Calcd. for $C_{23}H_{23}N_5OS$ (MW. 417.54): C, 66.16; H, 5.55; N, 16.77; S, 7.68. Found: C, 66.28; H, 5.66; N, 16.70; S, 7.72.

7-Benzyl-2-methylthio-10-(2-piperidinoethyl)-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24f**, R = methylthio, R^1 = 2-piperidinoethyl).

Prepared as **24e** (R = methylthio, R^1 = benzyl) using 6.64 g (0.045 mole) of 2-piperidinoethyl chloride in the form of a 17.3% solution in xylene instead of benzyl chloride, yield 7.16 g (53%), mp 109-111° (chloroform); ir: ν C=O = 1674 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.45 (m, 6H, piper. CH_2-3+4), 2.51 (t, 2H, CH_2-9), 2.61 (t, 4H, piper. NCH_2), 2.68 (s, 3H, SCH_3), 2.75 (t, 2H, CH_2-8), 2.91 (t, 2H, NCH_2), 3.61 (s, 2H, CH_2-6), 3.73 (s, 2H, CH_2Ph), 4.21 (t, 2H, NCH_2), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 13.9 (SCH_3), 24.1 (piper. C-4), 25.7* (piper. C-3), 26.2* (C-9), 48.1* (C-8), 48.2* (NCH_2), 48.9* (CH_2Ph), 54.4

(NCH_2), 56.3 (piper. C-2), 61.7 (C-6), 107.9 (C-5a), 127.2 (*p*-C-Ph), 128.3 (*o*-C-Ph), 128.8 (*m*-C-Ph), 145.2 (C-9a), 151.5 (C-10a), 153.8 (C=O), 165.6 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (30.1), 236 (29.2), 278 (12.4); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (26.8), 234 (24.6), 277 (11.2); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (28.7), 279 (12.9).

Anal. Calcd. for $C_{23}H_{30}N_6OS$ (MW. 438.60): C, 62.99; H, 6.89; N, 19.16; S, 7.31. Found: C, 63.09; H, 6.80; N, 19.02; S, 7.20.

7-Benzyl-10-(3-dimethylaminopropyl)-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**24g**, R = methylthio, R^1 = 3-dimethylaminopropyl).

Prepared as **24e** (R = methylthio, R^1 = benzyl) using 5.47 g (0.045 mole) of 3-dimethylaminopropyl chloride in the form of a 17% solution in xylene instead of benzyl chloride, yield 5.79 g (47%), mp 134-136° (2-propanol); ir: ν C=O = 1670 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.95 (qi, 2H, CCH_2C), 2.20 (s, 6H, $N(CH_3)_2$), 2.30 (t, 2H, NCH_2), 2.68 (s, 3H, SCH_3), 2.75 (t, 2H, CH_2-9), 2.87 (t, 2H, CH_2-8), 3.60 (s, 2H, CH_2-6), 3.73 (s, 2H, CH_2Ph), 4.20 (t, 2H, NCH_2), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 13.9 (SCH_3), 26.2* (C-9), 26.3* (CCH_2C), 45.1 (NCH_3), 46.0 (NCH_2), 48.1* (C-8), 48.2* (NCH_2), 49.8 (CH_2Ph), 61.7 (C-6), 107.9 (C-5a), 127.1 (*p*-C-Ph), 128.3 (*o*-C-Ph), 128.8 (*m*-C-Ph), 137.6 (*s*-C-Ph), 145.2 (C-9a), 151.5 (C-10a), 153.8 (C=O), 164.6 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 200 (15.6), 236 (17.2), 278 (7.0); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (14.1), 234 (16.1), 278 (6.9); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (21.7), 279 (9.7).

Anal. Calcd. for $C_{21}H_{28}N_6OS$ (MW. 412.56): C, 61.14; H, 6.84; N, 20.37; S, 7.77. Found: C, 61.22; H, 6.71; N, 20.41; S, 7.90.

7-Benzyl-10-methyl-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21a**, R = morpholino, R^1 = methyl).

