On Triazoles XVI [1]. The Reaction of 5-Amino-1,2,4-triazoles with β- and γ-Oxo Esters. A Novel *N*-Carbonylation Reaction [2]

József Reiter, Pál Vágó, Klára Esses-Reiter and László Pongó

EGIS Pharmaceuticals, 1475 Budapest, P.O.B. 100, Hungary

Hilda Molnár

Institute for Drug Research, 1375 Budapest, P.O.B. 82, Hungary

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5-Amino-1,2,4-triazoles reacted with alifatic β-oxo-esters to yield besides the unexpected 1,2,4-triazolo-[1,5-*a*]-1,3,5-benzotriazepin-5-one derivative **7** either the corresponding esters **5** and **6** or a 1:2 condensation product **8**. To the contrary alicyclic and heterocyclic β-oxo-esters formed in the above reaction only derivatives **7**. The proposed mechanism of the formation of **7** involving a novel *N*-carbonylation reaction was proved by the isolation of the by-products and the intermediate of the reaction. Repeating the above reaction with a γ-oxo-ester, namely the ethyl levulinate, derivatives **17** and **18**, respectively, representing two new ring systems were obtained.

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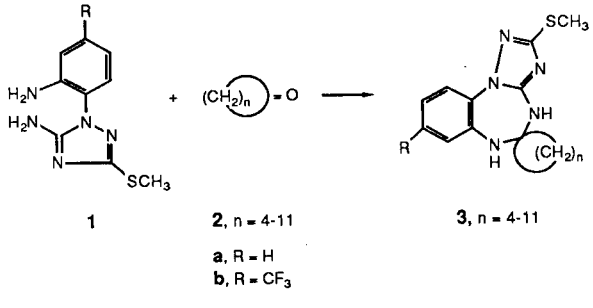
In a previous paper of this series [3] we have reported on the synthesis of 1-(2-aminophenyl)-3-methylthio-5-amino-1*H*-1,2,4-triazole derivatives **1**, and their cyclisation with different cyclic ketones **2** to give novel spiro-ring systems **3** (Scheme 1). It was also reported [4] that different 5-amino-1,2,4-triazoles could be acylated under mild conditions to the "ring acylated" 1-acyl-5-amino-1,2,4-triazole derivatives which could be thermally rearranged to their "acyl-amino" isomers, namely to the 5-acylamino-1,2,4-triazoles.

Scheme 1



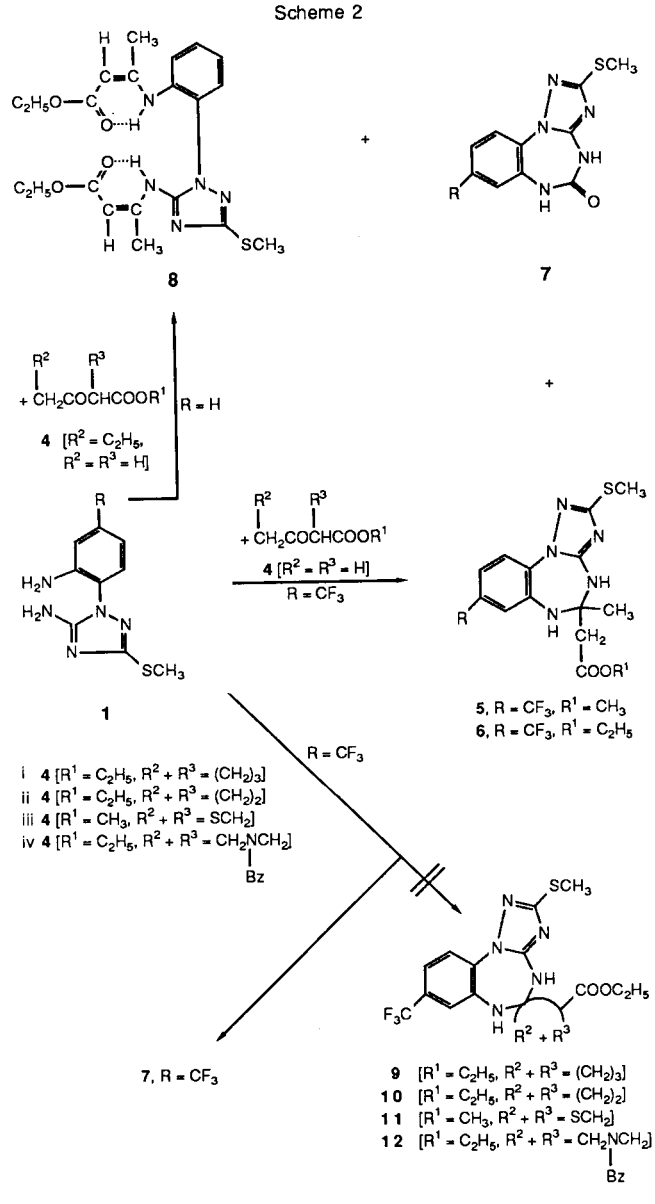
1 **2**, n = 4-11 **3**, n = 4-11

a, R = H
b, R = CF_3

In our further studies we reacted the **1** type triazoles with β- **4** and γ-oxo-esters **13**, respectively. These derivatives have two reactive groups thus they could react with the two different amino groups of **1** to form either the corresponding Schiff's bases, or amides or the **3**-type tricyclic derivatives, respectively.

