On Triazoles. XL [1]. Non Catalytic Dehalogenation of Some 5-Chloro-1,2,4-triazolo[1,5-*a*]pyrimidine Derivatives

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A non catalytic dehalogenation method of type **4** 5-chloro-1,2,4-triazolo[1,5-*a*]pyrimidine derivatives based on the hydrolysis of the corresponding type **5** *p*-toluenesulphonyl hydrazones with diluted aqueous sodium carbonate solution was elaborated. The method provides the required 5-unsubstituted derivatives **6** also in those cases when the simple hydrogenation is not possible. Using deuterium oxide as the solvent of the hydrolysis, deuterium atoms also could be inserted into position 5 of derivatives **6**. Different by-products of the reactions were also isolated, and a possible explanation was given for their formation.

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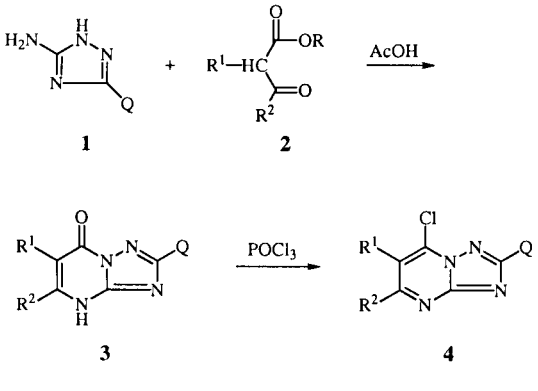
In previous papers of this series, we have reported the cyclisation of different 5-amino-1,2,4-triazoles **1** with aliphatic [2-3], homocyclic [4-6] and heterocyclic [6-9] β-ketoesters **2** to yield 1,2,4-triazolo[1,5-*a*]pyrimidin-5-ones **3**. As a continuation of the above work some bicyclic and tricyclic type **3** lactams were converted to the corresponding 5-chloro derivatives **4**, respectively [1] (Scheme 1). The reactive 5-chloro atoms of derivatives **4** could be converted with different amines and thiols to 5-alkyl- or dialkylamino, and 5-alkylthio-1,2,4-triazolo[1,5-*a*]pyrimidines, respectively, possessing strong cardiovascular activity [10].

Scheme 1

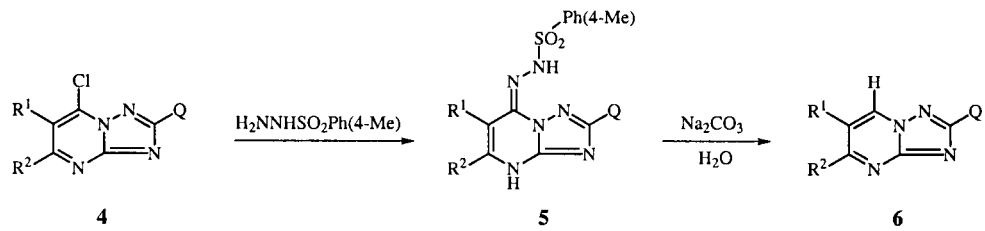


During the above work our interest turned to the 5-unsubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines **6** (Scheme 2). However, simple hydrogenation of derivatives **4f, 4g, 4j** and **4k** could not be performed as a consequence of the presence of benzyl groups. In the case of derivative **4b** the allyl groups was the problem while in the case of derivatives **4a, 4e, 4i, 4j** and **4k** the poisoning of the catalysts by the sulphur atoms present in the molecules may pose a problem.

Thus chlorides **4** were converted with *p*-toluenesulphonylhydrazide to the corresponding 5-(*p*-toluenesulphonylhydrazo) derivatives **5** that could be easily hydrolysed with aqueous sodium carbonate by a known method [11] to the 5-unsubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines **6** making possible the study of their spectral and biological properties (Scheme 2).

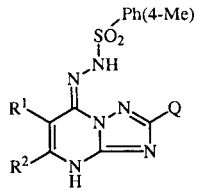
Derivatives **5** can exist also in the **5*** tautomeric form (Scheme 3). However, the close analogy between the cmr signals of derivatives **5** taken in dimethyl-d_6 sulfoxide solution with those of lactams **3**, respectively, as well as their difference from the corresponding aromatic derivatives **4** and **6**, respectively, (Scheme 4) seems to support at least in dimethyl-d_6 sulfoxide solution the tautomeric form **5**.

Scheme 2



a: Q = methylthio, R^1 = H, R^2 = methyl
b: Q = diallyamino, $R^1 + R^2$ = -$(CH_2)_3$-
c: Q = morpholino, $R^1 + R^2$ = -$(CH_2)_3$-
d: Q = H, $R^1 + R^2$ = -$(CH_2)_4$-
e: Q = methylthio, $R^1 + R^2$ = -$(CH_2)_4$-
f: Q = benzylamino, $R^1 + R^2$ = -$(CH_2)_4$-
g: Q = *N*-benzyl-*N*-methylamino, $R^1 + R^2$ = -$(CH_2)_4$-
h: Q = morpholino, $R^1 + R^2$ = -$(CH_2)_4$-
i: Q = methylthio, $R^1 + R^2$ = -S-$(CH_2)_3$-
j: Q = methylthio, $R^1 + R^2$ = -CH_2-N(Bn)-$(CH_2)_2$-
k: Q = methylthio, $R^1 + R^2$ = -$(CH_2)_2$-N(Bn)-CH_2-

Scheme 3



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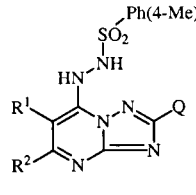
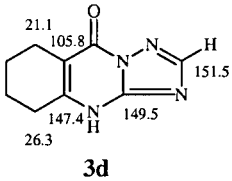
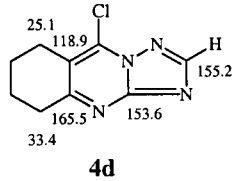


5*

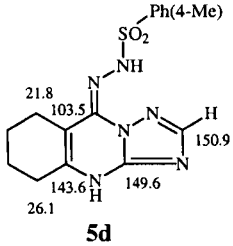
Scheme 4



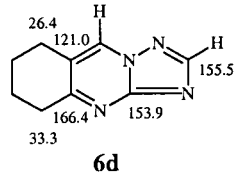
3d



4d



5d



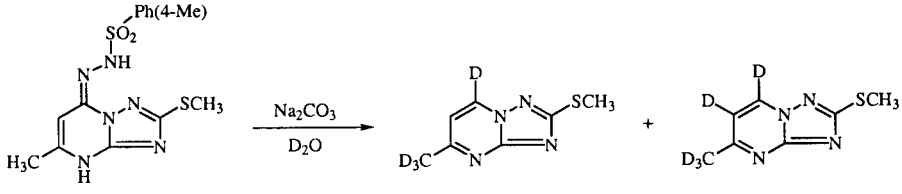
6d

It should be mentioned that the hydrolysis of derivatives **5** with aqueous sodium carbonate, analogous to previous observations [11] proceeded with much better yields in diluted solutions.

Using deuterium oxide as the solvent of the hydrolysis of derivatives **5** made it possible to insert a deuterium atom into position 5 of derivatives **6**. However, during these reactions some other active hydrogens were also deuterated to yield in the case of **5a** a 1:1 mixture of **7a** and **8a** (Scheme 5), in case of **5c** a 1:1 mixture of **9c** and **10c** (Scheme 6), and in case of **5d** and **5e** trideuterated products **11d** and **11e**, respectively (Scheme 7). The deuteration in position 8 of the cyclopenta derivative (see **10c**) and those of 9 of the cyclohexa derivatives (see **11d** and **11e**), respectively, is in agreement with the formation of types **12** and **13** by-products during the synthesis of compounds **4** from lactams **3** (Scheme 8) [12].

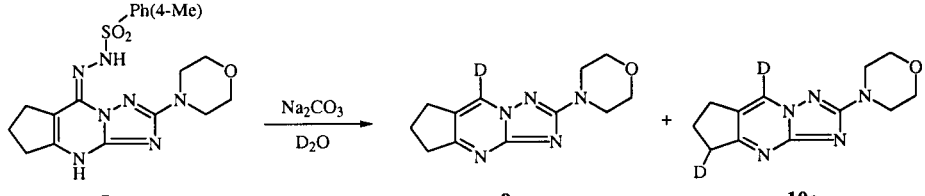
Interestingly, during the reaction of derivatives **4g** and **4k** with *p*-toluenesulphonylhydrazide besides the expected tosylhydrazo derivatives **5g** and **5k** (Scheme 9) the corresponding dimers **14g** and **14k** were also isolated. Their formation can be explained by nucleophilic attack of the strongly basic NH nitrogen atoms on carbon atom 5 of another molecule **4** to yield the corresponding derivatives **14** and *p*-toluenesulphonyl chloride (**15**) that could be isolated from the reaction mixture of **5g**. In case of **5k**, most probably as a consequence of the high temperature used,

Scheme 5



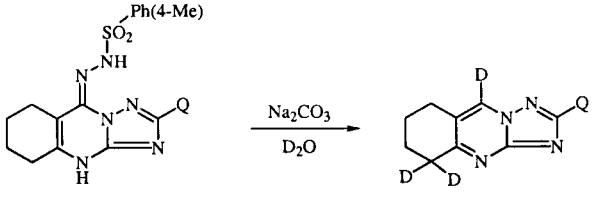
5a **7a** **8a**

Scheme 6



5c **9c** **10c**

Scheme 7

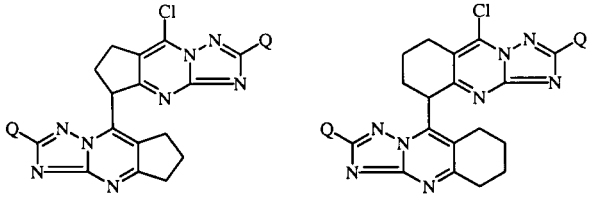


5d Q = H **11d**
5e Q = SCH_3 **11e**

p-toluenesulphonyl chloride once formed reacted with *p*-toluenesulphonylhydrazide starting material to yield di(*p*-toluenesulphonyl)hydrazide that decomposed by a known reaction [13] to **16** isolated from the reaction mixture.

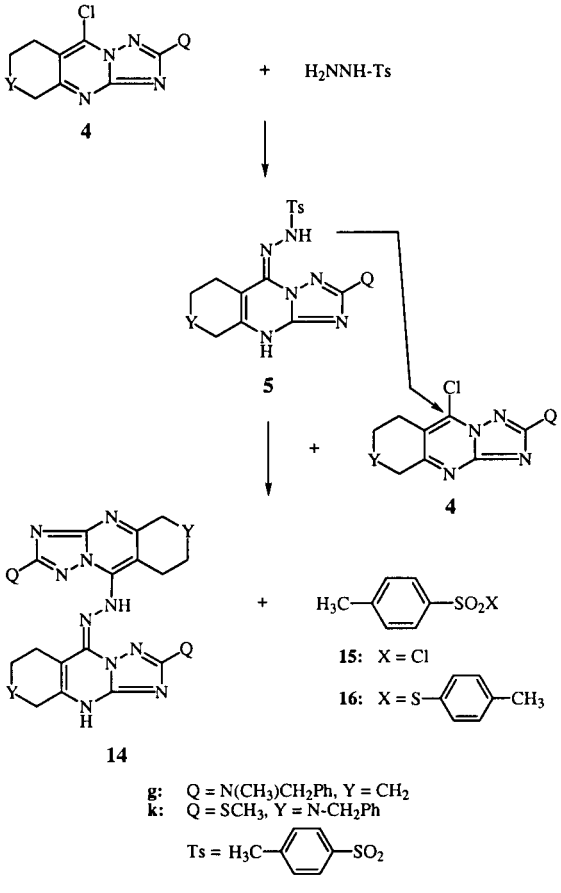
In the course of the hydrolysis of derivative **5i** with concentrated aqueous sodium carbonate solution a 5-amino derivative **17** (Scheme 10) was also formed as a by-product. This is in agreement with a previous experiment [11] in the

Scheme 8



12 13

Scheme 9



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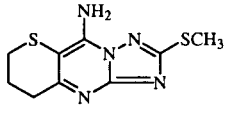
g: Q = N(CH$_3$)CH$_2$Ph, Y = CH$_2$
k: Q = SCH$_3$, Y = N-CH$_2$Ph

Ts = H$_3$C-C$_6$H$_4$-SO$_2$

Scheme 10



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presence of a 0.5 *N* sodium hydroxide solution at 120° where a small amount of a 5-aminoacridine derivative was also formed during the hydrolysis of the corresponding 5-(*p*-toluenesulphonylhydrazone).

