On Triazoles. VIII [1]. The Reaction of 5-Amino-1,2,4-Triazoles with Ethyl 2-Cyano-3-Ethoxyacrylate and 2-Cyano-3-Ethoxyacrylonitrile [2]

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The reaction of different 5-amino-3-Q-1*H*-1,2,4-triazoles **1** with ethyl 2-cyano-3-ethoxyacrylate (**5a**) and 2-cyano-3-ethoxyacrylonitrile (**5b**) to yield either the **a** type 5-amino-, or the **b** type 7-amino-1,2,4-triazolo[1,5-*a*]-pyrimidine derivatives **6-10** was studied. The structure of compounds **6** and **9** was proved by their degradation to the corresponding derivatives **17a** and **18a**, respectively, through intermediates **11a**, **12a**, **13a**, **14a**, **15a** and **16a**, respectively. The structure of derivatives **7**, **8** and **10** was proved on the basis of the analogy of their uv spectra with those of **6a** and **9a**, respectively. The isolation of the intermediates **19** and **20** helped to prove the mechanism of the reactions leading to the formation of **6a** and **9a**, respectively. In the reaction of the *N*-substituted 5-amino-1,2,4-triazoles with **5a** the expected condensed ring products were not formed. Instead the aminoacrylates **22** and **24** were obtained. The "*Z*"-"*E*" isomeric structure of derivatives **19**, **20**, **22** and **24** was proved with the help of their pmr spectra. The "*Z*" isomeric structure of the thermodynamically stabile **22** was corroborated with the help of its proton coupled cmr spectra, too.

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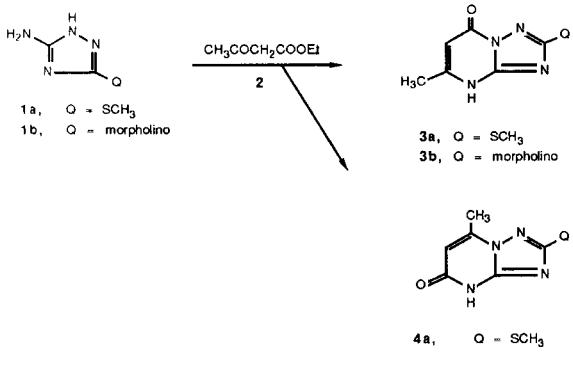
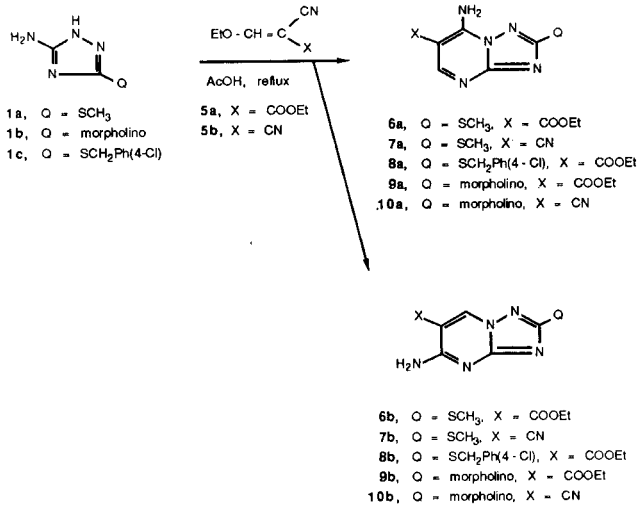
The reaction of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1a**, Q = SCH_3) with ethyl acetoacetate (**2**) yielded the mixture of 7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**3a**, Q = SCH_3) and 5-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-7(8*H*)-one (**4a**, Q = SCH_3) (Scheme 1) [3].

Scheme 1



Repeating the above reaction with ethyl 2-cyano-3-ethoxyacrylate (**5a**) and 2-cyano-3-ethoxyacrylonitrile (**5b**) again the mixture of derivatives **6a** and **6b**, and **7a** and **7b**, respectively was expected. However in these reactions as well as in all those provided with other 5-amino-1*H*-1,2,4-triazoles (*e.g.* with **1b**, Q = morpholino and **1c**, Q = 4-chlorobenzylthio) only one condensed ring derivative was formed having thus either structure **6a-10a** or the corresponding **6b-10b**, respectively (Scheme 2).

Scheme 2



The recorded ir, uv, pmr and cmr spectra (see Experimental) of all derivatives **6-10** were in full agreement with the proposed structures **6a-10a** or **6b-10b**, respectively, but as a consequence of the extreme symmetricity of both, the **a** and **b** type structures they could not differentiate between them. Moreover the proton coupled cmr spectra were also not characteristic for any of the structures **6a-10a** and **6b-10b**, respectively, as - again as a consequence of the unusual symmetricity - the ring carbon atoms were expected in both cases with the same multiplicity. The X-ray spectra were of course able to be differen-

tiated between structures **6a-10a** and **6b-10b**, respectively, but the compounds did not form crystals suitable for this measurement.

Consequently an other method had to be found for the differentiation between structures **6a-10a** and **6b-10b**, respectively, that made possible to increase the difference between the **a** and **b** type structures.

