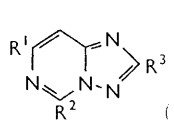
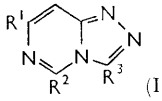
# 611. s-*Triazolopyrimidines. Part III.*[1] *Synthesis as Potential Therapeutic Agents*

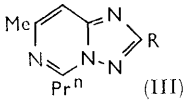
By W. Broadbent, G. W. Miller, and F. L. Rose

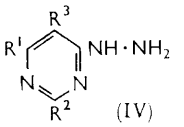
The interaction of carbon disulphide and 4-hydrazinopyrimidines, in a route to the corresponding mercapto-s-triazolopyrimidines (I and II; $R^3$ = SH), has been studied. The thiol group in series (I) has been converted into alkylsulphonyl, and sulphonyl chloride, and thence into sulphonamide.

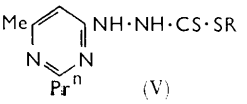
Parts I [2] and II [1] in this Series described the preparation of triazolo-[2,3-*c*]- and -[4,3-*c*]-pyrimidines (I) and (II) carrying for the most part either amino- or hydroxy-substituents ($R^3$) in the triazole ring, the former being of potential therapeutic interest as bronchodilatory agents, and the latter of value mainly as intermediates in their preparation. Synthesis was by ring-closure of the corresponding hydrazinopyrimidines (IV), it being supposed that compounds of type (II) were first formed to be followed in some cases by isomerisation to (I), depending upon the conditions. It seemed of interest to investigate the preparation

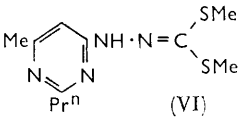

(I)

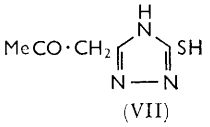

(II)


(III)


(IV)


(V)


(VI)


(VII)

of the analogous mercaptotriazolopyrimidines (I and II; $R^3$ = SH), in their own right as compounds having possible biological activity (cf. 6-mercaptopurine), and also as intermediates to such derivatives as the corresponding sulphonamides. As in the related studies, much of the experimental work centred upon the favoured hydrazinopyrimidine (IV; $R^1$ = Me, $R^2$ = $Pr^n$, $R^3$ = H), and the obvious route employing carbon disulphide to effect ring-closure. Condensation of these components occurred very rapidly at room temperature, for example in butanol, and a yellow acidic substance was precipitated. The same compound was formed when acetic acid was added to the solution obtained by stirring the hydrazine in cold aqueous potassium carbonate with carbon disulphide. It was thought to have the structure (V; R = H). On heating, decomposition occurred, even in solvents such as methanol, but in no case was the triazolopyrimidine formed. It was expected that success would attend similar experiments starting with the methyl derivative (V; R = Me), and methylation of (V; R = H) was attempted, but alkylation could not be stopped at the monomethyl stage. Always, two methyl groups were introduced into the molecule, and the use of one molecular proportion or less of the methylating agent (dimethyl sulphate or methyl iodide, in aqueous potassium carbonate) merely resulted in a proportion of unreacted thiocarbamate. By analogy with the known behaviour of the thiocarbamic acid derived from phenylhydrazine [3] in this respect, it seems that both sulphur atoms were capable of ready methylation, and that the product was (VI). The action of carbon disulphide on (IV; $R^1$ = Me, $R^2$ = $Pr^n$, $R^3$ = H) was examined under more vigorous conditions, for example, under pressure up to temperatures of 140°, with different proportions of the reactants, and in the presence of different solvents. At 130° in butanol, using two molecular proportions of carbon disulphide, an approximately 50% yield was obtained of a triazolopyrimidine whose analysis agreed with the structure (III; R = SH),

[1] Part II, G. W. Miller and F. L. Rose, preceding Paper.
[2] G. W. Miller and F. L. Rose, *J.*, 1963, 5642.
[3] E. Fischer, *Annalen*, 1877, **190**, 67.

and which from its absorption spectra was taken to have this structure rather than that of the isomeric triazolopyrimidine (II). The infrared spectrum was more consistent with the thione tautomer than with the mercaptotriazole formulated, although the latter representation will be used here for convenience.