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 a Perkin-Elmer 577 spectrophotometer. The pmr and cmr measurements were performed using Bruker WM-250 and Varian VXR-400 instruments. Standard Varian HSQC and HMBC programs were used. The mass spectra were observed with a KRATOS MS 25 RFA double focusing instrument in EI and CI modes. The dry-column flash chromatography was performed according to [14]. As adsorbents aluminium oxide G (Merck 1090 for thin layer chromatography) and Kieselgel 60H (Merck 7736 for thin layer chromatography) were employed.

N'-{7-Methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5a**).

To a solution of 10.34 g (0.0555 mole) of *p*-toluenesulphonylhydrazide in 250 ml of dichloromethane 11.92 g (0.0555 mole) of 5-chloro-7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidine (**4a**) [1,15] was added at room temperature. The solution obtained was allowed to stand at room temperature for 4 days. The crystals that precipitated were filtered and washed twice with 25 ml portions of dichloromethane to yield 20.03 g (90%) of crude *N'*-{7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5a•HCl**), mp 238-244° dec. To a suspension of 1.00 g (0.0025 mole) of the above crude hydrochloride salt in 20 ml of chloroform, 1.4 ml (1.01 g, 0.01 mole) of triethylamine was added with stirring. After 15 minutes the crystals were filtered and washed with 2 x 3 ml of chloroform to yield 0.31 g of pure *N'*-{7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5a**), mp 234-237° dec. The mother liquor was washed with 2 x 10 ml of water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue was triturated with 10 ml of acetonitrile and filtered to yield an additional amount (0.31 g) of the above product increasing the yield of pure product to 68%; ir: ν C=N = 1627 and 1596 cm^{-1}, ν SO_2N = 1353 and 1171 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 2.37 (s, 3H, CH_3), 2.40 (s, 3H, $PhCH_3$), 2.61 (s, 3H, SCH_3), 6.30 (s, 1H, CH-6), 7.41 [d (J = 8.2 Hz), 2H, PhH-3',5'], 7.72 [d (J = 8.2 Hz), 2H, PhH-2',6'], 10.4 (bs, 2H, NH-8 and NH-Ts).

Anal. Calcd. for $C_{14}H_{16}N_6O_2S_2$ (MW 364.45): C, 46.14; H, 4.43; N, 23.06; S, 17.60. Found: C, 46.25; H, 4.56; N, 22.95; S, 17.80.

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

To a solution of 5.30 g (0.05 mole) of sodium carbonate in 150 ml of water 2.00 g (1.80 g, 0.0045 mole) of crude *N'*-{7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5a•HCl**) was added and the mixture refluxed with stirring for 2 hours. After cooling the reaction mixture obtained it was extracted with 3 x 20 ml of chloroform, the collected organic phases were dried over anhydrous sodium sulphate, and evaporated to dryness *in vacuo*. The residue (0.69 g) was dry-column flash chromatographed on 9 g of aluminium oxide G, eluent ethyl acetate, then acetonitirile. The residue obtained after evaporation of the appropriate fractions to dryness *in vacuo* was triturated with 5 ml of ether and filtered to yield 0.54 g (67%) of 7-methyl-2-methylthio-1,2,4-triazolo-[1,5-*a*]pyrimidine (**6a**), mp 128-129.5°. Evaporation of the mother liquor yielded an additional amount of product (0.12 g)

increasing the total yield to 82%; ir: ν C=N = 1622 and 1532 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.687 (s, 3H, CH_3), 2.707 (s, 3H, SCH_3), 6.89 [d (J = 6.8 Hz), 1H, H-6], 8.55 [d (J = 6.8 Hz), 1H, H-5); cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 25.0 (CH_3-7), 110.1 (C-6), 133.7 (C-5), 155.6 (C-8a), 165.1 (C-7), 169.2 (C-2); ms: (EI) M^+ = 180.

Anal. Calcd. for $C_7H_8N_4S$ (MW 180.23): C, 46.65; H, 4.47; N, 31.09, S, 17.79. Found: C, 46.70; H, 4.63; N, 30.98, S, 17.65.

5-Deuterio-2-methylthio-7-trideuteriomethyl-1,2,4-triazolo[1,5-*a*]-pyrimidine (**7a**) and 5,6-Dideuterio-2-methylthio-7-trideuteriomethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**8a**).

To a solution of 5.30 g (0.05 mole) of sodium carbonate in 25 ml of deuterated water 2.00 g (~ 1.80 g, 0.0045 mole) of crude *N'*-{7-methyl-2-methylthio-1,2,4-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5a•HCl**) was added and the mixture refluxed with stirring for 2 hours. After cooling the reaction mixture it was extracted with 3 x 20 ml of chloroform, the collected organic phases were dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo*. The residue was dry-column flash chromatographed on 9 g of aluminium oxide G, eluent ethyl acetate, then acetonitirile. The residue obtained after evaporating the appropriate fractions *in vacuo* to dryness was triturated with 5 ml of ether and filtered to yield 0.48 g (59%) of a 1:1 mixture of 5-deuterio-2-methylthio-7-trideuteriomethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**7a**) and 5,6-dideuterio-2-methylthio-7-trideuteriomethyl-1,2,4-triazolo[1,5-*a*]pyrimidine (**8a**), mp 128.5-129.5°. Evaporation of the mother liquor yielded an additonal amount (0.09 g) of the above material increasing the total yield of the reaction to 70%; ir: ν C-D = 2299 and 2270 cm^{-1}; ν C=N = 1606 and 1505 cm^{-1}; **7a**: pmr (deuteriochloroform): δ, ppm 2.705 (s, 3H, SCH_3), 6.90 (s, 1/2 H, H-6); cmr (deuteriochloroform): δ, ppm 13.7 (SCH_3), ~24.0 (m, CD_3), 110.0 (C-6), 133.4 [t ($J_{C,D}$ = 28.5 Hz), C-5], 155.6 (C-8a), 165.0 (C-7), 169.1 (C-2); **8a**: pmr (deuteriochloroform): δ, ppm 2.705 (s, 3H, SCH_3); cmr (deuteriochloroform): δ, ppm 13.7 (SCH_3), ~24.0 (m, CD_3), 110.0 (m, C-6), 133.4 [t ($J_{C,D}$ = 28.5 Hz), C-5], 155.6 (C-8a), 165.0 (C-7), 169.1 (C-2); ms: (EI) M^+ = 184 and 185 (corresponding to **7a** and **8a**, respectively).

2-Diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**3b**).

To a suspension of 17.92 g (0.1 mole) of 3-diallylamino-5-amino-1*H*-1,2,4-triazole (**1b**) [16] in 30 ml of acetic acid, 17.36 g (≅ 15.62 g ≈ 0.1 mole) of ethyl 2-oxocyclopentanecarboxylate (Fluka, purity 90%) was added and the mixture refluxed with stirring for 2 hours. At 100° the reaction mixture became homogeneous and after a few minutes the product began to crystallise while hot. After cooling the crystals were filtered and washed with acetic acid and acetone to yield 16.0 g (59%) of 2-diallylamino-6,7-dihydro-8*H*-cyclopenta-[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**3b**) mp 250-252° dec. To the mother liquor 90 ml of water was added, and the crystals that precipitated were filtered to yield an additonal amount (5.62 g, 21%) of the above material, mp 247-249°, increasing the yield of the reaction to 80%; ir: ν C=O = 1655 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.14 [quint (J = 7.5 Hz), 2H, CH_2-7], 2.80 [t (J = 7.5 Hz), 2H, CH_2-6], 2.92 [t (J = 7.5 Hz), 2H, CH_2-8], 3.99 [d (J = 5.5 Hz), 4H, NCH_2], 5.0-5.2 (m, 4H, C=CH_2), 5.6-5.8 (m, 2H, CH); cmr (deuteriochloroform): δ, ppm 22.1 (C-7), 27.2 (C-6), 31.7 (C-8), 49.8 (NCH_2), 111.3 (C-5a), 116.9 (C=CH_2), 133.4 (CH), 150.4 (C-9a), 152.9 (C-8a), 155.2 (C-5), 164.0 (C-2).

Anal. Calcd. for $C_{14}H_{17}N_5O$ (MW 271.32): C, 61.98; H, 6.32; N, 25.81. Found: C, 61.83; H, 6.52; N, 25.66.

5-Chloro-2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4b**).

To a stirred suspension of 8.14 g (0.03 mole) of 2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(9*H*)-one (**3b**) and 14.0 ml (23.0 g, 0.15 mole) of phosphorus oxychloride, 0.475 g (0.006 mole) of pyridine was added. The suspension was stirred at 25° for 4 hours and the solution allowed to stand overnight. The brown solution was decomposed by pouring it into 300 g of cracked ice and stirred for 1 hour. The crystals that precipitated were filtered and washed to neutrality with water, dissolved while wet in 50 ml of chloroform, dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo* to yield 5.8 g of brown oil. The combined aqueous mother liquors were extracted three times with 25 ml portions of chloroform, the combined chloroform layers were washed to neutrality with water, dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo* to yield an additonal 3.0 g of brown oil. The combined brown oils were dry-column flash chromatographed on 30 g of Kieselgel 60 H (eluents: different mixtures of *n*-hexane and chloroform of continuously increasing polarity) to yield after evaporation of the appropriate fractions and triturating the residue with *n*-hexane 8.00 g (92%) of 5-chloro-2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**4b**), mp 58.5-60.5° (lit [15] mp 59-61°); ir: ν C=C = 1615 cm^{-1}, ν C=N = 1578 and 1535 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.23 [quint (J = 7.5 Hz), 2H, CH_2-7], 3.00 [t (J = 7.5 Hz), 2H, CH_2-6], 3.08 [t (J = 7.5 Hz), 2H, CH_2-8], 4.18 [d (J = 6.0 Hz), 4H, NCH_2], 5.15-5.30 (m, 4H, C=CH_2), 5.8-6.0 (m, 2H, CH); cmr (deuteriochloroform): δ, ppm 22.6 (C-7), 27.9 (C-6), 34.8 (C-8), 49.1 (NCH_2), 116.9 (C=CH_2), 120.6 (C-5a), 131.9 (C-5), 133.3 (CH), 156.2 (C-9a), 166.7 (C-2), 170.0 (C-8a).

Anal. Calcd. for $C_{14}H_{16}ClN_5$ (MW 289.77): C, 58.03; H, 5.57; N, 24.17; Cl, 12.23. Found: C, 58.16; H, 5.65; N, 24.23; Cl, 12.08.

N'-{2-Diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5b**).