Thus derivatives **6a** or **6b** and **9a** or **9b** were hydrolysed with sodium hydroxide to the sodium salts of the corresponding carbonic acids **11a** or **11b** and **12a** or **12b**, respectively (Scheme 3). From the above sodium salts the free acids **13a** or **13b** and **14a** or **14b**, respectively, were liberated with hydrochloric acid which were then thermally decarboxylated to the corresponding derivatives **15a** or **15b** and **16a** or **16b**, respectively. The amino groups of derivatives **15a** or **15b** and **16a** or **16b** were then diazotated and the diazonium salts obtained were hydrolysed to yield the corresponding ketones **17a** or **17b** and **18a** or **18b**, respectively. Derivatives **17a** or **17b** and **18a** or **18b** were just unsymmetrical enough to enable the differentiation between the **a** and **b** type structures on the basis of the analogy of the uv and cmr spectra with those of the previously prepared [3] derivatives **3**. On this basis derivatives **17** and **18** and consequently all their intermediates **11-18** should have structures **11a-18a**, respectively, proving the **6a** and **9a** structures of the materials obtained in the ring-closure reactions.

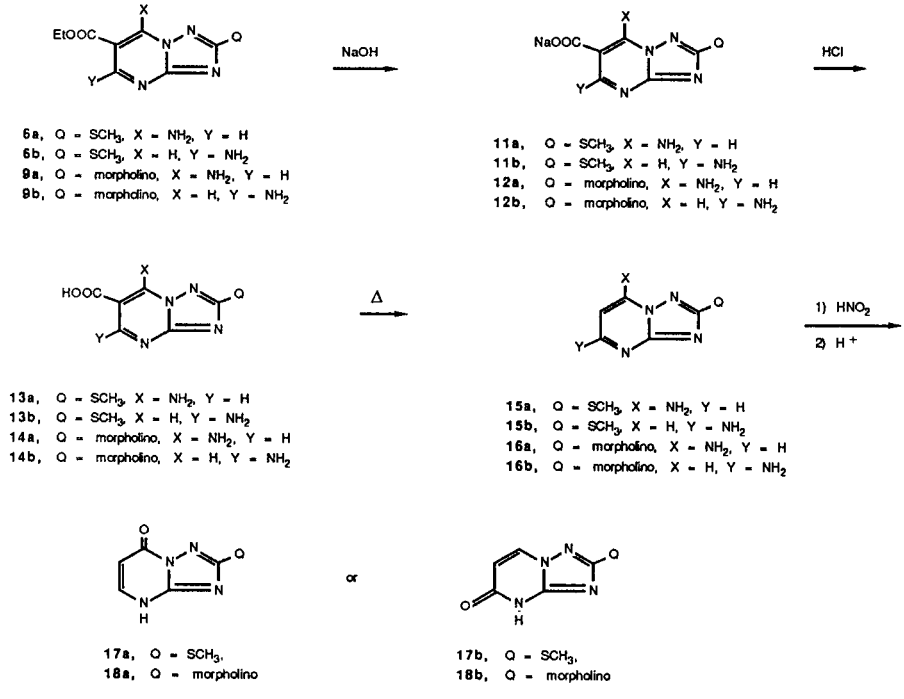
The uv spectra of the corresponding 2-(4-chlorobenzylthio)- **8a** or **8b**, as well as those of the 6-cyano- **7a** or **7b** and **10a** or **10b** derivatives were completely analogues with those of **6a** and **9a**, respectively, giving proof of their **8a**, **7a** and **10a** structures, respectively.

Using mild reaction conditions it was possible to isolate the intermediates **19** and **20** (Scheme 4) of the reactions leading to the formation of **6a** and **9a**, respectively. These aminoacrylates **19** and **20** could exist in the "*E*" and "*Z*" isomeric forms. The "*Z*" form is stabilised by an intramolecular hydrogen bond forming a six member ring. According to the pmr spectra taken in DMSO solution derivatives **19** and **20** were formed primarily in the "*E*" isomeric forms which were re-arranged upon heating to the thermodynalically stabile "*Z*"-isomeric forms.

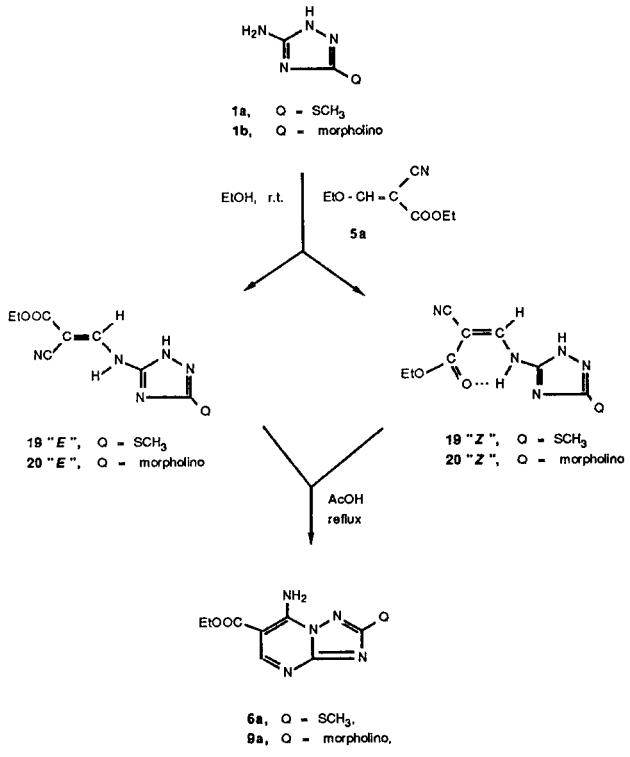
Refluxing the aminoacrylates **19** and **20** in acetic acid the expected condensed-ring derivatives **6a** and **9a**, respectively, were obtained giving a nice proof to the mechanism of their formation (Scheme 4).