Providing the reaction with different β-oxo-esters depending on the nature of the β-oxo-ester, the R substituent of **1** and the conditions of the reaction different products were obtained. Thus refluxing of **1b** (R = CF_3) with excess of methyl or ethyl acetoacetate (**4**, R^2 = R^3 = H, R^1 = methyl or ethyl, respectively) besides the main products **5** (R^1 = methyl) and **6** (R^1 = ethyl), respectively, in each case an unexpected ketone **7** (R = CF_3) was formed (Scheme 2). The structure of products **5** and **6** was proved

Scheme 2



8 **7**

4 [R^2 = C_2H_5, R^2 = R^3 = H]

R = H

1

4 [R^2 = R^3 = H]
R = CF_3

5, R = CF_3, R^1 = CH_3
6, R = CF_3, R^1 = C_2H_5

R = CF_3

i **4** [R^1 = C_2H_5, R^2 + R^3 = $(CH_2)_3$]
ii **4** [R^1 = C_2H_5, R^2 + R^3 = $(CH_2)_2$]
iii **4** [R^1 = CH_3, R^2 + R^3 = SCH_2]
iv **4** [R^1 = C_2H_5, R^2 + R^3 = CH_2NCH_2] (Bz)

7, R = CF_3

9 [R^1 = C_2H_5, R^2 + R^3 = $(CH_2)_3$]
10 [R^1 = C_2H_5, R^2 + R^3 = $(CH_2)_2$]
11 [R^1 = CH_3, R^2 + R^3 = SCH_2]
12 [R^1 = C_2H_5, R^2 + R^3 = CH_2NCH_2] (Bz)

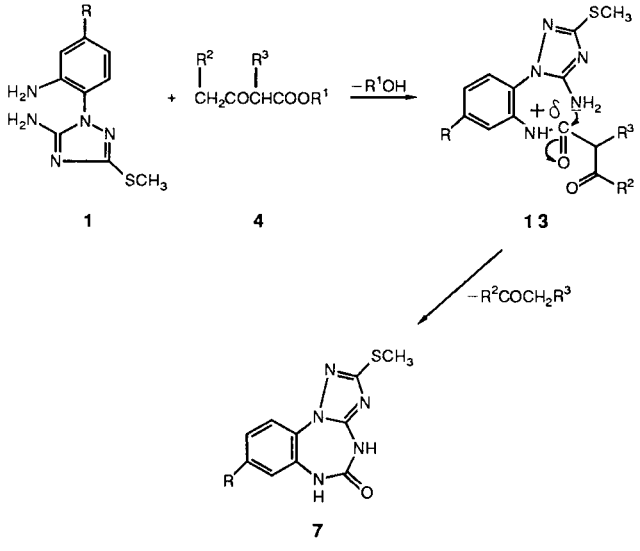
(besides other spectral data) by their cmr spectra where the newly built in carbon atoms 5 appeared as a consequence of their sp^3 character with the chemical shifts of 67.5 and 67.4 ppm, respectively. Derivative **7** was characterised with its two NH bands appearing at 9.7 ppm and 10.9 ppm, respectivly in the pmr spectra and the C=O band appearing at 1722 cm^{-1} in the ir and at 149.7 ppm in the cmr spectra.

Surprisingly the main product of the reaction of **1a** (R = H) with excess of ethyl acetoacetate (**4**, $R^2 = R^3 = H$, R^1 = ethyl) proved not to be the expected analogous 1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazine derivative but a 1:2 condensation product was formed, namely derivative **8**. The chelate character of **8** was fully supported by its pmr spectra where the NH singlets appeared shifted strongly upfield to 10.2 and 10.8 ppm, respectively. The by-product of this reaction was again a ketone **7** (R = H) characterised by its analogous spectra with **7** ($R = CF_3$).

On the other hand refluxing **1b** ($R = CF_3$) with either, the ethyl 2-oxocyclopentanecarboxylate [**4**, R^1 = ethyl, $R^2 + R^3 = (CH_2)_2$)], ethyl 2-oxocyclohexanecarboxylate [**4**, R^1 = ethyl, $R^2 + R^3 = (CH_2)_3$)], methyl 4-oxotetrahydrothiophene-3-carboxylate [**4**, R^1 = methyl, $R^2 + R^3 = SCH_2$) or methyl 1-benzyl-4-oxopiperidine-3-carboxylate [**4**, R^1 = methyl, $R^2 + R^3 = CH_2N(CH_2Ph)CH_2$], respectively derivatives **9-12** analogues to **5** and **6** were not formed but instead the unexpected derivative **7** ($R = CF_3$) proved to be again the main product of the reactions (Scheme 2).