To a solution of 1.30 g (0.007 mole) of *p*-toluenesulphonylhydrazide in 30 ml of dichloromethane, 2.03 g (0.007 mole) of 5-chloro-2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**4b**) was added at room temperature. The solution was allowed to stand at room temperature for 11 days and then evaporated to dryness *in vacuo*. The residue was triturated with 20 ml of ethyl acetate and a few drops of acetonitrile. After standing at room temperature for 30 minutes the crystals that precipitated were filtered and washed twice with 5 ml of ethyl acetate to yield 3.20 g (96%) of *N'*-{2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluene-sulphonylhydrazone hydrochloride (**5b•HCl**), mp 200° dec; pmr (deuteriochloroform): δ, ppm 2.15 [quint (J = 7.2 Hz), 2H, CH_2-7], 2.41 (s, 3H, CH_3), 3.08 [t (J = 7.2 Hz), 2H, CH_2-6], 3.35 [t (J = 7.2 Hz), 2H, CH_2-8], 4.07 [d (J = 5.2 Hz), 4H, NCH_2], 5.10-5.25 (m, 4H, C=CH_2), 5.7-5.85 (m, 2H, CH), 7.29 [d (J = 8.0 Hz), 2H, PhH-3',5'], 7.82 [d (J = 8.0 Hz), 2H, PhH-2',6'], 8.6 and 10.64 (two bs, 2 x 1H, NH-9 and NH-Ts). To a suspension of 2.80 g (0.0059 mole) of the above hydrochloride in 20 ml of chloroform, 2 ml (1.45 g, 0.0143 mole) of triethylamine was added with stirring at room temperature. After 30 minutes the crystals were filtered and washed three times with 5 ml portions of chloroform to yield 1.81 g (70%) of *N'*-{2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-

triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5b**), mp 250° dec. An additonal amount (0.62 g, 24%) of the above product was obtained from the chloroform containing mother liquors after their evaporation to dryness *in vacuo* and triturating the residue with water increasing the total yield to 94%; ir: ν C=C = 1628 cm^{-1}, ν C=N = 1575 cm^{-1}, ν SO_2N = 1348 and 1167 cm^{-1}; pmr (deuteriochloroform + trifluoroacetic acid): δ, ppm 2.25 [quint (J = 8.0 Hz), 2H, CH_2-7], 2.42 (s, 3H, CH_3), 3.07 [t (J = 8.0 Hz), 2H, CH_2-6], 3.38 [t (J = 8.0 Hz), 2H, CH_2-8], 4.02 [d (J = 5.5 Hz), 4H, NCH_2], 5.15-5.30 (m, 4H, C=CH_2), 5.7-5.85 (m, 2H, CH), 7.33 [d (J = 8.0 Hz), 2H, PhH-3',5'], 7.73 [d (J = 8.0 Hz), 2H, PhH-2',6'], 8.9 and 11.33 (two bs, 1H and 2H, protonated NH-9 and NH-Ts).

Anal. Calcd. for $C_{21}H_{25}N_7O_2S$ (MW 439.54): C, 57.39; H, 5.73; N, 22.31; S, 7.29. Found: C, 57.45; H, 5.87; N, 22.28; S, 7.23.

2-Diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**6b**).

To a solution of 2.54 g (0.024 mole) of sodium carbonate in 100 ml of water, 1.32 g (0.003 mole) of *N'*-{2-diallylamino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5b**) was added and the mixture refluxed with stirring for 2 hours. After cooling the reaction mixture was extracted with 3 x 20 ml of dichloromethane, the collected organic phases were washed with 10 ml of water, dried over anhydrous sodium sulphate and dry-column flash chromatographed on 10 g of aluminium oxide G, using dichloromethane as the eluent. After evaporation of the appropriate fractions to dryness *in vacuo* the residue was triturated with 5 ml of ether and filtered to yield 0.60 g (78%) of 2-diallylamino-6,7-dihydro-8*H*-cyclopenta-[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**6b**), mp 126-129°; ir: ν C=C = 1628 cm^{-1}, ν C=N = 1577, 1535 and 1512 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.21 [quint (J = 7.5 Hz), 2H, CH_2-7], 3.0 (m, 4H, CH_2-6 and 8), 4.16 [d (J = 5.5 Hz), 4H, NCH_2], 5.1-5.3 (m, 4H, C=CH_2), 5.8-6.0 (m, 2H, CH), 8.27 (s, 1H, CH-5); cmr (deuteriochloroform): δ, ppm 23.8 (C-7), 27.7 (C-6), 34.2 (C-8), 49.4 (NCH_2), 116.8 (C=CH_2), 122.2 (C-5a), 128.5 (C-5), 133.8 (CH), 155.6 (C-9a), 167.3 (C-2), 171.7 (C-8a);

Anal. Calcd. for $C_{14}H_{17}N_5$ (MW 255.33): C, 65.86; H, 6.71; N, 27.43. Found: C, 65.74; H, 6.85; N, 27.40.

5-Chloro-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4c**).

Compound **4c** was prepared as reported [1], yield 85%, mp 216-219° (lit [1] mp 218-218.5°, lit [15] mp 213-215°); pmr (deuteriochloroform): δ, ppm 2.26 [quint (J = 8 Hz), 2H, CH_2-7], 3.03 [t (J = 8 Hz), 2H, CH_2-6], 3.11 [t (J = 8 Hz), 2H, CH_2-8], 3.66 [m (J = 5 Hz), 4H, NCH_2], 3.81 [m (J = 5 Hz), 4H, OCH_2]; pmr (dimethyl-d_6 sulfoxide) (in [1] given erroneously as in deuteriochloroform): δ, ppm 2.16 [quint (J = 8 Hz), 2H, CH_2-7], 2.98 [t (J = 8 Hz), 2H, CH_2-6], 3.03 [t (J = 8 Hz), 2H, CH_2-8], 3.50 (t, 4H, NCH_2), 3.70 (t, 4H, OCH_2); cmr (deuteriochloroform): δ, ppm 22.9 (C-7), 28.2 (C-6), 35.2 (C-8), 45.7 (NCH_2), 66.4 (OCH_2), 121.4 (C-5a), 132.5 (C-5), 156.3 (C-9a), 167.3 (C-2), 171.0 (C-8a), assignment confirmed by HSQC and HMBC.

N'-{2-Morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5c**).

To a solution of 1.68 g (0.009 mole) of *p*-toluenesulphonylhydrazide in 30 ml of dichloromethane, 2.52 g (0.009 mole) of 5-chloro-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**4c**) was added at room temperature. The solution was allowed to stand at room temperature for 40 days. The crystals that precipitated were filtered and washed twice with 5 ml of dichloromethane to yield *N'*-{2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5c•HCl**), which during drying at 25° lost hydrochloric acid to yield 3.36 g (87%) of crude *N'*-{2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone base (**5c**), mp 250° dec. To a suspension of 1.69 g of the above crude base in 20 ml of chloroform, 2 ml (1.45 g, 0.0143 mole) of triethylamine was added with stirring at room temperature. After stirring for 1 hour, the crystals were filtered and washed twice with 10 ml portions of chloroform to yield 1.63 g of pure *N'*-{2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5c**), mp 250° dec; ir: ν C=N = 1629 and 1577 cm^{-1}, ν SO_2N = 1351 and 1168 cm^{-1}; pmr (deuteriochloroform + trifluoroacetic acid): δ, ppm 2.26 [quint (J = 7.3 Hz), 2H, CH_2-7], 2.43 (s, 3H, CH_3), 3.09 [t (J = 7.3 Hz), 2H, CH_2-6], 3.37 [t (J = 7.3 Hz), 2H, CH_2-8], 3.55 (m, 4H, NCH_2), 3.78 (m, 4H, OCH_2), 7.32 [d (J = 8.3 Hz), 2H, PhH-3',5'], 7.72 [d (J = 8.3 Hz), 2H, PhH-2',6'], 9.0 and 12.1 (two bs, 1H + 2H, protonated NH-9 and NH-Ts).

Anal. Calcd. for $C_{19}H_{23}N_7O_3S$ (MW 429.50): C, 53.13; H, 5.40; N, 22.83; S, 7.47. Found: C, 52.86; H, 5.60; N, 22.59; S, 7.33.

2-Morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidine (**6c**).

To a solution of 2.97 g (0.028 mole) of sodium carbonate in 100 ml of water 1.31 g (0.003 mole) of *N'*-{2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5c**) was added and the mixture refluxed with stirring at 130° for 4 hours. After cooling the reaction mixture was extracted three times with 25 ml portions of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate and dry-column flash chromatographed on 6 g of Kieselgel 60H (eluent dichloromethane, chloroform, and a 100:1 mixture of chloroform and methanol, respectively). The appropriate fractions were collected and evaporated to dryness to yield 0.65 g (87%) of crystalline 2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**6c**) which after recrystallisation from acetonitrile melted at 222-223°; ir: ν C=N = 1629 and 1566 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.27 [quint (J = 7.3 Hz), 2H, CH_2-7], 2.99 [dt (J = 7 and 1.2 Hz), 2H, CH_2-6], 3.04 [t (J = 7.7 Hz), 2H, CH_2-8], 3.61 (m, 4H, NCH_2), 3.82 (m, 4H, OCH_2), 8.28 [t (^{4}J = 1.2 Hz), 1H, CH-5]; cmr (deuteriochloroform): δ, ppm 23.6 (C-7), 27.5 (C-6), 34.0 (C-8), 45.5 (NCH_2), 66.1 (OCH_2), 122.5 (C-5a), 128.4 (C-5), 155.1 (C-9a), 167.4 (C-2), 172.0 (C-8a); INEPT (7 Hz): irradiated at 8.29 ppm polarisation transfer at 27.5, 122.5, 155.1 and 172.0; irradiated at 2.27 ppm, polarisation transfer at 27.5, 34.0, 122.5 and 172.0.

Anal. Calcd. for $C_{12}H_{15}N_5O$ (MW 245.29): C, 58.76; H, 6.16; N, 28.55. Found: C, 58.74; H, 6.25; N, 28.48.

5-Deuterio-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**9c**) and 5,8-Dideuterio-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**10c**).

To a solution of 3.18 g (0.03 mole) of sodium carbonate in 10 ml of deuterated water, 1.18 g (0.00275 mole) of *N'*-{2-mor-

pholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5c**) was added and the mixture refluxed with stirring at 130° for 6 hours. After cooling the reaction mixture, it was extracted with 2 x 20 ml of chloroform, the collected organic phases were washed with 10 ml of deuterated water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue (0.50 g) was dry-column flash chromatographed on 4 g of Kieselgel 60H (eluents: dichloromethane and chloroform) to yield 0.466 g (69%) of a *product* that after recrystallisation from acetonitrile proved to be a 1:1 mixture of 5-deuterio-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**9c**) and 5,8-dideuterio-2-morpholino-6,7-dihydro-8*H*-cyclopenta[1,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**10c**), mp 217-218°; ir: ν C-D = 2287 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.16 [quint (J = 7.6 Hz), 2H, CH_2-7], 2.91 [t (J = 7.6 Hz), 2H, CH_2-6], 2.97 [t (J = 7.6 Hz), ~1.5H, CH_2-8], 3.56 (m, 4H, NCH_2), 3.74 (m, 4H, OCH_2); cmr (deuteriochloroform): δ, ppm 23.72 [t (^2J = 10 Hz), C-7], 23.8 (C-7), 27.7 (C-6), 33.9 [t (J = 20 Hz), CD-8), 34.2 (C-8), 45.8 (NCH_2), 66.4 (OCH_2), 122.6 (C-5a), 122.63 [t (^2J = 2.0 Hz), C-5a], 128.4 [t (J = 27 Hz), C-5], 155.3 (C-9a), 167.6 (C-2), 172.3 (C-8a).

6,7,8,9-Tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3d**).

To a suspension of 17.7 g (0.2 mole) of 5-amino-1*H*-1,2,4-triazole (**1d**, Fluka, purity 95%) in 50 ml of acetic acid 37.8 g (0.2 mole) of ethyl 2-oxocyclohexanecarboxylate (Fluka, purity 90%) was added and the mixture refluxed with stirring for 2 hours. At 100° the reaction mixture became homogeneous and after about half an hour the product began to crystallise while hot. After cooling to room temperature the crystals were filtered and washed with acetic acid and acetone to yield 33.3 g (88%) of 6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3d**) which after recrystallisation from a 1:1 mixture of ethanol and water melted at 271-276° dec; ir: ν C=O = 1686 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.7 (m, 4H, CH_2-7,8), 2.40 [t (J = 5.5 Hz), 2H, CH_2-6], 2.63 [t (J = 5.5 Hz), 2H, CH_2-9], 8.16 (s, 1H, CH); cmr (dimethyl-d_6 sulfoxide): δ, ppm 20.8 (C-7), 21.1 (C-6,8), 26.3 (C-9), 105.8 (C-5a), 147.4 (C-9a), 149.5 (C-10a), 151.5 (C-2), 156.3 (C-5).