To a mixture of 0.50 g (0.00135 mole) of 7-benzyl-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino) and 15 ml of dimethylformamide 0.48 g (0.002 mole) of sodium hydride (80% suspension in paraffin oil) was added and stirred at 40-50° for 10 minutes. After cooling to 0° 0.36 g (0.16 ml, 0.0025 mole) of methyl iodide was added to the reaction mixture dropwise with stirring. The reaction was completed by stirring the mixture for 30 minutes. The mixture obtained was diluted with water, extracted with chloroform, the chloroform layer was separated, dried over anhydrous sodium sulphate, treated with charcoal, filtered and evaporated *in vacuo* to dryness to yield 0.34 g (66%) of the title product, mp 182-184° (2-propanol); ir: ν C=O = 1655 cm^{-1}; pmr (deuteriochloroform): δ ppm 2.61 (t, 2H, CH_2-9), 3.30 (t, 2H, CH_2-8), 3.33 (s, 3H, NCH_3), 3.40 (t, 4H, NCH_2), 3.79 (t, 4H, OCH_2), 4.63 (s, 2H, CH_2Ph), 4.86 (s, 2H, CH_2-5), 7.2-7.3 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 23.9 (C-9), 31.6 (NCH_3), 42.8 (C-5), 44.3 (C-8), 46.6 (NCH_2), 49.3 (CH_2Ph), 66.2 (OCH_2), 97.9 (C-5a), 127.2 (*p*-C-Ph), 127.8 (*o*-C-Ph), 128.4 (*m*-C-Ph), 137.3 (*s*-C-Ph), 143.1 (C-9a), 148.1 (C-10a), 163.6 (C-2), 164.5 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (26.2), 222 sh (13.3), 323 (8.7); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 202 (18.9), 232 sh (6.3), 324 (6.8); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 222 (15.1), 323 (12.8).

Anal. Calcd. for $C_{20}H_{24}N_6O_2$ (MW. 380.45): C, 63.14; H, 6.36; N, 22.09. Found: C, 63.05; H, 6.29; N, 22.17.

7,10-Dibenzyl-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21b**, R = morpholino, R^1 = benzyl).

Prepared as **24a** (R = morpholino, R^1 = benzyl) using 10.99 g (0.03 mole) of 7-benzyl-2-morpholino-5,7,8,9-tetrahydropyrido-[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino) instead of 7-benzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = morpholino), yield 2.74 g (20%), mp 142-144° (acetonitrile); ir: ν C=O = 1645 cm^{-1}; pmr (deuteriochloroform): δ ppm 2.45 (t, 2H, CH_2-9), 3.21 (t, 2H, CH_2-8), 3.37 (t, 4H, NCH_2), 3.78 (t, 4H, OCH_2), 4.58 (s, 2H, CH_2Ph-7), 4.92 (s, 2H, CH_2-5), 5.06 (s, 2H, CH_2Ph-10), 7.2-7.4 (m, 10H, ArH); cmr (deuteriochloroform, α-coupling only): δ ppm 24.3 (t, C-9), 43.0 (t, C-5), 44.7 (t, C-8), 46.8 (t, NCH_2), 48.2 (t, CH_2Ph-10), 49.3 (t, CH_2Ph-7), 66.4 (t, OCH_2), 98.9 (s, C-5a), 126.1, 127.4, 127.8, 128.1, 128.6 and 129.0 (all d, Ar), 137.0 and 137.4 (both s, *s*-C-Ph), 143.1 (s, C-9a), 148.6 (s, C-10a), 163.9 (s, C-2), 164.7 (s, C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (28.6), 237 sh (11.1), 321 (12.7); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (24.5), 235 sh (9.8), 322 (10.3); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 222 (20.6), 322 (9.5).

Anal. Calcd. $C_{26}H_{28}N_6O_2$ (MW. 456.55): C, 68.40; H, 6.18; N, 18.41. Found: C, 68.48; H, 6.12; N, 18.47.

7-Benzyl-10-(3-dimethylamino-2-methylpropyl)-2-morpholino-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21c**, R = morpholino, R^1 = 3-dimethylamino-2-methylpropyl).

Prepared as **21a** (R = morpholino, R^1 = methyl) using 6.10 g (0.045 mole) of 3-dimethylamino-2-methylpropyl chloride in the form of a 45.9% solution in xylene instead of methyl iodide, yield 10.90 g (78%), mp 144-146° (acetonitrile); ir: ν C=O = 1655 cm^{-1}; pmr (DMSO-d_6): δ ppm 0.81 (d, 3H, CCH_3), 2.00 (d, 2H, NCH_2CH), 2.13 (s, 6H, NCH_3), 2.74 (t, 2H, CH_2-9), 3.23 (t, 2H, CH_2-8), 3.40 (t, 4H, NCH_2), 3.70 (t, 4H, OCH_2), 3.96 (m, 1H, CH), 4.13 (d, 2H, $CHCH_2N$), 4.56 (s, 2H, CH_2Ph), 4.67 (s, 2H, CH_2-5), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 16.3 (CCH_3), 24.0 (C-9), 31.0 (NCH_2CH), 43.0 (C-5), 43.4 (NCH_3), 44.3 (C-8), 45.7 ($CHCH_2N$), 46.7 (NCH_2), 49.3 (CH_2Ph), 65.8 (OCH_2), 97.0 (C-5a), 127.2 (*o*-C-Ph), 127.9 (*p*-C-Ph), 129.5 (*m*-C-Ph), 138.1 (*s*-C-Ph), 144.7 (C-9a), 148.4 (C-10a), 163.3 (C-2), 164.4 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 201 (20.1), 223 sh (10.5), 324 (8.9); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (21.0), 226 (10.2), 319 (8.5); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 223 (12.2), 322 (8.1).