The reaction of ethyl 2-cyano-3-ethoxyacrylate (**5a**) with *N*-substituted 5-amino-3-methylthio-1,2,4-triazoles, *e.g.* with 5-amino-2-methyl-3-methylthio-2*H*-1,2,4-triazole (**21**) or 5-amino-1-(2,6-dimethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**23**) (Schemes 5 and 6) lead also to the corresponding aminoacrylates **22** and **24**. It is worth mentioning that these aminoacrylates were formed as mixtures of the "*E*" and "*Z*" isomeric forms. Their heating in acetic acid did

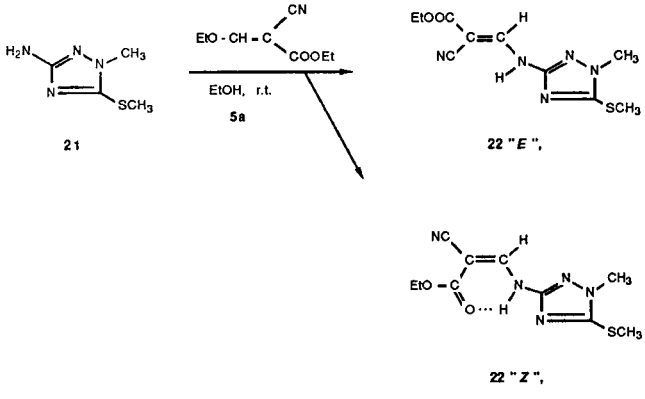
Scheme 3



Scheme 4

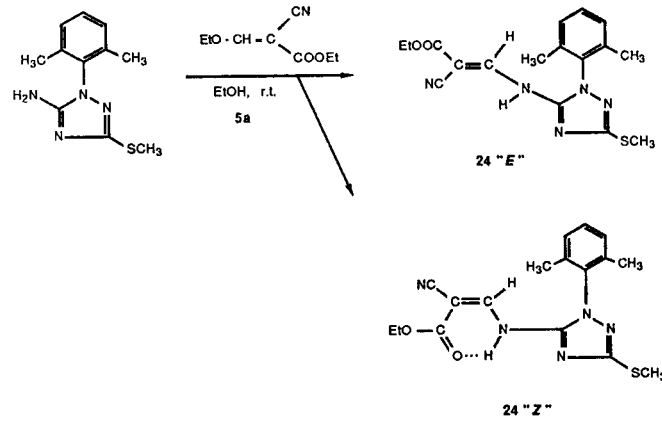


Scheme 5



not lead to the formation of the expected triazolo[1,5-*a*]-pyrimidine derivatives but to their re-arrangement to yield again the thermodinamically stable "*Z*" isomeric forms stabilised by the intamolecular hydrogen bond mentioned above. The "*Z*"-isomeric structure of **22** was corroborated by its proton coupled cmr spectra, too, where the $^{3}J_{C,H}$ coupling constants measured for the carboethoxy and the nitrile carbon atoms appeared with the value of 11.1 and 5.3 Hz, respectively, in excellent agreement with those of the previously prepared ethyl Z-2-cyano-3-benzylaminoacrylate being of the value of 10.6 and 5.2 Hz, respectively, and completely differed from those measured for its *E* isomer (3.6 and 10.0 Hz, respectively) [4].

Scheme 6



EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using Perkin-Elmer 577 spectrophotometer. The ultraviolet spectra were obtained by a Varian Cary 118 and a Pye Unicam SP 8-150 instrument. The pmr and the cmr measurements were performed using Varian XL-100, Brucker WM-250 and Brucker WP-80 SY instruments.

5-Amino-6-ethoxycarbonyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**6a**) by Direct Synthesis.

A mixture of 13.0 g (0.1 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1a**) [5], 16.9 g (0.1 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [6] and 50 ml of glacial acetic acid was refluxed for 5 hours. The solution obtained crystallised upon cooling. The crystals were filtered off and recrystallised from dimethylformamide to yield 17.6 g (70%) of the title compound, mp 211-213°; ir: ν NH = 3380 cm^{-1}, ν CO = 1690 cm^{-1}, ν C=N = 1640 and 1590 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.40 (t, 3H, CH_2CH_3), 2.73 (s, 3H, SCH_3), 4.23 (qa, 2H, CH_2), 8.6 (bs, 2H, NH_2), 8.83 (s, 1H, CH); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 251 (30.8), 296 sh (6.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 246 (29.5), 290 (7.6); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 245 (18.5), 268 sh (8.9), 324 (7.5).

Anal. Calcd. for $C_9H_{11}N_5O_2S$ (MW. 253.28): C, 42.68; H, 4.38; N, 27.65; S, 12.66. Found: C, 42.83; H, 4.63; N, 27.49; S, 12.90.