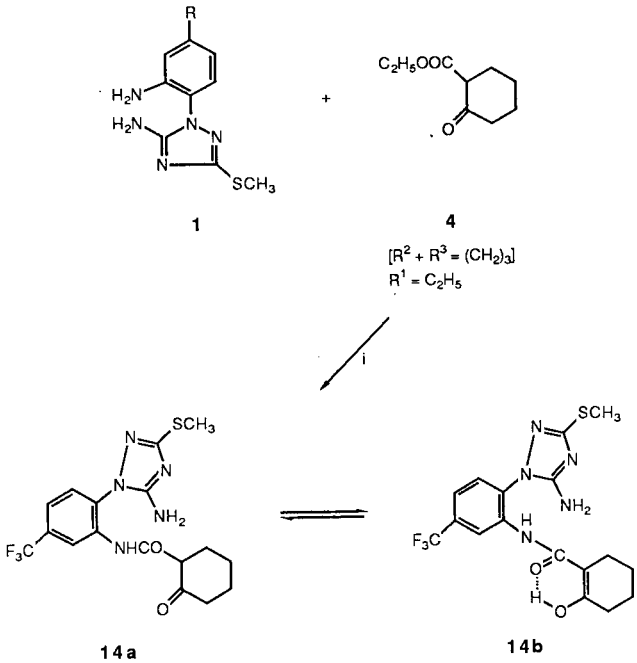
The following mechanism was proposed for the formation of **7** (Scheme 3). In the first step the ester group of **4** forms and amide with the more basic aromatic amino group of **1** to yield the intermediate **13**. This condensation is accompanied by the elimination of a corresponding alcohol. This is followed by the intramolecular nucleophilic attack of the exocyclic triazole amino group against the amide carbonyl to yield **7** which is accompanied with the elimination of a corresponding ketone.

Scheme 3



The proposed mechanism of the formation of **7** was corroborated by the study of the reaction of **1b** ($R = CF_3$) with ethyl 2-oxocyclohexanecarboxylate [**4**, R^1 = ethyl, $R^2 + R^3 = (CH_2)_3$)] in detail. A gc evalutation of the reaction mixture proved the presence of the corresponding alcohol (ethanol) and ketone (cyclohexanone) formed as by-products of the reaction. The work up of the reaction mixture yielded two products, the expected **7** ($R = CF_3$) and the amide **14** which is the intermediate of this reaction (Scheme 4). This product exists as proved by its pmr and cmr data as a mixture of the tautomeric forms **14a** and **14b**.

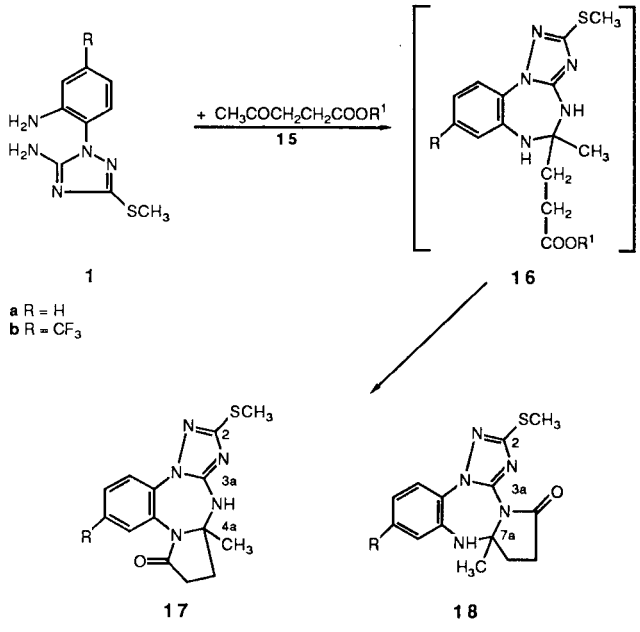
Scheme 4



The above results helped to prove unequivocally the mechanism of this newly observed *N*-carbonylation reaction in which the role of the carbonylating agent played the β-oxo-esters. As it was shown by the use of different aliphatic, alicyclic and heterocyclic β-oxo-esters this reaction was of rather general validity.

The reaction of derivatives **1** with a γ-oxo-ester, namely the ethyl levulinate (**15**) lead, most probably again through a not isolable intermediate **16**, to the mixture of derivatives **17** and **18**, respectively, representing two novel ring systems (Scheme 5). The structure of derivatives **17** and **18** was corroborated again with their cmr spectra where the newly built in carbon atoms 4a and 7a appeared as a consequence to their sp^3 character betwen 73 and 75 ppm. The uv spectra of derivatives **17** and **18** differed signifi-

Scheme 5



cantly from each other but gave no answer which one of them corresponded to which structure. The differentiation between structures **17** and **18** made possible the triazole carbon atoms 2 and 3a that appeared in derivatives **17** at about 160 ppm and 154 ppm, respectively, in good agreement with those of derivatives **5** (R^1 = methyl), **6** (R^1 = ethyl) and **3** (n = 4-11) [3] while in case of derivative **18b** at 160.9 ppm and 145.8 ppm, respectively, corroborating - if taken in account the steric hindrance of the pyrrolidinone ring - our previous results with 5-acylamino-1,2,4-triazoles [4].