Anal. Calcd. for $C_9H_{10}N_4O$ (MW 190.21): C, 56.83; H, 5.30; N, 29.46. Found: C, 56.71; H, 5.38; N, 29.34.

5-Chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4d**).

To a stirred suspension of 28.5 g (0.15 mole) of 6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3d**) and 44.6 ml (73.6 g, 0.48 mole) of phosphorus oxychloride, 1.45 ml (1.42 g, 0.018 mole) of pyridine was added. The suspension was heated to 80° and allowed to react at this temperature with stirring for 4 hours. After two hours of heating the mixture became homogenous, and after 4 hours crystals precipitated while hot. The mixture was cooled to ambient temperature and diluted with 100 ml of *n*-hexane. The crystals were filtered, and washed with *n*-hexane. The material thus obtained (representing either a complex of the *product* with phosphorus oxychloride or the *product's* dichlorophosphonate salt) was decomposed by adding it to 200 g of cracked ice. It was stirred until the ice melted. The insoluble crystals were filtered, washed until neutral with water and dried to yield 26.1 g (83%) of 5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4d**). The crude material was dry-column flash chromatographed on 30 g of Kieselgel 60H (eluent: different mixtures of *n*-hexane and chloroform of increasing polarity). Evaporation of the appropriate fractions *in vacuo* to dryness and trituration of the residue with ether yielded 24.3 g (78%) of pure 5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4d**). An analytical sample was recrystallised from ethyl acetate, mp 126-127° (lit [15] mp 126-127°); ir: ν C=N = 1609 and 1515 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.98 (m, 4H, CH_2-7,8), 2.93 (t, 2H, CH_2-6), 3.09 (t, 2H, CH_2-9), 8.43 (s, 1H, CH); cmr (deuteriochloroform): δ, ppm 21.5 (C-8), 21.6 (C-7), 25.1 (C-6), 33.4 (C-9), 118.9 (C-5a), 137.0 (C-5), 153.6 (C-10a), 155.2 (C-2), 165.5 (C-9a).

Anal. Calcd. for $C_9H_9ClN_4$ (MW 208.65): C, 51.81; H, 4.35; N, 26.85; Cl, 16.99. Found: C, 51.88; H, 4.43; N, 26.67; Cl, 17.04.

N'-{6,7,8,9-Tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5d**).

To a solution of 3.55 g (0.017 mole) of 5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4d**) in 10 ml of dichloromethane, a solution of 3.17 g (0.017 mole) of *p*-toluenesulphonylhydrazide in 50 ml of dichloromethane was added at room temperature. The solution was allowed to stand at room temperature for 5 days. The crystals that precipitated were filtered and washed with dichloromethane to yield 6.13 g (91%) of *N'*-{6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5d•HCl**) mp 136-140° dec. To a solution of 3.88 g (0.0098 mole) of the above hydrochloride in 30 ml of chloroform, 2.0 ml (1.45 g, 0.0143 mole) of triethylamine was added and stirred for 5 minutes. The mixture was extracted with 2 x 10 ml of water. During the second extraction the product crystallised, thus it was filtered, washed with water and chloroform to yield 1.89 g of pure *N'*-{6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5d**) base, mp 225-228° dec. Evaporation of the chloroform phase *in vacuo* to dryness and trituration of the residue with acetonitrile yielded a second (1.20 g) crop of base, mp 222-225° dec, increasing the total yield of the base to 88%; ir: ν C=N = 1612 and 1517 cm^{-1}, ν SO_2N = 1348 and 1167 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.65 (m, 4H, CH_2-7,8), 2.14 (m, 2H, CH_2-6), 2.35 (m, 5H, CH_2-9 + CH_3), 7.38 [d (J = 8.0 Hz), 2H, PhH-3',5'], 7.74 [d (J = 8.0 Hz), 2H, PhH-2',6'], 8.13 (s, 1H, H-2), 11.2 and 11.75 (two bs, 2 x 1H, NH-10 and NH-Ts); cmr (dimethyl-d_6 sulfoxide): δ, ppm 21.1 (two peaks C-7,8), 21.3 (CH_3), 21.8 (C-6), 26.1 (C-9), 103.5 (C-5a), 127.4 (PhC-3',5'), 129.7 (PhC-2',6'), 134.0 (PhC-4'), 135.6 (PhC-1'), 138.9 (C-5), 143.6 (C-9a), 149.6 (C-10a), 150.9 (C-2); ms: (CI) $(M+1)^+$ = 359.

Anal. Calcd. for $C_{16}H_{18}N_6O_2S$ (MW. 358.41): C, 53.61; H, 5.06; N, 23.45; S, 8.95. Found: C, 53.58; H, 5.20; N, 23.38; S, 9.05.

6,7,8,9-Tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6d**).

To a solution of 3.18 g (0.03 mole) of sodium carbonate in 100 ml of water, 1.08 g (0.003 mole) of *N'*-{6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5d**) was added and the mixture was stirred at 120° for 2 hours. After cooling the solution was extracted with 2 x 20 ml of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate and dry-column flash chromatographed

on 6 g of Kieselgel 60 H (eluent: dichloromethane, then chloroform). After evaporating the appropriate fractions to dryness *in vacuo*, 0.42 g (81%) of 6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6d**) was obtained that was triturated with ether and the crystals filtered to yield 0.39 g (75%) of pure 6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6d**) 128-129° {lit [17] mp 121-123°, lit [18], mp 125-126°}; ir: ν C=N = 1628 and 1522 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.87 (m, 2H, CH_2-7), 1.93 (m, 2H, CH_2-8), 2.86 [dt (J = 5.8 and 1.2 Hz), 2H, CH_2-6], 3.05 [t (J = 6.5 Hz), 2H, CH_2-9], 8.35 (s, 1H, CH-2), 8.48 [t (J = 1.2 Hz), 1H, CH-5]; cmr (deuteriochloroform): δ, ppm 22.0 (C-8), 22.1 (C-7), 26.4 (C-6), 33.3 (C-9), 121.0 (C-5a), 133.2 (C-5), 153.9 (C-10a), 155.5 (C-2), 166.4 (C-9a); assignment confirmed by HSQC and HMBC; ms: (EI) M^+ = 174.

Anal. Calcd. for $C_9H_{10}N_4$ (MW 174.21): C, 62.05; H, 5.79; N, 32.16. Found: C, 62.10; H, 5.88; N, 32.05.

5,9,9-Trideuterio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**11d**).

To a solution of 3.71 g (0.035 mole) of sodium carbonate in 20 ml of deuterated water, 1.25 g (0.0035 mole) of *N'*-{6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5d**) was added and the mixture was refluxed with stirring at 120° for 2 hours. After cooling the reaction mixture, it was extracted with 3 x 20 ml of chloroform. The collected organic phases were dried over anhydrous sodium sulphate and evaporated *in vacuo* to dryness. The residue (0.51 g) was dry-column flash chromatographed on 16 g of aluminium oxide G (eluent: ethyl acetate). The appropriate fractions were evaporated *in vacuo* to dryness to yield after trituration with ether 0.425 g (69%) of 5,9,9-trideuterio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**11d**), mp 133-134°; ir: ν C-D = 2266 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.90 (m, 2H, CH_2-7), 1.97 (m, 2H, CH_2-8), 2.91 [t (J = 6.4 Hz), 2H, CH_2-6], 8.39 (s, 1H, CH-2); cmr (deuteriochloroform): δ, ppm 21.8 (C-7,8), 25.8 (C-6), 32.5 [quint (J = 19 Hz), C-9], 120.7 (C-5a), 132.9 [t (J = 28.5 Hz), C-5], 154.0 (C-10a), 155.7 (C-2), 166.2 (C-9a); ms: (EI) M^+ = 177.

N'-{2-Methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5e**).

To a solution of 4.59 g (0.018 mole) of 5-chloro-2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4e**) [1,15] in 20 ml of dichloromethane, a solution of 3.35 g (0.018 mole) of *p*-toluenesulphonylhydrazide in 60 ml of dichloromethane was added at room temperature. The solution was allowed to stand at room temperature for 4 days. The crystals that precipitated were filtered and washed twice with 10 ml portions of dichloromethane to yield 6.81 g (86%) of *N'*-{2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5e•HCl**) containing a small amount (approximately 6%, pmr) of *p*-toluenesulphonylhydrazide, mp 239-242° dec. To a suspension of 0.66 g (0.0015 mole) of the above crude hydrochloride in 20 ml of chloroform, 2 ml (1.45 g, 0.0143 mole) of triethylamine was added with stirring. After 30 minutes the crystals were separated and washed with 2 x 3 ml of chloroform to yield 0.50 g (83%) of pure *N'*-{2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5e**), mp 236-240° dec; ir: ν C=N = 1675 and 1617 cm^{-1}, ν SO_2N = 1341 and 1158 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.63 (m, 4H, CH_2-7,8), 2.10 (m, 2H, CH_2-6), 2.35 (m, 5H, CH_2-9 + CH_3), 2.58 (s, 3H, SCH_3), 7.38 [d (J = 8 Hz), 2H, PhH-3',5'], 7.72 [d (J = 8 Hz), 2H, PhH-2',6'], 11.0 (bs, 1H, NH); ms: (EI) M^+ = 404.

Anal. Calcd. for $C_{17}H_{20}N_6O_2S_2$ (MW 404.52): C, 50.48; H, 4.98; N, 20.78; S, 15.85. Found: C, 50.31; H, 5.16; N, 20.71; S, 15.93.

2-Methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6e**).

To a solution of 5.30 g (0.05 mole) of sodium carbonate in 150 ml of water, 2.20 g (0.005 mole) of crude (approximately 94%) *N'*-{2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone monohydrochloride (**5e•HCl**) was added and the mixture refluxed with stirring for 2 hours. After cooling the reaction mixture was extracted with 50 and 2 x 20 ml of dichloromethane. The collected organic phases were dried over anhydrous sodium sulphate, evaporated to dryness *in vacuo* and dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluent: dichloromethane, then chloroform). The residue (0.93 g) obtained after evaporating the appropriate fractions to dryness *in vacuo* was triturated with 10 ml of ether and filtered to yield 0.76 g (73%) of 2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6e**), mp 114-116° {lit [17] mp 106-108° (methanol)}. An additional amount (0.15 g) of the above *product* was obtained after evaporation of the mother liquor to dryness *in vacuo* and triturating the residue with 2 ml of ether increasing the total yield of the reaction to 88%; ir: ν C=N = 1620 and 1504 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.9 (m, 4H, CH_2-7,8), 2.68 (s, 3H, SCH_3), 2.86 [t (J = 6.3 Hz), 2H, CH_2-6], 3.00 [t (J = 6.3 Hz), 2H, CH_2-9], 8.36 (s, 1H, 5-H); cmr (deuteriochloroform): δ, ppm 13.5 (SCH_3), 21.6 (C-7), 21.8 (C-8), 25.5 (C-6), 32.7 (C-9), 119.6 (C-5a), 132.0 (C-5), 154.6 (C-10a), 165.1 (C-9a), 168.4 (C-2); INEPT (7 Hz): irradiated at 2.68 ppm, polarisation transfer at 168.4 ppm, irradiated at 8.36 ppm, polarisation transfer at 25.5, 119.6, 154.6 and 165.1 ppm.

Anal. Calcd. for $C_{10}H_{12}N_4S$ (MW 220.30): C, 54.52; H, 5.49; N, 25.43; S, 14.55. Found: C, 54.38; H, 5.57; N, 25.40; S, 14.50.

5,9,9-Trideuterio-2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazoline (**11e**).