Anal. Calcd. for $C_{25}H_{35}N_7O_2$ (MW. 465.60): C, 64.49; H, 7.58; N, 21.06. Found: C, 64.59; H, 7.51; N, 21.18.

7-Benzyl-10-methyl-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21d**, R = methylthio, R^1 = methyl) by Methylation of **5** (R = methylthio).

Prepared as **21a** (R = morpholino, R^1 = methyl) using 0.327 g (0.001 mole) of 7-benzyl-2-methylthio-5,7,8,9-tetrahydropyrido-[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = methylthio) instead of 7-benzyl-2-morpholino-6,7,8,9-tetrahydropyrido-[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = morpholino), yield 0.24 g (69%), mp 158-160° (ethyl acetate); ir: ν C=O = 1660 cm^{-1}; pmr (deuteriochloroform): δ ppm 2.57 (s, 3H, SCH$_3$), 2.62 (t, 2H, CH$_2$-9), 3.38 (t, 2H, CH$_2$-8), 3.39 (s, 3H, NCH$_3$), 4.63 (s, 2H, CH$_2$Ph), 4.97 (s, 2H, CH$_2$-5), 7.2-7.3 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 14.3 (SCH$_3$), 24.1 (C-9), 32.0 (NCH$_3$), 42.6 (C-5), 45.0 (C-8), 49.6 (CH$_2$Ph), 98.3 (C-5a), 127.1 (*p*-C-Ph), 128.0 (*o*-C-Ph), 128.6 (*m*-C-Ph), 137.4 (*s*-C-Ph), 143.2 (C-9a), 149.9 (C-10a), 159.4 (C-2), 164.5 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (21.8), 238 sh (8.1), 316 (9.4); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 205 (18.5), 235 sh (7.0), 330 (7.3); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 223 (18.2), 320 (12.7).

Anal. Calcd. for $C_{17}H_{19}N_5OS$ (MW. 341.44): C, 59.80; H, 5.61; N, 20.51; S, 9.39. Found: C, 59.68; H, 5.69; N, 20.60; S, 9.33.

7-Benzyl-10-methyl-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21d**, R = methylthio, R^1 = methyl) from **2c** and **18**.

A mixture of 2.88 g (0.02 mole) of 5-methylamino-3-methylthio-1*H*-1,2,4-triazole (**18**) [8], 5.67 g (0.02 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate hydrochloride (**2c**) [4] and 8 ml of acetic acid was refluxed for 0.5 hours. After cooling 20 ml of concentrated ammonium hydroxide solution was added to the reaction mixture, the crystals precipitated were filtered off, washed with water and recrystallized from 2-propanol to yield 3.96 g (58%) of the title product, mp 152-154°. The product is identical (ir, mixed mp) with that of **21d** (R = methylthio, R^1 = methyl) obtained in the previous preparation.

7-Benzyl-2-methylthio-10-(2-piperidinoethyl)-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21e**, R = methylthio, R^1 = 2-piperidinoethyl).

Prepared as **24f** (R = methylthio, R^1 = 2-piperidinoethyl) using 9.82 g (0.03 mole) of 7-benzyl-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = methylthio) instead of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = methylthio), yield 7.21 g (58%), mp 117-119° (acetonitrile); ir: ν C=O = 1660 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.45 (m, 6H, piper. CH$_2$-3+4), 2.4 (m, 4H, piper. CH$_2$-2), 2.51 (t, 2H, NCH$_2$), 2.57 (s, 3H, SCH$_3$), 2.72 (t, 2H, CH$_2$-9), 3.38 (t, 2H, CH$_2$-8), 3.85 (t, 2H, NCH$_2$), 4.64 (s, 2H, CH$_2$Ph), 4.97 (s, 2H, CH$_2$-5), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 14.3 (SCH$_3$), 24.1* (C-9), 24.3* (piper. C-4), 26.1 (piper. C-3), 43.2* (C-5), 43.4* (NCH$_2$), 45.1 (C-8), 46.6 (NCH$_2$), 49.5 (CH$_2$Ph), 55.1 (piper. C-2), 98.0 (C-5a), 127.4 (*p*-C-Ph), 128.0 (*o*-C-Ph), 128.6 (*m*-C-Ph), 137.5 (*s*-C-Ph), 143.7 (C-9a), 149.6 (C-10a), 159.5 (C-2), 164.4 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 205 (26.9), 240 sh (9.1), 317 (11.3); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 203 (31.8), 240 sh (8.6) 314 (10.3); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 238 (6.8), 319 (8.3).