5-Amino-6-ethoxycarbonyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**6a**) by the Cyclisation of Ethyl *Z,E*-2-cyano-3-(3-methylthio-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**19**).

A solution of 0.5 g (0.002 mole) of ethyl *Z,E*-2-cyano-3-(3-methylthio-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**19**) in 3 ml of glacial acetic acid was refluxed for 5 hours. The crystals precipitated after cooling were filtered off and re-crystallised from 2-propanol to yield 0.3 g (60%) of the title compound, mp 212-214°; ir spectrum identical with that of the compound obtained by direct synthesis.

5-Amino-6-cyano-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**7a**).

A mixture of 6.5 g (0.05 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1a**) [5], 6.1 g (0.05 mole) of 2-cyano-3-ethoxyacrylonitrile (**5b**) [7] and 15 ml of glacial acetic acid was refuxed for 30 minutes. After cooling the crystals precipitated were filtered off and re-crystallised from dimethylformamide to yield 4.5 g (44%) of the title product, mp 299-301°; ir: ν NH_2 = 3390 cm^{-1}, ν CN = 2230 cm^{-1}, ν C=N = 1640 and 1590 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.68 (s, 3H, SCH_3), 8.60 (s, 1H, CH), 9.15 (bs, 1H, NH); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 250 (22.5), 298 sh (3.5); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 250 (20.9), 298 sh (3.5); uv (10% ethanol + 90% 0.1 *N* sodium

hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 238 (10.6), 268 sh (4.9), 276 sh (4.5), 316 (5.3).

Anal. Calcd. for $C_7H_6N_6S$ (MW. 206.23): C, 40.76; H, 2.93; N, 40.75; S, 15.55. Found: C, 40.85; H, 2.99; N, 40.56; S, 15.63.

5-Amino-2-(4-chlorobenzylthio)-6-ethoxycarbonyl-1,2,4-triazolo[1,5-*a*]-pyrimidine (**8a**).

A mixture of 19.2 g (0.08 mole) of 5-amino-3-(4-chlorobenzylthio)-1*H*-1,2,4-triazole (**1c**) [5]. 13.9 g (0.082 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [6] and 50 ml of glacial acetic acid was refluxed for 4 hours. The solution obtained crystallised upon cooling. The crystals were filtered off and re-crystallised from dimethylformamide to yield 16.1 g (55 %) of the title product, mp 222-224°; ir: ν NH 3385 cm^{-1}, ν CO = 1680 cm^{-1}, ν C=N = 1640 and 1600 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.35 (t, 3H, CH_3), 4.37 (qa, 2H, OCH_2), 4.53 (s, 3H, SCH_2), 8.6 (bs, 2H, NH_2), 8.75 (s, 1H, CH); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 252 (36.0), 294 sh (8.4); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 244 (19.2), 296 sh (6.2).

Anal. Calcd. for $C_{15}H_{14}ClN_5O_2S$ (MW. 363.83): C, 49.52; H, 3.88; N, 19.25; S. 8.81; Cl, 9.75. Found: C, 49.72; H, 4.01; N, 19.23; S, 8.94; Cl, 9.76.

5-Amino-6-ethoxycarbonyl-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**9a**) by Direct Synthesis.

A mixture of 16.9 g (0.1 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1b**) [5] 16.9 g (0.1 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [6] and 50 ml of glacial acetic acid was refluxed for 1 hour. The solution obtained crystallised upon cooling. The crystals were filtered off and re-crystallised from dimethylformamide to yield 18.6 g (64%) of the title product, mp 223-225°; ir: ν NH = 3400 cm^{-1}, ν CO = 1680 cm^{-1}, ν C=N = 1630 and 1615 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.35 (t, 3H, CH_3), 3.30 (b, 4H, NCH_2), 3.67 (t, 4H, OCH_2), 4.29 (qa, 2H, OCH_2CH_3), 8.3 (bs, 2H, NH_2), 8.63 (s, 1H, CH); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 257 (44.1), 294 sh (5.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 249 (31.3), 298 sh (5.8); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 249 (38.5), 295 sh (6.8).

Anal. Calcd. for $C_{12}H_{16}N_6O_3$ (MW. 292.30): C, 49.31; H, 5.52; N, 28.75. Found: C, 49.54; H, 5.78; N, 28.64.

5-Amino-6-ethoxycarbonyl-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**9a**) by the Cyclisation of Ethyl *Z,E*-2-Cyano-3-(3-morpholino-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**20**).

A solution of 1.5 g (0.00516 mole) of ethyl *Z,E*-2-cyano-3-(3-morpholino-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**20**) in 3 ml of glacial acetic acid was refluxed for 5 hours. The crystals precipitated after cooling were filtered off to yield 1.2 g (80%) of the title compound, mp 237-240°; ir identical with that of the compound obtained by direct synthesis.

5-Amino-6-cyano-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**10a**).