To a solution of 5.30 g (0.05 mole) of sodium carbonate in 20 ml of deuterated water, 2.20 g (0.005 mole) of crude (approximately 94%) *N'*-(2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazolin-5-yl)-*p*-toluenesulphonylhydrazone monohydrochloride (**5e•HCl**) was added and the mixture refluxed with stirring for 8 hours. After cooling the reaction mixture it was extracted with 30 and 2 x 20 ml of dichloromethane. The collected organic phases were dried over anhydrous sodium sulphate, evaporated to dryness *in vacuo* and dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluent: dichloromethane, then chloroform). The residue obtained after evaporating the appropriate fractions to dryness *in vacuo* was triturated with 10 ml of ether and filtered to yield 0.62 g (56%) of 5,9,9-trideuterio-2-methylthio-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazoline (**11e**), mp 116-118°; ir: ν C-D = 2266 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.89 (m, 2H, CH_2-7), 1.95 (m, 2H, CH_2-8), 2.69 (s, 3H, SCH_3), 2.85 [t (J = 6.4 Hz), 2H, CH_2-6]; cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 21.9 (C-7,8), 25.8 (C-6), 32.3 [quint (J = 19.4 Hz), C-9], 119.7 (C-5a), 131.8 [t (J = 28.0 Hz), C-5], 154.5 (C-10a), 165.2 (C-9a), 168.4 (C-2); ms: (EI) M^+ = 223.

2-Benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3f**).

To a suspension of 18.92 g (0.1 mole) of 5-benzylamino-5-amino-1*H*-1,2,4-triazole (**1f**) [16] in 50 ml of acetic acid, 17.7 ml (18.9 g, 0.1 mole) of ethyl 2-oxocyclohexanecarboxylate (Fluka, purity 90%) was added and the mixture refluxed with stirring for 1 hour. At 100° the reaction mixture became homogeneous and after a few minutes the product began to crystallise while hot. After cooling, the crystals were filtered and washed with acetic acid and acetone to yield 28.05 g (95%) of 2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3f**) that after recrystallisation from a mixture of dimethylformamide and water melted at 308-315° dec; ir: ν C=O = 1679 cm^{-1}; pmr (deuteriochloroform + trifluoroacetic acid): δ, ppm 1.95 (m, 4H, CH_2-7,8), 2.66 (t, 2H, CH_2-6), 2.85 (t, 2H, CH_2-9), 4.63 (s, 2H, NCH_2), 7.3-7.4 (m, 5H, PhH); cmr (deuteriochloroform + trifluoroacetic acid): δ, ppm 20.6 (C-7,8), 21.5 (C-6), 27.3 (C-9), 47.4 (NCH_2), 114.1 (C-5a), 127.5 (PhC-2',6'), 128.7 (PhC-4'), 129.3 (PhC-3',5'), 135.4 (PhC-1'), 144.8 (C-9a), 150.0 (C-10a), 154.3 (C-5), 156.3 (C-2).

Anal. Calcd. for $C_{16}H_{17}N_5O$ (MW 295.35): C, 65.07; H, 5.80; N, 23.71. Found: C, 65.11; H, 5.92; N, 23.66.

2-Benzylamino-5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazoline (**4f**).

To a stirred suspension of 4.43 g (0.015 mole) of 2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3f**) and 8.4 ml (13.8 g, 0.09 mole) of phosphorus oxychloride, 5 drops of pyridine were added. The suspension was heated to 70° and allowed to react at this temperature with stirring for 2 hours. The solution crystallised while hot. The mixture was cooled to ambient temperature and diluted with 20 ml of diethyl ether. The crystals were filtered and washed with ether. The crystals thus obtained (representing either a complex of the *product* with phosphorus oxychloride or the *product's* dichlorophosphonate salt) were decomposed by their addition to 80 g of cracked ice and stirred until the ice melted. The crystals thus obtained were filtered, washed until neutral with water and dried to yield 4.22 g (89%) of 2-benzylamino-5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4f**) that after recrystallisation from acetonitrile melted at 180-182° (lit [15] mp 177-179°); ir: ν C=N = 1596 and 1517 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.9 (m, 4H, CH_2-7,8), 2.80 (t, 2H, CH_2-6), 2.97 (t, 2H, CH_2-9), 4.67 [d (J = 6.1 Hz), 2H, NCH_2], 5.26 [t (J = 6.1 Hz), 1H, NH], 7.2-7.4 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 22.1 (C-7,8), 25.1 (C-6), 33.2 (C-9), 46.9 (NCH_2), 116.0 (C-5a), 127.1 (PhC-4'), 127.5 (PhC-2',6'), 128.3 (PhC-3',5'), 135.4 (C-5), 139.2 (PhC-1'), 154.2 (C-10a), 162.4 (C-9a), 167.2 (C-2).

Anal. Calcd. for $C_{16}H_{16}ClN_5$ (MW 313.79): C, 61.24; H, 5.14; N, 22.32; Cl, 11.30. Found: C, 61.15; H, 5.23; N, 22.37; Cl, 11.28.

N'-{2-Benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5f**).

To a suspension of 2.20 g (0.007 mole) of 2-benzylamino-5-chloro-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4f**) in 20 ml of dichloromethane, a solution of 1.30 g (0.007 mole) of *p*-toluenesulphonylhydrazide in 30 ml of dichloromethane was added at room temperature. The solution was allowed to stand at room temperature for 3 days and then evaporated to dryness *in vacuo*. The residue was triturated with ethyl acetate, the crystals which precipitated were filtered and washed with ethyl acetate to yield 3.54 g of crude *N'*-{2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5f•HCl**), mp 132-139°. The hydrochloride was suspended in 30 ml of chloroform, 3 ml (2.18 g, 0.0215 mole) of triethylamine and 10 ml of water were added and the organic layer was separated. After adding 10 ml of water to the organic phase, the base crystallised from the chloroform-water mixture. The crystals were separated and washed with chloroform and acetonitrile to yield 1.89 g (58%) of *N'*-{2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5f**), mp 219-223° dec. An additional amount (0.68 g, 21% , mp 210-216°) of the above product could be obtained from the above chloroform solutions after their evaporation to dryness *in vacuo* and triturating the residue with acetonitrile increasing the total yield to 79% ; ir: ν C=N = 1591 and 1522 cm^{-1}, ν SO_2N = 1341 and 1165 cm^{-1} ; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.6 (m, 4H, CH_2-7,8), 2.05 (m, 2H, CH_2-6), 2.25 (m, 2H, CH_2-9), 2.33 (s, 3H, CH_3), 4.30 [d (J = 6.0 Hz), 2H, $NHCH_2$], 7.25-7.35 (m, 7H, PhH-"benzyl" + PhH-3',5'), 7.4 [t (J = 6.0 Hz), 1H, NH], 7.60 [d (J = 8.6 Hz), 2H, PhH-2',6'], 11.4 and 11.6 (two bs, 2 x 1H, NH-10 and NH-Ts).

Anal. Calcd. for $C_{23}H_{25}N_7O_2S$ (MW 463.57): C, 59.59; H, 5.44; N, 21.15; S, 6.92. Found: C, 59.60; H, 5.55; N, 21.13; S, 6.85.

2-Benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6f**).

To a solution of 3.18 g (0.03 mole) of sodium carbonate in 100 ml of water, 1.39 g (0.003 mole) of *N'*-{2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5f**) was added and the mixture refluxed with stirring for 2 hours. After cooling the solution it was extracted with 3 x 20 ml of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate, filtered and evaporated to dryness *in vacuo*. The residue was dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluent: dichloromethane, then chloroform). The residue after evaporating the appropriate fractions *in vacuo* to dryness was triturated with ether and filtered to yield 0.68 g (81%) of 2-benzylamino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6f**), mp 165-167°; ir: ν C=N = 1583 and 1529 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.8-2.0 (m, 4H, CH_2-7,8), 2.74 [t (J = 6.0 Hz), 2H, CH_2-6], 2.95 [t (J = 6.2 Hz), 2H, CH_2-9], 4.62 (s, 2H, $NHCH_2$), 5.6 (bs, 1H, NH), 7.24-7.42 (m, 5H, PhH), 8.06 (s, 1H, CH-5); pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.70-1.85 (m, 4H, CH_2-7,8), 2.71 [t (J = 6.0 Hz), 2H, CH_2-6], 2.82 [t (J = 6.4 Hz), 2H, CH_2-9], 4.44 (bs, 2H, $NHCH_2$), 7.21 (m, 1H, NH), 7.27-7.35 (m, 5H, PhH), 8.70 (s, 1H, CH-5); cmr (dimethyl-d_6 sulfoxide): δ, ppm 21.9 (C-8), 22.1 (C-7), 25.1 (C-6), 32.4 (C-9), 45.7 ($NHCH_2$), 117.6 (C-5a), 126.8 (PhC-4'), 127.3 (PhC-2', 6'), 128.4 (PhC-3',5'), 133.1 (C-5), 140.6 (PhC-1'), 153.8 (C-10a), 162.0 (C-9a), 167.3 (C-2).

Anal. Calcd. for $C_{16}H_{17}N_5$ (MW 279.35): C, 68.80; H, 6.13; N, 25.07. Found: C, 68.60; H, 6.22; N, 25.01.

2-(*N*-Benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazolin-5(10*H*)-one (**3g**).

To a solution of 6.10 g (0.03 mole) of 3-(*N*-benzyl-*N*-methyl)amino-5-amino-1*H*-1,2,4-triazole (**1g**) [19] in 20 ml of acetic acid, 4.8 ml (5.11 g, 0.03 mole) of ethyl 2-oxocyclo-

hexanecarboxylate (Merck) was added and the mixture refluxed with stirring for 4 hours. After 3.5 hours the product began to crystallise while hot. The thick reaction mixture was diluted with 20 ml of acetic acid. After cooling the crystals were filtered and washed with acetic acid and acetone to yield 6.90 g (74%) of chromatographically pure 2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-one (**3g**). An analytical sample was recrystallised from a 1:1 mixture of acetonitrile and dimethylformamide to yield a product which melted at 270-275° dec; ir: ν C=O = 1670 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.70-1.85 (m, 4H, CH_2-7,8), 2.48 (m, 2H, CH_2-6), 2.60 (m, 2H, CH_2-8), 3.02 (s, 3H, NCH_3), 4.69 (s, 2H, NCH_2), 7.2-7.35 (m, 5H, PhH), 12.4 (bs, 1H, NH);

Anal. Calcd. for $C_{17}H_{19}N_5O$ (MW 309.36): C, 66.00; H, 6.19; N, 22.64. Found: C, 66.08; H, 6.22; N, 22.56.

5-Chloro-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4g**).

To a stirred suspension of 6.18 g (0.02 mole) of 2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazolin-5(10*H*)-one (**3g**) and 11.2 ml (18.4 g, 0.12 mole) of phosphorus oxychloride, 0.48 ml (0.47g, 0.006 mole) of pyridine was added. The suspension was refluxed with stirring for 80 minutes. The solution was cooled, decomposed by pouring it into 200 g of cracked ice and stirred for 1 hour. The oily product was extracted with 100 and 20 ml of chloroform. The combined chloroform layers ware washed with water, 3% aqueous sodium hydrocarbonate solution, dried over anhydrous sodium sulphate and evaporated to dryness *in vacuo* to yield 7.6 g of yellow oil that was dry-column flash chromatographed on 30 g of Kieselgel 60 H (eluents: different mixtures of cyclohexane and diethyl ether of continuously increasing polarity) to yield after evaporation of the appropriate fractions *in vacuo* and triturating the residue with cyclohexane, 5.45 g (83%) of chromatographically pure 5-chloro-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4g**). An analytical sample was recrystallised from a 1:1 mixture of cyclohexane and ethyl acetate to yield the *product* melting at 108-110°; ir: ν C=N = 1572 and 1517 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.9 (m, 4H, CH_2-7,8), 2.79 (m, 2H, CH_2-6), 2.97 (m, 2H, CH_2-8), 3.10 (s, 3H, NCH_3), 4.81 (s, 2H, $PhCH_2$), 7.25-7.40 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 22.0 (two peaks, C-7,8), 25.1 (C-6), 33.1 (C-9), 34.7 (NCH_3), 53.6 ($PhCH_2$), 115.7 (C-5a), 127.2 (Ph-4'), 128.0 (Ph-2',6'), 128.4 (Ph-3',5'), 135.3 (C-5), 137.8 (Ph-1'), 154.5 (C-10a), 162.1 (C-9a), 168.1 (C-2).