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 ^{1}H-nmr and the ^{13}C-nmr measurements were performed using Varian XL-100, Bruker WM-250 and Bruker WP-80 SY instruments.

Methyl{4,5-Dihydro-5-methyl-2-methylthio-8-trifluoromethyl-6*H*-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepine-5-yl}acetate (**5**, R^1 = CH_3) and 4,5-Dihydro-2-methylthio-8-trifluoromethyl-1,2-4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3).

A solution of 2.89 g (0.01 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] in 25 ml of methyl acetoacetate (**4**, R^1 = CH_3, R^2 = R^3 = H) was refluxed for 5 hours. The solution obtained was evaporated *in vacuo* to dryness and the residue was recrystallised from acetonitrile to yield 0.65 g (17%) of methyl {4,5-dihydro-5-methyl-2-methylthio-8-trifluoromethyl-6*H*-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepine-5-yl}acetate (**5**, R^1 = CH_3), mp 180-182°; ir: ν CO = 1745 cm^{-1}, ν NH = 3345 and 3250 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.59 (s, 3H, CCH_3), 2.52 (t, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.51 (s, 3H, OCH_3), 6.70 (bs, 1H, NH), 7.32 (d, 1H, ArH^9), 7.4 (bs, 1H, NH), 8.01 (d, 1H, ArH^{10}), 8.49 (s, 1H, ArH^7); cmr (DMSO-d_6): δ, ppm 13.3 (SCH_3), 27.0 (CCH_3), 44.6 (CCH_2), 51.3 (OCH_3), 67.5 (C^5), 118.0 (C^9), 120.8 (C^7), 122.0 (C^{10}), 124.1 (CF_3), 125.8 (C^8), 131.3 (C^{10a}), 135.5 (C^{6a}), 153.8 (C^{3a}), 159.7 (C^2), 169.2 (CO); uv (ethanol): λ max nm (ε.10^{-3}) 211 (23.6), 232 (19.5), 296 (5.3), 326 (7.0); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 232 sh (18.7), 296 (6.4), 318 (6.8); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 203 (24.0), 232 (14.7), 320 (3.4).

Anal. Calcd. for $C_{15}H_{16}F_3N_5O_2S$ (MW. 387.38): C, 46.50, H, 4.16, N, 18.08, S, 8.28, F, 14.71. Found: C, 46.32, H, 4.20, N, 18.14, S, 8.35, F, 14.56.

The mother liquor of **5** (R^1 = methyl) was evaporated to dryness and the residue chromatographed on a silica-gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to yield 0.25 g (8%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), mp 284-286° (acetonitrile); ir: ν CO = 1722 cm^{-1}; pmr (DMSO-d_6): δ, ppm 2.51 (s, 3H, SCH_3), 7.55 (m, 2H, $ArH^{7,9}$), 7.83 (d, 1H, ArH^{10}), 9.7 (b s, 1H, NH), 10.9 (b s, 1H, NH); cmr (DMSO-d_6): δ, ppm (C, F coupling indicated only) 13.4 (SCH_3), 118.0 (q, $J_{C,F}$ = 3.8 Hz, C^9), 121.2 (q, $J_{C,F}$ = 3.8 Hz, C^7), 121.9 (C^{10}), 123.5 (q, $J_{C,F}$ = 272.5 Hz, CF_3), 128.5 (q, $J_{C,F}$ = 32.7 Hz, C^8), 129.5* (C^{6a}), 129.7* (C^{10a}), 149.7 (C=O), 155.9 (C^{3a}), 162.0 (C^2); uv (ethanol): λ max nm (ε.10^{-3}) 209 (35.2), 234 sh (22.1), 298 (7.0); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 245 (29.5), 310 (3.9); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 206 (29.5), 230 sh (19.9), 298 (5.2).

Anal. Calcd. for $C_{11}H_8F_3N_5OS$ (MW. 315.28): C, 41.90; H, 2.57; N, 22.22; S, 10.17; F, 18.08. Found: C, 42.05; H, 2.66; N, 22.09; S, 10.08; F, 18.13.

Continuing the chromatography a further 1.2 g (31%) crop of **5** (R^1 = methyl) was obtained, mp 179-181°, increasing the total yield of **5** (R^1 = methyl) to 48%.

Ethyl {4,5-Dihydro-5-methyl-2-methylthio-8-trifluoromethyl-6*H*-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepine-5-yl}acetate (**6**, R^1 = C_2H_5) and 4,5-Dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3).