A mixture of 16.9 g (0.1 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1b**) [5], 12.2 g (0.1 mole) of 2-cyano-3-ethoxyacrylonitrile (**5b**) [7] and 50 ml of glacial acetic acid was refluxed for 30 minutes. After cooling the crystals precipitated were filtered off and re-crystallised from dimethyl sulfoxide to yield 17.2 g (70%) of the title product, mp >360°; ir: ν NH_2 = 3390 cm^{-1}, ν CN = 2220 cm^{-1}, ν C=N = 1640 and 1600 cm^{-1}; pmr (DMSO-d_6): δ ppm 3.32 (t, 4H, NCH_2), 3.70 (t, 4H, OCH_2), 8.55 (s, 1H, CH), 9.20 (bs, 2H, NH_2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 256 (31.2), 296 sh (5.3); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 251 (28.9), 298 sh (5.7); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 240 (21.9), 268 sh (11.6), 318 (12.6).

Anal. Calcd. for $C_{10}H_{11}N_7O$ (MW. 245.24): C, 48.97; H, 4.52; N, 39.98. Found: C, 49.11; H, 4.67; N, 40.06.

Sodium 5-Amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate (**11a**).

5-Amino-6-ethoxycarbonyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**6a**) (5.06 g, 0.02 mole) was stirred with heating with 25 ml (0.025 mole) of 1 *N* sodium hydroxide solution. At 86° the starting material dissolved and the stirring was continued at this temperature for further 5 minutes. After cooling the solution crystallised. The crystals were filtered off to yield 4.4 g (78%) of the title product, mp 316-318°; ir: ν NH_2 = 3415 and 3315 cm^{-1}, ν CO = 1664 cm^{-1}, ν C=N = 1593 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.66 (s, 3H, SCH_3), 8.78 (s, 1H, CH), 8.23 (bs, 1H, NH_2), 10.17 (bs, 1H, NH_2); uv (water): λ max nm ($\epsilon \cdot 10^{-3}$) 244 (29.5), 292 sh (8.0).

Anal. Calcd. for $C_7H_6N_5O_2SNa$ (MW. 247.22): C, 34.01; H, 2.45; N, 28.33; S, 12.97. Found: C, 34.11; H, 2.67; N, 28.25; S, 13.05.

Sodium 5-Amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidin-6-carboxylate (**12a**).

5-Amino-6-ethoxycarbonyl-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**9a**) (4.38 g, 0.015 mole) was stirred with heating with 17 ml (0.017 mole) of 1 *N* sodium hydroxide solution. The material dissolved at 80°. The stirring was continued at this temperature for a further 15 minutes, then the solution was allowed to cool to the laboratory temperature. After adding 40 ml of acetone 2.4 g (56%) of the title product crystallised from the reaction mixture which after re-crystallisation from water melted at 307-310°; ir: ν NH_2 = 3300 cm^{-1}, ν C=O = 1645 cm^{-1}; pmr (DMSO-d_6): δ ppm 3.39 (t, 4H, NCH_2), 3.71 (t, 4H, OCH_2), 8.67 (s, 1H, CH), 7.61 (bs, 1H, NH_2), 9.89 (bs, 1H, NH_2); uv (water): λ max nm ($\epsilon \cdot 10^{-3}$) 246 (35.2), 296 sh (6.4).

Anal. Calcd. for $C_{10}H_{11}N_6O_3Na$ (MW. 286.23): C, 41.96; H, 3.87; N, 29.36. Found: C, 42.12; H, 4.01; N, 29.23.

5-Amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylic Acid (**13a**).

The solution of 2.83 g (0.01 mole) of sodium 5-amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate dihydrate (**11a**) in 40 ml of water was acidified with concentrated hydrochloric acid to *p*H = 1. The product crystallised was filtered off and washed with distilled water to yield 1.81 g (80%) of the title product, mp 278-281°; ir ν OH = 3500 cm^{-1}, ν NH = 3340 cm^{-1}, ν CO = 1700 cm^{-1}, ν C=N = 1640 and 1580 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.68 (s, 3H, SCH_3), 5.7 (b, 1H, OH), 8.6 (b, 1H, NH), 8.74 (s, 1H, CH); uv (ethanol):λ max nm ($\epsilon \cdot 10^{-3}$) 248 (33.9), 294 sh (7.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 250 (31.3), 292 sh (8.4); uv (10% ethanol + 90% sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 244 (30.7), 292 (8.2).

Anal. Calcd. for $C_5H_7N_5O_2S$ (MW. 225.23): C, 37.33; H, 3.13; N, 31.10; S, 14.24. Found: C, 37.41; H, 3.42; N, 31.04; S, 14.07.

5-Amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylic Acid (**14a**).

A solution of 1.61 g (0.005 mole) of sodium 5-amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylate dihydrate (**12b**) in 10 ml of water was acidified with acetic acid to *p*H = 4. The crystals precipitated were filtered off to yield 1.12 g (100%) of the title product, mp 275-277°; ir: ν NH_2 + ν OH = 3420 and 3250-3050 cm^{-1}, ν C=O = 1700 cm^{-1}, ν C=N = 1670, 1630 and 1600 cm^{-1}; pmr (DMSO-d_6 + deuteriochloroform): δ ppm 8.65 (s, 1H, CH), 3.80 (t, 4H, OCH_2), 3.40 (t, 4H, NCH_2); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 246 (26.1), 292 sh (4.4); uv (10% ethanol + 90% hydrochloric acid): λ max nm ($\epsilon \cdot 10^{-3}$) 250 (19.2), 296 sh (4.0); uv (10% ethanol + 90% sodium hydroxide): λ max nm ($\epsilon \cdot 10^{-3}$) 246 (25.2), 294 sh (4.4).