Anal. Calcd. for $C_{17}H_{18}ClN_5$ (MW 327.80): C, 62.28; H, 5.53; N, 21.37; Cl, 10.82. Found: C, 62.08; H, 5.65; N, 21.33; Cl, 10.76.

N'-{2-(*N*-Benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5g**), *N'*-{2-(*N*-Benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-hydrazone (**14g**) and *p*-Toluenesulphonylchloride (**15**).

To a solution of 1.12 g (0.006 mole) of *p*-toluenesulphonylhydrazide in 25 ml of dichloromethane, 1.97 g (0.006 mole) of 5-chloro-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4g**) was added at room temperature. The solution was allowed to stand at room temperature for 2 months. The crystals that precipitated were filtered and washed with dichloromethane to yield 0.60 g of crude *N'*-{2-(*N*-Benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5(10*H*)-hydrazone hydrochloride (**14g•HCl**). Compound **14g•HCl** was dissolved in 20 ml of chloroform and to the solution 1.0 ml (0.726 g, 0.0072 mole) of triethylamine was added, stirred for 5 minutes and evaporated to dryness *in vacuo*. The residue was triturated with 20 ml of water, the insoluble crystals were filtered and washed thoroughly with water, methanol, acetonitrile and ether, respectively, to yield 0.46 g (25%) of pure *N'*{2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]-quinazoline-5(10*H*)-hydrazone (**14g**), mp 252-256 dec; ir: ν C=N = 1667 and 1560 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.76 (bs, 8H, CH_2-7,8,7',8'), 2.35 (bs, 2H, CH_2-6), 2.40 (bs, 2H CH_2-9), 2.80 (m, 2H, CH_2-6'), 2.88 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3'), 3.31 (m, 2H, CH_2-9'), 4.62 (s, 2H, $PhCH_2$), 4.64 (s, 2H, $PhCH_2$'), 7.15-7.30 (m, 10H, PhH and Ph'H), 11.4 (s, 1H, NH-5'), 12.8 (s, 1H, NH-10); ms: (CI) $(M+1)^+$ = 615.

The dichloromethane containing mother liquor of crude **14g•HCl** was evaporated to dryness *in vacuo* and the residue was triturated with a small amount of ethyl acetate to yield crystals that were filtered. [The ethyl acetate containing mother liquor was evaporated to dryness *in vacuo* and the residue was dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluent: diethyl ether) to yield 0.15 g of *p*-toluenesulphonyl chloride (**15**, X = Cl), mp 66-68° (mixed mp with an authentic sample 66-69°, the ms confirms the structure)].

The above crystals (2.10 g) were suspended in 20 ml of chloroform, and to the suspension, 1.5 ml (1.09 g, 0.0108 mole) of triethylamine was added with stirring at room temperature. After stirring for 5 minutes the solution was evaporated to dryness *in vacuo*, the residue was suspended in 15 ml of water, the crystals precipitated were filtered and washed with water to yield 1.81 g (63%) of crude product. This was dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluents: different mixtures of chlorofom and methanol of continuously increasing polarity) to yield pure *N'*-{2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5g**), which after triturating with acetonitrile and filtering melted at 220-225° dec; ir: ν C=N = 1620 and 1572 cm^{-1}, ν SO_2N = 1339 and 1166 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.6 (m, 4H, CH_2-7,8), 2.09 (m, 2H, CH_2-6), 2.29 (m, 2H, CH_2-9), 2.35 (s, 3H, $PhCH_3$), 2.98 (s, 3H, NCH_3), 4.56 (s, 2H, $PhCH_2$), 7.25-7.40 (m, 7H, PhH + TsH-3',5'), 7.63 [d (J = 8 Hz), 2H, TsH-2',6'], 11.5 and 11.65 (two bs, 2 x 1H, NH-10 and NHTs); ms: (CI) $(M+1)^+$ = 478.

Anal. Calcd. for $C_{24}H_{27}N_7O_2S$ (MW 477.57): C, 60.36; H, 5.70; N, 20.53; S, 6.71. Found: C, 60.27; H, 5.85; N, 20.57; S, 6.64.

2-(*N*-Benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo-[5,1-*b*]quinazoline (**6g**).

To a solution of 3.18 g (0.03 mole) of sodium carbonate in 120 ml of water, 1.43 g (0.003 mole) of *N'*-{2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5g**) was added and the mixture was refluxed with stirring for 4 hours. After cooling the reaction mixture was extracted with 3 x 20 ml of dichloromethane, the collected organic phases were dried over anhydrous

sodium sulphate and dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluents: dichloromethane, then chloroform). After evaporation of the appropriate fractions to dryness *in vacuo* the residue was triturated with 5 ml of ether and filtered to yield 0.75 g (85%) of 2-(*N*-benzyl-*N*-methyl)amino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6g**), mp 138-140°; ir: ν C=N = 1592 and 1521 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.83 [quint (J = 6.5 Hz), 2H, CH_2-7], 1.92 [quint (J = 6.5 Hz), 2H, CH_2-8], 2.77 [t (J = 6.5 Hz), 2H, CH_2-6], 2.96 [t (J = 6.5 Hz), 2H, CH_2-9], 3.07 (s, 3H, NCH_3), 4.78 (s, 2H, $PhCH_2$), 7.20-7.35 (m, 5H, PhH), 8.20 (s, 1H, CH-5); cmr (deuteriochloroform): δ, ppm 22.2 (C-7), 22.3 (C-8), 25.8 (C-6), 32.7 (C-9), 34.8 (NCH_3), 53.6 ($PhCH_2$), 117.6 (C-5a), 127.1 (PhC-4'), 127.8 (PhC-2',6'), 128.4 (PhC-3',5'), 131.7 (C-5), 137.9 (PhC-1'), 154.6 (C-10a), 162.7 (C-9a), 168.3 (C-2); ms: (EI) M^+ = 293.

Anal. Calcd. for $C_{17}H_{19}N_5$ (MW 293.36): C, 69.60; H, 6.53; N, 23.87. Found: C, 69.66, H, 6.68, N, 23.75.

N'-{2-Morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5h**).

To a solution of 1.49 g (0.008 mole) of *p*-toluenesulphonylhydrazide in 25 ml of dichloromethane, 2.35 g (0.008 mole) of 5-chloro-2-morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**4h**) [1,15] was added at room temperature. The solution was allowed to stand at room temperature for 3 days. The crystals were filtered and washed twice with 5 ml portions of dichloromethane to yield 3.11 g (81%) of *N'*-{2-morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5h•HCl**), mp 246-250° dec. To a suspension of 1.49 g (0.0031 mole) of the above crude hydrochloride in 20 ml of chloroform, 2 ml (1.45 g, 0.0143 mole) of triethylamine was added with stirring. After 15 minutes the crystals were separated and washed with 2 x 5 ml of chloroform to yield 1.17 g (86%) of *N'*-{2-morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5h**), mp 241-244° dec; ir: ν C=N = 1620 and 1572 cm^{-1}, ν SO_2N = 1350 and 1166 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.62 (m, 4H, CH_2-7,8), 2.09 (m, 2H, CH_2-6), 2.3 (m, 2H, CH_2-9), 2.35 (s, 3H, CH_3), 3.35 (m, 4H, NCH_2), 3.72 (m, 4H, OCH_2), 7.37 [d (J = 7.6 Hz), 2H, PhH-3',5'], 7.69 [d (J = 7.6 Hz), 2H, PhH-2',6'], 11.45 and 11.6 (two bs, 2 x 1H, NH-10 and NH-Ts).

Anal. Calcd. for $C_{20}H_{25}N_7O_3S$ (MW 443.53): C, 54.16; H, 5.68; N, 22.11; S, 7.23. Found: C, 54.30; H, 5.85; N, 22.01; S, 7.35.

2-Morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6h**).

To a solution of 2.65 g (0.025 mole) of sodium carbonate in 80 ml of water, 1.11 g (0.0025 mole) of *N'*-{2-morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-5-yl}-*p*-toluenesulphonylhydrazone (**5h**) was added and the mixture was refluxed with stirring for 2.5 hours. After cooling the solution was extracted with 3 x 20 ml of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate and dry-column flash chromatographed on 6 g of Kieselgel 60 H (eluent: dichloromethane, then chloroform). The residue obtained after evaporating the appropriate fractions to dryness *in vacuo* was recrystallised from acetonitrile to yield 0.52 g (80%) of 2-morpholino-6,7,8,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazoline (**6h**), mp 194-197°; ir: ν C=N = 1627 and 1549 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.8-2.0 (m, 4H, CH_2-7,8), 2.80 [t J = 6.0 Hz), 2H, CH_2-6], 2.97 [t (J = 6.0 Hz), 2H, CH_2-9], 3.63 (m, 4H, NCH_2), 3.82 (m, 4H, OCH_2), 8.22 (s, 1H, 5-H); cmr (deuteriochloroform): δ, ppm 21.9 (C-8), 22.0 (C-7), 25.4 (C-6), 32.5 (C-9), 45.6 (NCH_2), 66.1 (OCH_2), 117.5 (C-5a), 131.5 (C-5), 154.1 (C-10a), 162.6 (C-9a), 167.7 (C-2); ms: (EI) M^+ = 259.

Anal. Calcd. for $C_{13}H_{17}N_5O$ (MW 259.31): C, 60.21; H, 6.61; N, 27.01. Found: C, 60.09; H, 6.62; N, 27.11.

5-Chloro-7,8-dihydro-2-methylthio-9*H*-thiopyrano[3,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4i**).

To a stirred suspension of 6.87 g (0.027 mole) of 7,8-dihydro-2-methylthio-9*H*,10*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidin-5-one (**3i**) [7] and 27.0 ml (44.5 g, 0.29 mole) of phosphorus oxychloride, 0.25 ml (0.24 g, 0.003 mole) of pyridine was added. The suspension was allowed to react at 90° with stirring for 16 hours. Then an additonal amount (13.0 ml, 21.5 g, 0.14 mole) of phosphorus oxychloride and 0.56 ml (0.55 g, 0.007 mole) of pyridine were added to the reaction mixture and allowed to react at 90° for an additional 16 hours. The homogeneous reaction mixture crystallised upon cooling. After standing overnight the mixture was diluted with 80 ml of diethyl ether, the ether phase was decanted, and the remaining partly crystalline mixture was washed with 20 ml of ether. To the residue, 150 g of cracked ice was added and stirred until the ice melted. The insoluble crystals were filtered, washed to neutrality with a 3% aqueous solution of sodium hydrogen carbonate and water and dried to yield 6.84 g of crude 5-chloro-2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4i**) that was dry-column flash chromatographed on 30 g of Kieselgel 60H (eluent: different mixtures of light petroleum (bp 40-70°) and chloroform of increasing polarity). Evaporation of the appropriate fractions *in vacuo* led to 5.17 g (70%) of pure 5-chloro-2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidine (**4i**), mp 142-143° (acetonitrile) {lit [15] mp 142-143° (ethyl acetate}; ir: ν C=N = 1603 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.30 [quint (J = 6 Hz), 2H, CH_2-8] 2.72 (s, 3H, SCH_3), 3.14 [t (J = 6.2 Hz), 2H, CH_2-9], 3.17 [t (J = 5.8 Hz), 2H, CH_2-7]; cmr (deuteriochloroform): δ, ppm 14.0 (SCH_3), 22.6 (C-8), 27.4 (C-7), 33.9 (C-9), 117.6 (C-5a), 131.3 (C-5), 153.2 (C-10a), 160.0 (C-9a), 168.8 (C-2), assignment confirmed by HSQC and HMBC; ms: (EI) M^+ = 272.