A solution of 2.89 g (0.01 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] in 25 ml of ethyl acetoacetate (**4**, R^1 = C_2H_5, R^2 = R^3 = H) was refluxed for 5 hours. The solution obtained was evaporated *in vacuo* to dryness and the residue was recrystallised from isopropanol to yield 0.75 g (19%) of ethyl {4,5-dihydro-5-methyl-2-methylthio-8-trifluoromethyl-6*H*-1,2,4-triazolo-[1,5-*a*]-1,3,5-benzotriazepine-5-yl}acetate (**6**, R^1 = C_2H_5), mp 170-171°; ir: ν CO = 1738 cm^{-1}, ν NH = 3350 and 3250 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.10 (t, 3H, CH_2CH_3), 1.61 (s, 3H, CCH_3), 2.54 (s, 5H, SCH_3 + CCH_2), 3.97 (qa, 2H, OCH_2), 6.7 (b s, 1H, NH), 7.30 (d, 1H, ArH^9), 7.4 (b s, 1H, NH), 8.05 (d, 1H, ArH^{10}), 8.50 (s, 1H, ArH^7); cmr (DMSO-d_6): δ, ppm 13.3 (SCH_3), 13.6 (CH_2CH_3), 26.9 (CCH_3), 44.7 (CCH_2), 60.0 (OCH_2), 67.4 (C^5), 117.4 (C^9), 118.1 (C^7), 120.6 (C^{10}), 123.9 (CF_3), 125.5 (C^8), 131.2 (C^{10a}), 135.4 (C^{6a}), 153.9 (C^{3a}), 159.7 (C^2), 168.8 (CO), uv (ethanol): λ max nm (ε.10^{-3}) 210 (22.5), 232 (19.2), 276 (5.5), 305 (7.0); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 214 (32.9), 274 (6.2), 288 (6.4); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 230 (15.2), 300 (3.7).

Anal. Calcd. for $C_{16}H_{16}F_3N_5O_2S$ (MW. 405.40): C, 46.50; H, 4.16; N, 18.08; S, 8.28; F, 14.71. Found: C, 46.32; H, 4.20; N, 18.14; S, 8.35; F, 14.56.

The mother liquor of **6** (R^1 = ethyl) was evaporated to dryness and the residue chromatographed on a silica-gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to yield 0.30 g (10%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), mp 284-285° (acetonitrile).

Continuing the chromatography further 1.0 g (25%) crop of **6** (R^1 = ethyl) was obtained, mp 169-170°, increasing the total yield of **6** (R^1 = ethyl) to 44%.

Ethyl[1-[2-(1-Ethoxycarbonylprop-1-en-2-ylamino)phenyl]-3-methylthio-1*H*-1,2,4-triazole-5-yl]-3-methyl-3-aminoacrylate (**8**).

A mixture of 0.88 g (0.004 mole) of 5-amino-1-(2-aminophenyl)-3-methylthio-1*H*-1,2,4-triazole (**1a**, R = H) [3] and 10 ml of ethyl acetoacetate (**4**, $R^1 = C_2H_5$, $R^2 = R^3 = H$) was refluxed for 10 hours. After cooling the solution obtained was evaporated *in vacuo* to dryness and the residue was recrystallised from 2-propanol to yield 0.65 g (36%) of the title product, mp 112-114°; ir: ν CO 1665 and 1660 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.12 (t, 3H, CH_2CH_3), 1.18 (t, 3H, CH_2CH_3''), 1.96 (s, 3H, CCH_3), 2.32 (s, 3H, CCH_3''), 2.58 (s, 3H, SCH_3), 3.99 (qa, 2H, OCH_2), 4.00 (qa, 2H, OCH_2''), 4.71 (s, 1H, CH), 4.95 (s, 1H, CH''), 7.45 (dd, 2H, $PhC^{4,5}$), 7.63 (d, 2H, $PhC^{3,6}$), 10.2 (s, 1H, NH), 10.8 (s, 1H, NH''); cmr (DMSO-d_6): δ ppm 13.4 (SCH_3), 14.0 (CH_2CH_3), 14.3 (CH_2CH_3''), 19.5 (CCH_3), 20.6 (CCH_3''), 58.3 (OCH_2), 59.1 (OCH_2''), 87.9 (C=*C*H), 91.9 (C=*C*H''), 125.9 and 126.3 (Ph-$C^{3,6}$), 128.4 and 128.5 (Ph-$C^{4,5}$), 131.0 (Ph-C^2, 135.7 (Ph-C^1), 152.7 (150.0) (triazole C^5), 155.2 (CH=*C*), 157.9 (CH=*C''*), 159.7 (triazole C^3), 168.9 and 169.0 (CO and CO''); uv (ethanol): λ max nm (ε.10^{-3}) 262 sh (17.0), 294 (30.2); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 267 (13.6), 306 (7.5); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 224 sh (13.2), 282 (1.4).

Anal. Calcd. for $C_{21}H_{27}N_5O_4S$ (MW. 445.53): C, 56.61; H, 6.11; N, 15.72; S, 7.20. Found: C, 56.45; H, 6.10; N, 15.83; S, 7.22.

The mother liquor was evaporated *in vacuo* to dryness and the residue was chromatographed on a silica gel column [eluent a 1:2 mixture of benzene and ethyl acetate] to yield 0.28 g (28%) of 4,5-dihydro-2-methylthio-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = H) which after recrystallisation from ethanol melted at 300-302° ir: ν C=O = 1730 cm^{-1}; pmr (DMSO-d_6): δ ppm 2.56 (s, 3H, SCH_3), 7.2-7.4 (m, 4H, ArH), 9.6 (b s, 1H, NH), 10.6 (b s, 1H, NH); ms: M^+ = 247 (100%).