Anal. Calcd. for $C_{10}H_{12}N_6O_3$ (MW. 264.24): C, 45.45; H, 4.58; N, 31.81. Found: C, 45.71; H, 4.36; N, 32.05.

5-Amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**15a**).

A mixture of 1.13 g (0.005 mole) of 5-amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**13a**) and 50 ml of diphenyl ether was heated at 250° for 3 hours. The solution obtained was filtered off while hot and let to crystallise. The crystals precipitated after cooling were filtered off and washed with diethylether to yield 0.8 g (88%) of the title product, mp 231-233°; ir: ν NH_2 = 3310 and 3105 cm^{-1}, ν C=N = 1640 and 1575 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.67 (s, 3H, SCH_3), 6.28 (d, 1H, CH^6), 8.20 (d, 1H, CH^7), 8.10 (s, 2H, NH_2); cmr (DMSO-d_6): δ ppm 165.8 (C^2), 156.5 (C^{8a}), 153.0 (C^7), 148.3 (C^5), 91.2 (C^6), 13.4 (SCH_3); uv (ethanol): λ max nm ($\epsilon \cdot 10^{-3}$) 237 (30.0), 290 (11.0); uv (10% ethanol +

90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 228 (22.5), 274 (14.9); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 235 (24.4), 287 (11.2).

Anal. Calcd. for $C_6H_7N_5S$ (MW. 181.22): C, 39.76; H, 3.89; N, 38.65; S, 17.69. Found: C, 39.85; H, 3.97; N, 38.47; S, 17.52.

5-Amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**16a**).

A mixture of 2.64 g (0.01 mole) of 5-amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxylic acid (**14a**) and 100 ml of diphenyl ether was heated at 250° for 6 hours. The solution obtained was filtered off while hot and let to crystallise. The crystals precipitated after cooling were filtered off and washed with diethylether to yield after re-crystallisation from dimethylforlmamide 1.7 g (77%) of the title product, mp 304-306°; ir: ν NH_2 = 3360 cm⁻¹, ν C=N = 1655, 1585 and 1540 cm⁻¹; pmr (DMSO-d_6): δ ppm 3.49 (t, 4H, NCH_2), 3.71 (t, 4H, OCH_2), 6.15 (d, 1H, CH^6), 7.69 (bs, 2H, NH_2), 8.02 (d, 1H, CH^7); cmr (DMSO-d_6): δ ppm 166.5 (C^2), 156.0 (C^{8a}), 151.6 (C^7), 147.7 (C^5), 90.7 (C^6), 65.8 (OCH_2), 45.8 (NCH_2); uv (ethanol): λ max nm (ε·10⁻³) 234 (32.0), 286 (9.5); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 230 (21.7), 246 (10.7), 284 (10.7); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 232 (31.7), 286 (9.5).

Anal. Calcd. for $C_9H_{12}N_6O$ (MW. 220.23): C, 49.08; H, 5.49; N, 38.16. Found: C, 49.25; H, 5.67; N, 38.17.

2-Methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine-5(8*H*)-one (**17a**).

5-Amino-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**15a**) (1.81 g, 0.01 mole) was dissolved in the mixture of 0.539 g (0.29 ml = 0.005 mole) of concentrated sulfuric acid and 10 ml of water. To the solution thus obtained the solution of 1.38 g (0.02 mole) of sodium nitrite in 15 ml of water was added dropwise while cooling under -5°. The solution of the diazonium salt obtained was decomposed by dropping it into 50 ml of boiling 2 *N* sulfuric acid. The solution thus obtained was concentrated *in vacuo* to the volume of about 20 ml and the product was salted out with sodium sulfate to yield 1.3 g (71%) of the title product which after re-crystallisation from ethanol melted at 165-167°; ir: ν NH = 3250 cm⁻¹, ν C=O = 1686 cm⁻¹, ν C=N = 1645 and 1605 cm⁻¹; pmr (DMSO-d_6): δ ppm, 2.70 (s, 3H, SCH_3), 6.58 (d, 1H, C^6), 8.31 (d, 1H, C^7), 8.35 (bs, 1H, NH); uv (ethanol): λ max nm (ε·10⁻³) 237 (20.3), 290 (7.1); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 238 (14.8), 284 (9.9); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 236 (15.9), 288 (7.2).

Anal. Calcd. for $C_6H_6N_4OS$ (MW. 182.21): C, 39.55; H, 3.32; N, 30.75; S, 17.60. Found: C, 39.77; H, 3.55; N, 30.72; S, 17.65.

2-Morpholino-1,2,4-triazolo[1,5-*a*]pyrimidin-5(8*H*)-one (**18a**).