Anal. Calcd. for $C_{23}H_{30}N_6OS$ (MW. 438.60): C, 62.99; H, 6.89; N, 19.16; S, 7.31. Found: C, 62.89; H, 6.81; N, 19.32; S, 7.37.

7-Benzyl-10-(3-dimethylaminopropyl)-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**21f**, R = methylthio, R^1 = 3-dimethylaminopropyl).

Prepared as **24g** (R = methylthio, R^1 = 3-dimethylaminopropyl) using 9.82 g (0.03 mole) of 7-benzyl-2-methylthio-5,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-6(10*H*)-one (**5**, R = methylthio) instead of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-1,2,4-triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3c**, R = methylthio), yield 8.25 g (67%), mp 125-127° (acetonitrile); ir: ν C=O = 1645 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.81 (qi, 2H, CC*H*$_2$C), 2.17 (s, 6H, N(CH$_3$)$_2$), 2.27 (t, 2H, NCH$_2$), 2.57 (s, 3H, SCH$_3$), 2.70 (t, 2H, CH$_2$-9), 3.37 (t, 2H, CH$_2$-8), 3.83 (t, 2H, NCH$_2$), 4.63 (s, CH$_2$Ph), 4.97 (s, 2H, CH$_2$-5), 7.3-7.4 (m, 5H, ArH); cmr (deuteriochloroform): δ ppm 14.2 (SCH$_3$), 24.8 (C-9), 26.9 (C*C*H$_2$C), 43.0 (C-5), 43.2 (NCH$_2$), 45.0* (C-8), 45.1* (NCH$_3$), 45.2* (NCH$_2$), 49.5 (CH$_2$Ph), 98.1 (C-5a), 127.3 (*p*-C-Ph), 127.9 (*o*-C-Ph), 128.5 (*m*-C-Ph), 137.4 (*s*-C-Ph), 143.3 (C-9a), 149.9 (C-10a), 159.5 (C-2), 164.6 (C=O); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (35.7), 223 sh (16.9), 316 (11.3); uv (10% ethanol + 90% 0.1*N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 204 (43.2), 235 (20.3), 314 (10.8); uv (10% ethanol + 90% 0.1*N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 236 sh (11.2), 320 (11.2).

Anal. Calcd. for $C_{21}H_{28}N_6OS$ (MW. 412.57): C, 61.14; H, 6.84; N, 20.37; S, 7.77. Found: C, 61.22; H, 6.75; N, 20.52; S, 7.89.

7,10-Dibenzyl-2-morpholino-6,7,8,9-tetrahydropyrido[4,3-*e*]-1,2,4-triazolo[1,5-*a*]pyrimidin-9(10*H*)-one (**4c**, R = morpholino).

The mixture of 1.30 g (0.005 mole) of 5-benzylamino-3-morpholino-1*H*-1,2,4-triazole (**25**) [2] and 1.48 g (0.006 mole) of methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (prepared by partitioning the corresponding hydrochloride (**2c**) between 5*N* sodium hydroxide solution and chloroform, separating the layers, washing the organic phase with water, drying and evaporating *in vacuo* to dryness) was heated at 180° for 30 minutes. During the reaction a melt was formed. After cooling the melt obtained was chromatographed on a silica gel column (eluent: benzene) to yield 0.95 g (42%) of the title product mp 154-156° (ethyl acetate); ir: ν C=O = 1668 cm^{-1}; pmr (DMSO-d$_6$): δ ppm 2.77* (t, 2H, CH$_2$-6), 2.86* (t, 2H, CH$_2$-5), 3.22 (s, 2H, CH$_2$-8), 3.35 (t, 4H, NCH$_2$), 3.67 (s, 2H, NCH$_2$-7), 3.67 (t, 4H, OCH$_2$), 5.20 (s, 2H, NCH$_2$-10); cmr (DMSO-d$_6$): δ ppm 24.3 (C-5), 45.9 (NCH$_2$ + C-6), 47.7 and 48.5 (Ph-NCH$_2$), 61.1 (C-8), 65.6 (OCH$_2$), 109.3 (C-8a), 127.1, 127.6, 128.0, 128.3, 128.4 and 128.8 (*o*-, *m*-, *p*-Ph), 136.0 and 137.9 (*s*-Ph), 142.3 (C-4a), 149.8 (C-10a), 158.0 (C=O), 164.4 (C-2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 209 (25.5), 310 (8.3).

Anal. Calcd. for $C_{26}H_{28}N_6O_2$ (MW. 456.55): C, 68.40; H, 6.18; N, 18.41. Found: C, 68.48; H, 6.30; N, 18.24.

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