Anal. Calcd. for $C_{10}H_9N_5OS$ (MW. 247.28): C, 48.57; H, 3.67; N, 28.32; S, 12.97. Found: C, 48.46; H, 3.73; N, 28.21; S, 13.07.

Reaction of 5-Amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) with Ethyl 2-Oxocyclopentanecarboxylate [**4**, $R^1 = C_2H_5$, $R^2 + R^3 = (CH_2)_2$].

A mixture of 0.29 g (0.001 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] and 0.5 ml of ethyl 2-oxocyclopentanecarboxylate (**4**, $R^1 = C_2H_5$, $R^2 + R^3 = (CH_2)_2$) was refluxed for 4 hours. The solution obtained was evaported *in vacuo* to dryness and the residue was chromatographed on a silica gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to yield 0.15 g (48%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), mp 284-285° (acetonitrile).

Reaction of 5-Amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) with Ethyl 2-Oxocyclohexanecarboxylate (**4**, $R^1 = C_2H_5$, $R^2 + R^3 = (CH_2)_3$).

A mixture of 2.89 g (0.01 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] and 5 ml of ethyl 2-oxocyclohexanecarboxylate was refluxed with stirring for 150 minutes. The solution thus obtained contained according to gc besides the starting materials ethanol, cyclohexanone, **14** and **7** (R = CF_3), (gc conditions for proving the presence of ethanol and cyclohexanone: Column OV-1, Carrier Hydrogen, Flow rate 40 ml/minute. Temperature program: 100°/2 minutes; raise by 20°/minute to 150°; 150°/1 minute; raise by 10°/minute to 170°; 170°/1 minute; raise by 40°/minute to 245°; Detector FID, Retention times: ethanol, 1.2 minutes, cyclohexanone, 3.0 minutes, ethyl 2-oxocyclohexanecarboxylate, 8.1 minutes). The solution thus obtained crystallised upon cooling to yield 1.5 g (36%) of 5-amino-3-methylthio-1-[2-(2-oxocyclohexanecarboxamido)-4-trifluoromethylphenyl]-1*H*-1,2,4-triazole (**14**), which after recrystallisation from 2-propanol melted at 189-190°. The product exists according to nmr in dimethylsulfoxide solution as a mixture of **14a** and **14b**, keto and enol forms, respectively; ir: ν CO (keto) = 1655 cm^{-1}, ν CO (amide) = 1630 cm^{-1}, ν C=N = 1597 and 1558 cm^{-1}, ν NH_2 = 3390 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.65 (m, $CH_2^{4,5''}$, **14a**, **14b**), 2.20 (m, $CH_2^{6''}$, **14a**), 2.34 (t, $CH_2^{3''}$, **14a**), 2.46 (t, $CH_2^{3''}$, **14b**), 2.50 (t, $CH_2^{6''}$, **14b**), 2.50 and 2.51 (s, SCH_3, **14a** and **14b**), 3.65 (m, CH'', **14a**), 6.6 and 6.8 (b s, NH_2, **14a** and **14b**), 7.56 (d, CH^5, **14a** and **14b**), 7.62 (d, $CH^{6'}$, **14b**), 7.66 (d, $CH^{6'}$, **14a**), 8.56 (s, $CH^{3'}$, **14b**), 8.62 (s, $CH^{3'}$, **14a**), 9.6 (s, OH...O, **14b**); cmr (DMSO-d_6): δ, ppm 13.2 (SCH_3, **14a** and **14b**), 22.0* ($C^{5''}$, **14b**), 22.3* ($C^{4''}$, **14b**), 23.0* ($C^{4''}$, **14a**), 26.4 ($C^{5''}$, **14a**), 29.1* ($C^{6''}$, **14a**), 29.6* ($C^{6''}$, **14b**), 41.3* ($C^{3''}$, **14a**), 41.4* ($C^{3''}$, **14b**), 57.3 ($C^{1''}$, **14a**), 98.2 ($C^{1''}$, **14b**), 118.6 ($C^{5'}$, **14b**), 118.8 ($C^{5'}$, **14a**), 119.2* ($C^{3'}$, **14b**), 119.4* ($C^{3'}$, **14a**), 120.8* ($C^{6'}$, **14b**), 120.9* ($C^{6'}$, **14a**), 124.2 (CF_3, **14a**, **14b**), 126.1 ($C^{4'}$, **14b**), 127.4 ($C^{4'}$, **14a**), 130.0 ($C^{1'}$, **14b**), 130.1 ($C^{1'}$, **14a**), 133.4* ($C^{2'}$, **14b**), 134.2* ($C^{2'}$, **14a**), 156.5 (C^5, **14a**, **14b**), 159.8* (C^3, **14a**), 160.4* (C^3, **14b**), 168.5* ($C^{2''}$, **14b**), 170.0* (CO, **14b**), 171.0* (CO, **14a**), 207.3 ($CO^{2''}$, **14a**) (* could be interchanged); uv (ethanol): λ max nm (ε.10^{-3}) 208 (24.3), 244 sh (12.1), 278 (14.7); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 246 (15.4), 325 (17.0); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 206 (26.0), 232 (15.1), 270 sh (4.8).