5-Amino-2-morpholino-1,2,4-triazolo[1,5-*a*]pyrimidine (**16a**) (2.2 g 0.01 mole) was dissolved in the mixture of 0.49 g (0.27 ml = 0.005 mole) of concentrated sulfuric acid and 10 ml of water. To the solution thus obtained the solution of 1.38 g (0.02 mole) of sodium nitrite in 15 ml of water was added dropwise while cooling between 0-5°. The solution of the diazonium salt obtained was decomposed by dropping it into 50 ml of boiling 2 *N* sulfuric acid. The solution thus obtained was concentrated *in vacuo* to the volume of about 20 ml and the product was salted out with sodium sulfate to yield 1.8 g (82%) of the title product, which after re-crystallisation from methanol melted at 244-246°; ir: ν NH = 3600-2500 cm⁻¹, ν CO = 1657 cm⁻¹, ν C=N = 1580 and 1540 cm⁻¹; pmr (DMSO-d_6): δ ppm 3.41 (t, 4H, NCH_2), 3.72 (t, 4H, OCH_2), 6.25 (d, 1H, CH^6), 8.07 (d, 1H, CH^7), 8.30 (bs, 1H, NH); cmr (DMSO-d_6): δ ppm 166.1 (C^2), 152.8 (C^5), 148.9 (C^{8a}), 146.7 (C^7), 92.2 (C^6), 65.8 (OCH_2), 45.8 (NCH_2); uv (ethanol): λ max nm (ε·10⁻³) 235 (32.7), 286 (8.7); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 232 (19.0), 248 sh (9.0), 286 (9.2); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 232 (29.8), 285 (8.2).

Anal. Calcd. for $C_9H_{11}N_5O_2$ (MW. 221.22): C, 48.86, H, 5.01; N, 31.68. Found: C, 48.72; H, 5.11; N, 31.75.

Ethyl *E*-2-Cyano-3-(3-methylthio-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**19**''*E*'').

To a solution of 1.3 g (0.01 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole (**1a**) [4] in 40 ml of tetrahydrofurane the solution of 1.69 g (0.01 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [5] in 10 ml of tetrahydrofurane was added at room temperature and let to stay for four days. The solution was evaporated *in vacuo* to dryness. The residue was dissolved at room temperature in 30 ml of dimethylformamide and to the solution obtained 200 ml of water was added by dropping it through a dropping funnel. The crystals precipitated were filtered off and washed with 2-propanol to yield 1.9 g (75%) of the title product, mp 167-170°; ir: ν CN = 2220 cm⁻¹, ν CO = 1720 cm⁻¹, ν C=N = 1640 cm⁻¹, ν NH = 3280 cm⁻¹; pmr (DMSO-d_6): δ ppm 1.29 (t, 3H, CH_3), 2.60 (s, 3H, SCH_3), 4.16 (qa, 2H, CH_2), 8.40 (s, 1H, CH), 10.5 [b, 1H, NH (exo)], 12.5 [(b, 1H, NH (triazole)]; uv (ethanol): λ max nm (ε·10⁻³) 205 (14.5), 242 sh (7.1), 309 (20.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 204 (16.5), 240 (3.0), 302 (12.3); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 231 (21.8), 304 (11.4), 313 (10.1).

Anal. Calcd. for $C_9H_{11}N_5O_2S$ (MW. 253.28): C, 42.68; H, 4.38; N, 27.65; S, 12.66. Found: C, 42.55; H, 4.50; N, 27.75; S, 12.72.

Ethyl *Z,E*-2-Cyano-3-(3-morpholino-1*H*-1,2,4-triazol-5-yl)aminoacrylate (**20**).

To a solution of 3.38 g (0.02 mole) of 5-amino-3-morpholino-1*H*-1,2,4-triazole (**1b**) [4] in 30 ml of ethanol the solution of 3.38 g (0.02 mole) ethyl 2-cyano-3-ethoxyacrylate (**5a**) [5] in 10 ml of ethanol was added at room temperature. The solution thus obtained started to crystallise upon standing within 5 minutes. After 2 hours the crystals precipitated were filtered off to yield 4.2 g (72%) of the title product, mp 225-227°. The mother liquor crystallised again upon standing to give a further 1.3 g (22%) crop of title product, mp 225-228° increasing the total yield of the reaction to 94%. The product is on the basis of pmr a 4:1 mixture of the *Z* and *E* isomers; ir: ν NH_2 3380 and 3240 cm⁻¹, ν CN 2212 cm⁻¹, ν CO 1713 and 1700 cm⁻¹, ν C = N 1640 and 1590 cm⁻¹; pmr (DMSO-d_6): δ ppm 1.23 [t, CH_3 (''*E*'')], 1.26 [t, CH_3 (''*Z*'')], 3.29 (t, 4H, NCH_2), 3.72 (t, 4H, OCH_2), 4.17 [qa, OCH_2CH_3 (''*E*'')], 4.24 [qa, OCH_2CH_3 (''*Z*'')], 8.20 [d (J = 12 Hz), CH (''*Z*'')], 8.50 [s, CH (''*E*'')], 10.45 [d (J = 12 Hz), NH (''*Z*'')], 10.57 [s, NH (''*E*'')], 12.47 (bs, NH (triazole) (''*E*'')], 12.53 (bs, NH (triazole) (''*Z*'')]; uv (ethanol): λ max nm (ε·10⁻³) 258 (11.7), 309 (16.0); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 264 sh (6.1), 305 (17.9); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 245 (18.1), 325 (14.1).

Anal. Calcd. for $C_{12}H_{16}N_6O_3$ (MW. 292.30): C, 49.31; H, 5.52; N, 28.75. Found: C, 49.22; H, 5.55; N, 28.81.