Anal. Calcd. for $C_9H_9ClN_4S_2$ (MW 272.78): C, 39.63; H, 3.33; N, 20.54; S, 23.51, Cl, 13.00. Found: C, 39.55; H, 3.28; N, 20.57; S, 23.44, Cl, 12.88.

N'-{2-Methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5i**).

To a solution of 2.73 g (0.01 mole) of 5-chloro-2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**4i**) in 10 ml of chloroform a solution of 1.86 g (0.01 mole) of *p*-toluenesulphonylhydrazide in 30 ml of chloroform was added at room temperature. The solution was allowed to stand at room temperature for 3 weeks. The crystals were filtered and washed with chloroform to yield 4.52 g of *N'*-{2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5i•HCl**) that was suspended in 25 ml of chloroform. To the suspension, 2.5 ml (1.82 g, 0.018 mole) of triethylamine was added and stirred for 1 hour. The crystals were filtered and washed thoroughly with chloroform to yield 3.75 g

(89%) of *N'*-{2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5i**), mp 238-241° dec; ir: ν C=N = 1635 and 1593 cm^{-1}, ν SO_2N = 1338 and 1164 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 1.99 (m, 2H, CH_2-8), 2.37 (s, 3H, CH_3), 2.5 (m, 2H, CH_2-7 overlapped by dimethyl-d_6 sulfoxide), 2.58 (s, 3H, SCH_3), 2.85 (m, 2H, CH_2-9), 7.38 [d (J = 8.0 Hz), 2H, Ph H-3',5'], 7.75 [d (J = 8.0 Hz), 2H, Ph H-2',6'], 10.9 and 12.0 (two bs, 2 x 1H, NH-10 and NH-Ts).

Anal. Calcd. for $C_{16}H_{18}N_6O_2S_3$ (MW 422.55): C, 45.48; H, 4.29; N, 19.89; S, 22.76. Found: C, 45.70; H, 4.40; N, 19.73; S, 22.70.

2-Methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidine (**6i**).

To a solution of 5.30 g (0.05 mole) of sodium carbonate in 200 ml of water, 2.12 g (0.005 mole) of *N'*-{2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5i**) was added and the mixture was refluxed with stirring at 125° for 2 hours. After cooling the crystals were filtered to yield 0.89 g of crude 2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidine (**6i**). The mother liquor was extracted with 3 x 25 ml portions of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate and evaporated to dryness to yield an additonal 0.16 g of crude *product*. The combined crude products were dry-column flash chromatographed on 10 g of Kieselgel 60 H (eluents: dichloromethane, then chloroform). After evaporating the appropriate fractions to dryness *in vacuo* 1.00 g (84%) of pure 2-methylthio-7,8-dihydro-9*H*-thiopyrano-[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**6i**) was obtained which after recrystallisation from ethyl acetate melted at 146.5-147.5°; ir: ν C=N = 1610 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.29 (m, 2H, CH_2-8), 2.69 (s, 3H, SCH_3), 3.1 (m, 4H, CH_2-7 and 9), 8.42 (s, 1H, CH-5); cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 22.8 (C-8), 26.7 (C-7), 33.4 (C-9), 118.0 (C-5a), 129.2 (C-5), 153.6 (C-10a), 161.1 (C-9a), 168.6 (C-2); ms: (CI) $(M+1)^+$ = 239.

Anal. Calcd. for $C_9H_{10}N_4S_2$ (MW 238.34): C, 45.36; H, 4.23; N, 23.51; S, 26.91. Found: C, 45.40; H, 4.52; N, 23.44; S, 26.88.

2-Methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidine (**6i**) and 5-Amino-2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**17**).

To the solution of 3.71 g (0.035 mole) of sodium carbonate in 10 ml of water, 1.48 g (0.0035 mole) of *N'*-{2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5i**) was added and the mixture was refluxed with stirring at 120° for 1 hour. After cooling, 10 ml of water and 30 ml of chloroform were added to the reaction mixture, the insoluble material was filtered, the phases were separated and the organic phase evaporated to dryness *in vacuo* to yield 0.68 g of brown oil, that was dry-column flash chromatographed on 8 g of Kieselgel 60 H (eluents: different mixtures of dichloromethane and chloroform of increasing polarity). After evaporating the appropriate fractions to dryness *in vacuo* and triturating the residue with ether, 0.51 g (61%) of 2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**6i**) was obtained, mp 146-147.5°. The material is identical (mixed mp, ir) with that obtained in the previous experiment.

Continuing the chromatography and evaporating the appropriate fractions to dryness *in vacuo* 0.056 g (6%) of 5-amino-2-methylthio-7,8-dihydro-9*H*-thiopyrano[3,2-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidine (**17**) was obtained that after triturating with ethyl ether decomposed at 240-243°; ir: ν NH_2 = 3415 and 3128 cm^{-1}, ν C=N = 1631 and 1603 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 2.12 [quint (J = 6.2 Hz), 2H, CH_2-8], 2.63 (s, 3H, SCH_3), 2.84 [t (J = 6.2 Hz), 2H, CH_2-7], 3.04 [t (J = 6.2 Hz), 2H, CH_2-9], 7.81 (s, 2H, NH_2); cmr (dimethyl-d_6 sulfoxide): δ, ppm 13.4 (SCH_3), 23.4 (C-8), 26.4 (C-7), 32.9 (C-9), 94.6 (C-5a), 143.7 (C-5), 153.5 (C-10a), 158.8 (C-9a), 165.3 (C-2); ms: (CI) $(M+1)^+$ = 254.

Anal. Calcd. for $C_9H_{11}N_5S_2$ (MW 253.35): N, 27.64. Found: N, 27.55

7-Benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4j**).

To a stirred suspension of 16.37 g (0.05 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 (**3j**) [8] and 46.5 ml (76.7 g, 0.5 mole) of phosphorus oxychloride, 0.8 ml (0.79 g, 0.01 mole) of pyridine was added. The suspension was allowed to react at 95° with stirring for 33 hours, then cooled to 5°. The crystals that precipitated were filtered and washed with ether to yield 6.5 g of crude salt. The salt was suspended in 100 ml of chloroform and to the suspension 5 ml (3.63 g, 0.036 mole) of triethylamine was added, stirred for 5 minutes and extracted with 2 x 25 ml of water. The chloroform layer was dried over anhydrous sodium sulphate, filtered and evaporated to dryness *in vacuo*. The crystalline residue was triturated with ether and filtered to yield 4.5 g of crude 7-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido-[4,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4j**).

The phosphorus oxychloride containing mother liquor was decomposed by pouring it with stirring into 1000 g of cracked ice. To the mixture still containing ice, 200 ml of chloroform was added and made alkaline with 250 ml of concentrated aqueous ammonium hydroxide. The phases were separated and the aqueous phase was extracted with 2 x 100 ml of chloroform. The combined organic phases were washed with 2 x 50 ml of water, dried over anhydrous sodium sulphate, filtered and evaporated to dryness *in vacuo* to yield an additonal 7.0 g of crude 7-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**4j**).

The combined crude products were dry-column flash chromatographed on 40 g of Kieselgel 60 H (eluents: different mixtures of *n*-hexane and chloroform of continuously increasing polarity) to yield after evaporation of the appropriate fractions, 10.9 g (63%) of pure 7-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4j**) decomposing at 163-166° (ethyl acetate) (lit [15] mp 163-165°); ir: ν C=N = 1607 and 1486 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.72 (s, 3H, SCH_3), 2.88 [t (J = 6.0 Hz), 2H, CH_2-8], 3.15 [t (J = 6.0 Hz), 2H, CH_2-9], 3.74 (s, 2H, CH_2-6), 3.80 (s, 2H, $PhCH_2$), 7.3-7.4 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 13.9 (SCH_3), 33.1 (CH_2-9), 49.0 (CH_2-8), 51.6 (CH_2-6), 62.1 ($PhCH_2$), 116.3 (C-5a), 127.6 (Ph-4'), 128.6 (Ph-2',6'), 128.9 (Ph-3',5'), 134.6 (C-5), 137.1 (Ph-1'), 154.8 (C-10a), 162.6 (C-9a), 169.6 (C-2); assignment confirmed by HSQC and HMBC.

Anal. Calcd. for $C_{16}H_{16}ClN_5S$ (MW 345.85): C, 55.56; H, 4.66; N, 20.25; S, 9.27; Cl, 10.25. Found: C, 55.48; H, 4.70; N, 20.21; S, 9.33, Cl, 10.18.

N'-{7-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5j**).

To a solution of 2.79 g (0.015 mole) of *p*-toluenesulphonylhydrazide in 70 ml of dichloromethane, 2.59 g (0.0075 mole) of 7-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4j**) was added at room temperature. The solution was refluxed for 5 days. The crystals which precipitated were filtered and washed with dichloromethane to yield 1.25 g of crude hydrochloride **5j•HCl**. This was suspended in 30 ml of chloroform and to the suspension 1.0 ml (0.73 g, 0.0072 mole) of triethylamine was added with stirring at room temperature. To the suspension 8 ml of water was added to yield a solution which after stirring a few minutes crystallised again. The crystals were filtered and washed with 2 x 5 ml of water, then with 3 ml of chloroform to yield 1.05 g (28%) of *N'*-{7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5j**), mp 193-196° dec. The dichloromethane mother liquor was refluxed for 5 days and worked up as above to yield an additonal 1.40 g (38%) of *N'*-{7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido-[4,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5j**) increasing the total yield to 66%; ir: ν C=N = 1620 and 1581 cm^{-1}, ν SO_2N = 1352 and 1166 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 2.36 (s, 3H, $PhCH_3$), ~2.45 [m, xH (overlapped by dimethyl sulphoxide), CH_2-9], 2.57 (s, 3H, SCH_3), 2.67 [t (J ~ 6 Hz), 2H, CH_2-8], 3.00 (s, 2H, CH_2-6), 3.66 (s, 2H, $PhCH_2$), 7.25 [d (J = 8.0 Hz), 2H, TsH- 3',5'], 7.37 (m, 5H, PhH), 7.58 [d (J = 8 Hz), 2H, TsH-2',6'], 10.8 and 11.9 (two bs, 2 x 1H, NH-10 and NH-Ts); ms: (CI) $(M+1)^+$ = 496.

Anal. Calcd. for $C_{23}H_{25}N_7O_2S_2$ (MW 495.60): C, 55.74; H, 5.08; N, 19.78; S, 12.94. Found: C, 55.66; H, 5.12; N, 19.91; S, 12.80.

7-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**6j**).

To a solution of 1.70 g (0.016 mole) of sodium carbonate in 60 ml of water, 0.79 g (0.0016 mole) of *N'*-{7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5j**) was added and the mixture stirred at 140° for 6 hours. After cooling, the reaction mixture was extracted with 3 x 20 ml of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate and dry-column flash chromatographed on 6 g of Kieselgel 60 H using different mixtures of dichloromethane and chloroform of continuously increasing the polarity of the eluents. After evaporation of the fractions to dryness *in vacuo*, the residue was triturated with 5 ml of ether and filtered to yield 0.30 g (60%) of 7-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[4,3-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**6j**), mp 131-133°; ir: ν C=N = 1628 and 1517 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.69 (s, 3H, SCH_3), 2.92 [t (J = 6.0 Hz), 2H, CH_2-8], 3.16 [t (J = 6.0 Hz), 2H, CH_2-9], 3.67 (s, 2H, CH_2-6), 3.75 (s, 2H, $PhCH_2$), 7.3-7.4 (m, 5H, PhH), 8.32 (s, 1H, CH-5); cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 32.8 (C-9), 49.9 (C-8), 52.2 (C-6), 62.2 ($PhCH_2$), 117.9 (C-5a), 127.6 (PhC-4'), 128.5 (PhC-2',6'), 129.0 (PhC-3',5'), 130.7 (C-5), 137.3 (PhC-1'), 155.0 (C-10a), 162.9 (C-9a), 169.1 (C-2), assignment confirmed by HSQC.