Anal. Calcd. for $C_{17}H_{16}F_3N_5SO_2$ (MW. 413.42) C, 49.39; H, 4.39; N, 16.94; S, 7.76; F, 13.79. Found: C, 49.64; H, 4.44; N, 17.10; S, 8.01; F, 13.60.

The mother liquor of **14** was evaporated to dryness and the residue chromatographed on a silica gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to yield 1.30 g (41%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), mp 283-285° (acetonitrile).

Reaction of 5-Amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) with Methyl 4-Oxotetrahydrothiophene-3-carboxylate (**4**, $R^1 = CH_3$, $R^2 + R^3 = (CH_2)_2$).

A mixture of 2.89 g (0.01 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] and 3.5 g (0.02 mole) of methyl 4-oxotetrahydrothiophene-3-carboxylate (**4**, $R^1 = CH_3$, $R^2 + R^3 = SCH_2$) [5] was refluxed with stirring for 180 minutes. To the still hot melt 5 ml of acetonitrile was added and let to crystallise. After cooling the crystals precipitated were filtered off and recrystallised from acetonitrile to yield 0.5 g (16%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), mp 285-286°. The combined mother liquors were evaporated to dryness and chromatographed on a silica gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to obtain a further 2.1 g (63%) crop of **7** (R = CF_3) to increase the total yield of **7** (R = CF_3) to 79%.

Reaction of 5-Amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) with Methyl 1-Benzyl-4-oxopiperidine-3-carboxylate [**4**, $R^1 = CH_3$, $R^2 + R^3 = CH_2N(CH_2Ph)CH_2$].

A mixture of 0.29 g (0.001 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] and 0.49 g (0.002 mole) of methyl 1-benzyl-4-oxopiperidine-3-carboxylate [**4**, $R^1 = CH_3$, $R^2 + R^3 = CH_2N(CH_2Ph)CH_2$] (prepared from the corresponding hydrochloride [6] by partitioning it between 10 *N* cold sodium hydroxyde solution and chloroform, separating the layers, drying the organic one and evaporating *in vacuo* to dryness) was refluxed with stirring for 3 hours. The residue was chromatographed on a silica gel column (eluent a 1:2 mixture of benzene and ethyl acetate) to obtain 0.17 g (54%) of 4,5-dihydro-2-methylthio-8-trifluoromethyl-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(6*H*)-one (**7**, R = CF_3), which after recrystallisation from acetonitrile melted at 285-286°.

4-Methyl-2-methylthio-4a,5,6,7-tetrahydropyrrolo[2,1-*d*]-1,2,4-triazolo-[1,5-*a*]-1,3,5-benzotriazepin-7(4*H*)-one (**17a**, R = H).

The mixture of 0.88 g (0.004 mole) of 5-amino-1-(2-aminophenyl)-3-methylthio-1*H*-1,2,4-triazole (**1a**, R = H) [3] and 5 ml of ethyl 4-oxopentanecarboxylate (**15**, R^1 = ethyl) was refluxed with stirring for 7 hours. The solution crystallised upon cooling. The crystals were filtered off and recrystallized from dimethylformamide to yield 0.6 g (50%) of 4-methyl-2-methylthio-4a,5,6,7-tetrahydropyrrolo[2,1-*d*]-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-7(4*H*)-one (**17a**, R = H), mp 254-255°; ir: ν CO = 1710 cm^{-1}, ν C=N = 1620 and 1590 cm^{-1}; 1.31 (s, 3H, CCH_3), 2.21 (t, 2H,

CH_2^6), 2.51 (m, 2H, CH_2^5), 2.54 (s, 3H, SCH_3), 7.34 (d, 1H, ArH^9), 7.48 (dd, 2H, $ArH^{10,11}$), 8.01 (d, 1H, ArH^{12}), 8.7 (b s, 1H, NH); cmr (DMSO-d_6): δ ppm 13.3 (SCH_3), 26.8 (CCH_3), 29.1 (CH_2^6), 33.1 (CH_2^5), 73.9 (C^{4a}), 120.6 (C^{12}), 124.8* (C^{11}), 125.6* (C^9), 128.2 (C^{10}), 129.1 (C^{8a}), 133.8 (C^{12a}), 153.7 (C^{3a}), 159.6 (C^2), 173.8 (C=O); uv (ethanol): λ max nm (ε.10^{-3}) 230 (20.8), 278 (10.7); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 229 sh (18.6), 274 (9.1); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 224 sh (19.3), 268 (9.5).

Anal. Calcd. for $C_{14}H_{15}N_5OS$ (MW. 301.37): C, 55.79; H, 5.02; N, 23.24; S. 10.64. Found: C, 55.66, H, 4.98; N,, 23.16; S, 10.71.

4-Methyl-2-methylthio-4a,5,6,7-tetrahydro-10-trifluoromethylpyrrolo-[2,1-*d*]-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-7(4*H*)-one (**17b**, R = CF_3) and 7a-Methyl-2-methylthio-5,6,7,7a-tetrahydro-10-trifluoromethylpyrrolo[1,2-*c*]-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(8*H*)-one (**18b**, R = CF_3).