Ethyl *Z,E*-2-Cyano-3-(2-methyl-3-methylthio-2*H*-1,2,4-triazol-5-yl)aminoacrylate (**22**).

To a solution of 2.88 g (0.02 mole) of 5-amino-2-methyl-3-methylthio-2*H*-1,2,4-triazole (**21**) [4] in 20 ml of ethanol the solution of 3.38 g (0.02 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [5] in 20 ml of ethanol was added at room temperature. After allowing to stand overnight the crystals which precipitated were filtered off to yield 3.3 g (62%) of the title compound, mp 102-114°. The product is according to pmr a 1:1 mixture of the *Z* and *E* isomers; ir: ν CN = 2230 and 2220 cm⁻¹, ν C=O = 1710 and 1690 cm⁻¹, ν C=N = 1640 cm⁻¹; pmr (deuteriochloroform): δ ppm 1.31 [t, CH_2CH_3 (''*E*'')], 1.35 [t, CH_2CH_3 (''*Z*'')], 2.66 [s, SCH_3 (''*Z* + *E*'')], 3.67 [s, NCH_3 (''*Z*'')], 3.70 [s, NCH_3 (''*E*'')], 4.25 [qa, OCH_2 (''*E*'')], 4.29 [qa, OCH_2 (''*Z*'')], 8.21 [d, CH (''*Z*'')], 8.85 [qa, CH (''*E*'')], 10.4 [b, NH (''*Z*'')], 10.8 [s, NH (''*E*'')]; uv (ethanol): λ max nm (ε·10⁻³) 241 sh (5.6), 307 (22.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10⁻³) 240 (6.1), 307 (23.4); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10⁻³) 232 (10.9), 321 (27.6).

Anal. Calcd. for $C_{10}H_{13}N_5O_2S$ (MW. 267.31): C, 44.93; H, 4.90; N, 26.20; S, 12.00. Found: C, 45.07; H, 5.11; N, 26.31; S, 11.83.

Ethyl *Z*-2-Cyano-3-(2-methyl-3-methylthio-2*H*-1,2,4-triazol-5-yl)aminoacrylate (**22**''*Z*'').

The mixture of the *Z-E* isomers prepared above (0.53 g, 0.005 mole)

was heated at 120° for 3 hours. The melt obtained crystallised upon cooling. It was re-crystallised from 2-propanol to yield 0.4 g (76%) of the pure *Z* isomer, mp 104-105°; ir: ν CN = 2220 cm^{-1}, ν C=O = 1690 cm^{-1}, ν C=N = 1640 cm^{-1}, ν NH = 3290 cm^{-1}; pmr (deuteriochloroform): δ ppm 1.35 (t, 3H, CH_2CH_3), 2.65 (s, 3H, SCH_3), 3.66 (s, 3H, NCH_3), 4.28 (qa, 2H, OCH_2), 8.20 (d, 1H, CH), 10.4 (d, 1H, NH); cmr (deuteriochloroform): δ ppm 14.2 (qa, SCH_3), 15.5 (qa, CH_2CH_3), 35.3 (qa, NCH_3), 60.8 (dqa, CH_2), 77.2 [d, =*C*(CN)COOE], 116.8 [d (J = 5.3 Hz), *C*N], 151.3 (qa, triazole C^3), 153.7 (d, -*C*H=C), 155.9 (d, triazole C^5), 166.3 [d (J = 11.1 Hz), *C*=O]; uv (ethanol): λ max nm (ε·10^{-3}) 241 sh (5.6), 307 (22.5); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10^{-3}) 240 (5.6), 304 (22.8); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10^{-3}) 232 (12.0), 321 (28.0).

Ethyl *Z*-2-Cyano-3-[1-(2,6-dimethylphenyl)-3-methylthio-1*H*-1,2,4-triazol-5-yl]aminoacrylate (**24**"*E*").

To a solution of 2.34 g (0.01 mole) of 5-amino-1-(2,6-dimethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**23**) [4] in 10 ml of ethanol a solution of 1.69 g (0.02 mole) of ethyl 2-cyano-3-ethoxyacrylate (**5a**) [5] in 10 ml of ethanol was added at room temperature and let to stand at room temperature for 7 days. After evaporating *in vacuo* to dryness the residue was re-crystallised from 2-propanol to yield 1.3 g (36%) of the title product, mp 176-178°; ir ν CN = 2225 cm^{-1}, ν CO = 1690 cm^{-1}, ν C=N = 1630 cm^{-1}, ν NH = 3270 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.26 (t, 3H, CH_3), 2.04 (s, 6H, $ArCH_3$), 2.56 (s, 3H, SCH_3), 4.21 (qa, 2H, CH_2), 7.1-7.4 (m, 3H, ArH), 8.48 (s, 1H, CH), 10.5 (s, 1H, NH); uv (ethanol): λ max nm (ε·10^{-3}) 214 sh (11.1), 262 sh (3.1), 334 (33.2); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε·10^{-3}) 216 sh (20.5), 245 (8.0), 306 (22.5); uv (10% ethanol + 90% 0.1 *N* sodium hydroxide): λ max nm (ε·10^{-3}) 225 sh (13.5), 260 sh (3.5), 326 (31.6).

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