Anal. Calcd. for $C_{16}H_{17}N_5S$ (MW 311.40): C, 61.71; H, 5.50; N, 22.49; S, 10.30. Found: C, 61.58; H, 5.67; N, 22.36; S, 10.35.

8-Benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4k**).

To a stirred suspension of 21.83 g (0.06 mole) of 8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidin-5(10*H*)-one monohydrochloride (**3k•HCl**) [21] and 39.0 ml (64.4 g, 0.42 mole) of phosphorus oxychloride, 0.8 ml (0.79 g, 0.01 mole) of pyridine was added. The suspension was allowed to react at 80° with stirring for 27 hours. The suspension was cooled to 5°, diluted with 100 ml of ether, stirred for 30 minutes, the crystals were filtered and washed with ether to yield the crude salt. The salt was decomposed by pouring it with stirring into 300 g of cracked ice. To the mixture 150 ml of chloroform was added and made alkaline (*p*H = 8) with concentrated aqueous ammonium hydroxide solution. The insoluble crystals were filtered to yield 6.4 g of unreacted 8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5(10*H*)-one (**3k**). The phases of the mother liquor were separated and the aqueous phase was extracted with 2 x 25 ml of chloroform. The collected organic phases were dried over anhydrous sodium sulphate, filtered and evaporated to dryness *in vacuo*. The residue was dry-column flash chromatographed on 35 g of aluminium oxide G (eluents: different mixtures of *n*-hexane and chloroform of continuously increasing polarity) to yield after evaporation of the appropriate fractions and trituration with ether, 8.56 g (41%) of pure 8-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine (**4k**), mp 94-97° (lit [15] mp 98-101°). Taking into account the regenerated starting material the total yield of the above reaction was 60%; ir: ν C=N = 1612 and 1487 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.72 (s, 3H, SCH_3), 2.85 [t (J = 5.0 Hz), 2H, CH_2-7], 2.95 [t (J = 5.0 Hz), 2H, CH_2-6], 3.75 (s, 2H, $PhCH_2$), 3.82 (s, 2H, CH_2-9), 7.3-7.4 (m, 5H, PhH); cmr (deuteriochloroform): δ, ppm 13.9 (SCH_3), 25.3 (C-6), 48.8 (C-7), 58.4 (C-9), 61.9 ($PhCH_2$), 116.1 (C-5a), 127.6 (Ph-4'), 128.5 (Ph-2',6'), 129.0 (Ph-3',5'), 136.4 (C-5), 137.1 (Ph-1'), 154.7 (C-10a), 161.9 (C-9a), 169.6 (C-2), assignment confirmed by HSQC and HMBC; ms: (EI) M^+ = 345.

Anal. Calcd. for $C_{16}H_{16}ClN_5S$ (MW 345.85): C, 55.56; H, 4.66; N, 20.25; S, 9.27; Cl, 10.25. Found: C, 55.62; H, 4.75; N, 20.18; S, 9.30, Cl, 10.31.

N'-{8-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5k**), *N'*-{8-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5(10*H*)-hydrazone (**14k**) and Di-*p*-tolyl Disulfide 1,1-Dioxide (**16**).

To a solution of 2.98 g (0.016 mole) of *p*-toluenesulphonylhydrazide in 30 ml of chloroform, 2.77 g (0.008 mole) of 8-benzyl-5-chloro-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**4k**) was added at room temperature. The solution was refluxed for 24 hours. The crystals which precipitated were filtered and washed with chloroform to yield 0.5 g of *N'*-{8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5(10*H*)-hydrazone (**14k**) that after dry-column flash chromatography on 15 g of alumium oxide G (eluents: different mixtures of chloroform and methanol) decomposed at 225°; ir: ν C=N = 1675 and 1570 cm^{-1}; ms: (CI) $(M+1)^+$ = 651.

The mother liquor was evaporated to dryness to yield a product that crystallised upon standing overnight. This was triturated with

15 ml of acetonitrile, the crystals were filtered and washed with 5 ml of acetonitrile to yield 2.48 g of crude *N'*-{8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo-[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone hydrochloride (**5k•HCl**). Compound **5k•HCl** was suspended in 20 ml of chloroform. To the suspension, 2.0 ml (1.45 g, 0.0143 mole) of triethylamine was added and stirred for 5 minutes. The crystals which precipitated were filtered and washed with chloroform to yield 0.75 g (19%) of pure *N'*-{8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5k**), mp 189-192° dec. The mother liquor was extracted with 2 x 10 ml of water, dried over anhydrous sodium sulphate and evaporated to dryness to yield after trituration with ether and filtering an additonal 1.23 g (31%) of pure *N'*-{8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5k**), increasing the total yield of the reaction to 50%; ir: ν C=N = 1618 and 1580 cm^{-1}, ν SO_2N = 1352 and 1167 cm^{-1}; pmr (dimethyl-d_6 sulfoxide): δ, ppm 2.36 (s, 3H, $PhCH_3$), ~2.50 [m, xH (overlapped by dimethyl sulphoxide), CH_2-6], 2.58 (s, 3H, SCH_3), 2.65 (bs, 2H, CH_2-7), 3.33 (s, 2H, CH_2-9), 3.63 (s, 2H, $PhCH_2$), 7.2-7.4 (m, 7H, TsH- 3',5' and PhH)], 7.70 [d (J = 7.8 Hz), 2H, TsH-2',6'], 10.9 (bs, 1H, NH); ms: (CI) $(M+1)^+$ = 496.

Anal. Calcd. for $C_{23}H_{25}N_7O_2S_2$ (MW 495.60): C, 55.74; H, 5.08; N, 19.78; S, 12.94. Found: C, 55.76; H, 5.03; N, 19.74; S, 13.01.

The collected mother liquors were evaporated to dryness and the residue was flash vacuum chromatographed on 9 g of aluminium oxide G (eluents: different mixtures of *n*-hexane and ether) to yield after evaporation of the appropriate fractions to dryness *in vacuo* and triturating the residue with cyclohexane, 0.175 g (4%) of di-*p*-tolyl disulfide 1,1-dioxide [**16**, X = S-Ph(*p*-CH_3)], mp 76-78°, lit [13] mp 72-73.5°, lit [22] mp 76°; pmr (deuteriochloroform): δ, ppm 2.38 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.15-7.27 (m, 6H, PhH + TsH-3' and 5'), 7.46 [d (J = 8.4 Hz), 2H, TsH-2'and 6']; ms: (EI) M^+ = 278.

8-Benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]-triazolo[1,5-*a*]pyrimidine (**6k**).

To a solution of 2.12 g (0.02 mole) of sodium carbonate in 65 ml of water 1.04 g (0.0021 mole) of *N'*-{8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*][1,2,4]triazolo[1,5-*a*]pyrimidin-5-yl}-*p*-toluenesulphonylhydrazone (**5k**) was added and the mixture stirred at 140° for 2 hours. After cooling the reaction mixture was extracted with 3 x 20 ml of chloroform, the collected organic phases were dried over anhydrous sodium sulphate and dry-column flash chromatographed on 6 g of Kieselgel 60 H using chloroform as eluent. After evaporation of the appropriate fractions to dryness *in vacuo,* the residue (0.5 g) was chromatographed again on 10 g of aluminium oxide G (eluent ethyl acetate). Evaporation of the appropriate fractions to dryness *in vacuo* yielded 0.46 g of a crystalline product that was triturated with 5 ml of ether and filtered to yield 0.43 g (66%) of pure 8-benzyl-2-methylthio-6,7,8,9-tetrahydropyrido[3,4-*d*]-[1,2,4]triazolo[1,5-*a*]pyrimidine (**6k**), mp 153-156° dec; ir: ν C=N = 1622 and 1511 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.68 (s, 3H, SCH_3), 2.82 [t (J = 6.0 Hz), 2H, CH_2-7], 2.96 [t (J = 6.0 Hz), 2H, CH_2-6], 3.76 (s, 2H, $PhCH_2$), 3.84 (s, 2H, CH_2-9), 7.25-7.4 (m, 5H, PhH), 8.43 (s, 1H, CH-5); cmr (deuteriochloroform): δ, ppm 13.8 (SCH_3), 25.4 (C-6), 49.0 (C-7), 58.4 (C-9), 62.0 ($PhCH_2$), 117.4 (C-5a), 127.6 (PhC-4'), 128.5 (PhC-2',6'), 129.1 (PhC-3',5'), 132.5 (C-5), 137.0 (PhC-1'), 154.6 (C-10a), 162.1 (C-9a), 169.1 (C-2); ms: (EI) M^+ = 311.

Anal. Calcd. for $C_{16}H_{17}N_5S$ (MW 311.40): C, 61.71; H, 5.50; N, 22.49; S, 10.30. Found: C, 61.87; H, 5.65; N, 22.44; S, 10.28.

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[19] This compound was prepared from dimethyl *N*-cyanoimidodithiocarbonate and *N*-methyl-benzylamine in ether as the solvent to yield according to [20] the corresponding isothiourea derivative, mp 59-60° (ether); ir: ν CN = 2181 cm^{-1}; pmr (deuteriochloroform): δ, ppm 2.83 (s, 3H, SCH_3), 3.15 (s, 3H, NCH_3), 4.82 (s, 2H, $PhCH_2$), 7.2 (m, 2H, PhH-2',6'), 7.35 (m, 3H, PhH-3',4',5'). The isothiourea derivative was ring closed with hydrazine hydrate in ether as the solvent according to

"Method C" of [16] to yield the corresponding triazole, mp 161-162° (acetonitrile); pmr (dimethyl-d_6 sulphoxide): δ, ppm 2.72 (s, 3H, NCH_3), 4.44 (s, 2H, $PhCH_2$), 5.6 (bs, 2H, NH_2), 7.2-7.4 (m, 5H, PhH), 10.9 (bs, 1H, NH).

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[21] Compound **3k** was prepared, by reluxing 10.4 g (0.08 mole) of 5-amino-3-methylthio-1*H*-1,2,4-triazole [16] with 23.8 g (0.08 mole) of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride (Aldrich) in 25 ml of acetic acid for 8 hours. The reaction mixture crystallised upon cooling was diluted with 100 ml of acetonitrile, stirred for 2 hours, the crystals were filtered and washed with acetonitrile to yield 23.5 g (81%) of **3k•HCl**, mp 205-220° dec. An analytical sample was recrystallised from a 1:1 mixture of water and acetonitrile to yield a dihydrate **3k•HCl•2H$_2$O**, mp 175-190° dec; ir: ν C=O = 1706 cm^{-1}, ν C=N = 1649 and 1615 cm^{-1}, pmr (dimethyl-d_6 sulphoxide + deuterium oxide): δ, ppm 2.60 (s, 3H, SCH_3), 2.81 [t (J = 6.6 Hz), 2H, CH_2-6], 3.53 (m, 2H, CH_2-7), 4.23 (s, 2H, CH_2-9), 4.52 (s, 2H, $PhCH_2$), 7.50-7.54 (m, 3H, PhH-3',4',5'), 7.60-7.64 (m, 2H, PhH-2',6'); cmr (dimethyl-d_6 sulphoxide + deuterium oxide): δ, ppm 14.0 (SCH_3), 19.1 (C-6), 48.3 (C-9), 48.5 (C-7), 58.8 ($PhCH_2$), 104.1 (C-5a), 129.7 (C-3',5'), 129.8 (C-4'), 130.5 (C-1'), 131.8 (C-2',6'), 139.9 (C-9a), 150.9 (C-10a), 155.0 (C-5), 164.0 (C-2); ms: (EI) M^+ = 327; for **3k** base see [9].

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