The mixture of 2.89 g (0.01 mole) of 5-amino-1-(2-amino-4-trifluoromethylphenyl)-3-methylthio-1*H*-1,2,4-triazole (**1b**, R = CF_3) [3] and 7.2 g (0.05 mole) of ethyl 4-oxopentanecarboxylate (**15**, R^1 = ethyl) was refluxed with stirring for 7 hours. The solution obtained was evaporated *in vacuo* to dryness and the residue recrystallized first from ethanol, then twice from 2-propanol to yield 0.6 g (16%) of 4a-methyl-2-methylthio-4a,5,6,7-tetrahydro-10-trifluoromethylpyrrolo[2,1-*d*]-1,2,4-triazolo-[1,5-*a*]-1,3,5-benzotriazepin-7(4*H*)-one (**17b**, R = CF_3), mp 235-237°; ir: ν CO = 1711 cm^{-1}, ν NH = 3410 cm^{-1}, ν C=N = 1614 and 1528 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.34 (s, 3H, CCH_3), 2.22 (t, 2H, CH_2^6), 2.47 (t, 1H, CH_2^5 shielded H), 2.56 (s, 3H, SCH_3), 2.66 (t, 1H, CH_2^5, not shielded H), 7.75 (d, 1H, ArH^{11}), 7.82 (s, 1H, ArH^9), 8.23 (d, 1H, ArH^{12}), 9.0 (b s, 1H, NH); cmr (DMSO-d_6): δ ppm 13.2 (SCH_3), 26.5 (CCH_3), 29.0 (CH_2^6), 32.9 (CH_2^5), 73.5 (C^{4a}), 121.7 (C^{11} and C^{12}), 124.1 (CF_3), 124.9* (C^9), 125.1* (C^{10}), 126.1 (C^{8a}), 136.7 (C^{12a}), 154.4 (C^{3a}), 160.8 (C^2), 173.8 (C=O); uv (ethanol): λ max nm (ε.10^{-3}) 210 (24.0), 241 (18.3), 292 (10.2); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 234 sh (18.0), 290 (7.0); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 208 (22.4), 230 sh (17.2), 280 (9.0).

Anal. Calcd. for $C_{15}H_{14}F_3N_5OS$ (369.37): C, 48.77, H, 3.82; N, 18.96; F, 15.43. Found: C, 48.64; H, 3.98; N, 18.99; F, 15.34.

The combined mother liquors were evaporated *in vacuo* to dryness and the residue chromatographed on a silica gel column [eluent a 1:2 mixture of benzene and ethyl acetate] to yield 1.05 g (28%) of the isomeric 7a-methyl-2-methylthio-5,6,7,7a-tetrahydro-10-trifluoromethylpyrrolo-[1,2-*c*]-1,2,4-triazolo[1,5-*a*]-1,3,5-benzotriazepin-5(8*H*)-one (**18b**, R = CF_3) which, after recrystallization from 2-propanol melted at 250-252°; R_f = 0.45 (benzene:ethyl acetate 1:2), ir: ν CO = 1725 cm^{-1}, ν C=N = 1620, 1540 and 1500 cm^{-1}, ν NH = 3320 cm^{-1}; pmr (DMSO-d_6): δ ppm 1.43 (s, 3*H*, CCH_3), 2.39 (t, 2H, CH_2^6), 2.55 (m, 1H, CH_2^7 shielded H), 2.66 (s, 3H, SCH_3), 2.67 (t, 1H, CH_2^7 not shielded H), 7.31 (dd, 1H, ArH^{11}), 7.41 (s, 1H, ArH^9), 8.24 (d, 1H, ArH^{12}); cmr (DMSO-d_6): δ ppm 13.3 (SCH_3), 25.3 (CCH_3), 29.4 (C^6), 33.0 (C^7), 74.9 (C^{7a}), 117.4 (C^{11}), 121.5 (C^9), 122.7 (C^{12}), 124.1 (CF_3), 126.7 (C^{10}), 128.1 (C^{12a}), 135.8 (C^{8a}), 145.8 (C^{3a}), 160.9 (C^2), 171.8 (C=O), uv (ethanol): λ max nm (ε.10^{-3}) 220 (43.0), 326 (10.8); uv (10% ethanol + 90% 0.1 *N* sodium hydroxyde): λ max nm (ε.10^{-3}) 230 (26.4), 304 (10.6); uv (10% ethanol + 90% 0.1 *N* hydrochloric acid): λ max nm (ε.10^{-3}) 220 (33.1), 316 (7.6).

Anal. Calcd. for $C_{15}H_{14}F_3N_5OS$ (369.37): C, 48.77; H, 3.82; N, 18.96; F, 15.43. Found: C, 48.67; H, 3.78; N, 19.00; F, 15.38.

Continuing the chromatography a further 1.3 g (35%) crop of **17b** (R = CF_3), R_f = 0.32 (benzene:ethyl acetate 1:2) was obtained, increasing its total yield to 51%.

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