Attempts were made to prepare the isomeric structures (II; $R^3 = SH$). Compound (IV; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = H$), with carbon disulphide in butanol in the presence of triethylamine, gave a condensation product having the same analytical composition as that described above but differing from it in physical properties, including its ultraviolet absorption, which to some extent resembled those of (II; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = NH_2$ and OH) belonging to the authentic triazolo[4,3-*c*]pyrimidine series. The infrared spectrum was consistent with the thione form. Treatment with aqueous sodium hydroxide gave (III; R = SH) so that the new compound might have the structure (II; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = SH$). Treatment of (III; R = SH) with boiling N-hydrochloric acid gave a strong smell of butyric acid, and a crystalline product which separated on cooling, was considered, from its physical and chemical properties, to be (VII), in line with the related 3-acetonyl-5-methyl-*s*-triazole obtained by similar degradation [2] of (I; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = NH_2$).

Attempted desulphurisation of (III; R = SH) to (III; R = H) using excess of Raney nickel in ethanol failed, giving instead a small yield of 6-amino-4-methyl-2-n-propylpyrimidine, which at least showed that the pyrimidine ring was intact in the mercaptotriazolopyrimidine. Alkylation reactions were more successful. They were conducted in the presence of aqueous or alcoholic alkali, and led, for example, to (III; R = SMe, SEt, $SPr^n$, and $S{\cdot}CH_2{\cdot}CO_2H$). The first two members of this series were also successfully oxidised in good yield, using ammonium persulphate in concentrated sulphuric acid, to the corresponding sulphones (III; $R = SO_2Me$ and $SO_2Et$). This oxidation led to a marked change in the ultraviolet absorption spectra, but the change was probably not inconsistent with that expected from the reversal of the electron shift at position 2. Anyway, evidence for oxidation at the thiol group came from the conversion of the supposed alkyl sulphones into the corresponding amino-derivatives, *e.g.*, (I; $R^1 = Me$, $R^2 = Pr^n$, $R^3 = NMe_2$ and $N[CH_2]_5$), identical with the compounds described earlier in this Series.

Finally, a series of 2-sulphonamides has been prepared. Compound (III; R = SH) suspended in a cooled chloroform–water mixture, with bromine or chlorine, gave directly the corresponding sulphonyl bromide or chloride, and these with the appropriate amines yielded (III; $R = SO_2{\cdot}NH_2$, $SO_2{\cdot}NHMe$, $SO_2{\cdot}NMe_2$, and $SO_2{\cdot}NHPh$). The sulphonyl chloride, when heated in dilute sodium carbonate, gave the corresponding sulphonic acid, isolated as its cetyltrimethylammonium salt.

## Experimental

*4-Methyl-2-n-propyl-6-2'-dithiocarboxyhydrazinopyrimidine* (V; R = H).—Carbon disulphide (7·6 g.) was added to a solution of 4-hydrazino-6-methyl-2-n-propylpyrimidine (8·3 g.) [2] and potassium carbonate (13·8 g.) in water (50 ml.), and the mixture was shaken in a loosely stoppered bottle for 1½ hr. at 20°. The solution was clarified with charcoal and adjusted to pH 7 by addition of acetic acid, when the *dithio-acid* separated as pale yellow prisms (10·2 g.), m. p. 128° (decomp.) (Found: C, 44·7; H, 5·8; N, 23·3; S, 25·8. $C_9H_{14}N_4S_2$ requires C, 44·6; H, 5·8; N, 23·15; S, 26·45%). Attempts to recrystallise the acid from hot solvents led to loss of carbon disulphide and re-formation of the hydrazine.

*4-Bis(methylthio)methylenehydrazino-6-methyl-2-n-propylpyrimidine* (VI).—The precipitate (5 g.) which formed when a solution of the dithio-acid (4 g.) and potassium carbonate (5 g.) in water (20 ml.) was shaken with methyl iodide (2·2 ml.) for 1 hr. at 20° was dissolved in water (30 ml.) and a small amount of hydrochloric acid. Addition of concentrated hydrochloric acid (10 ml.) gave the *hydrazone hydrochloride* (4 g.) as pale yellow prismatic needles, m. p. 121—123° (Found: C, 40·5; H, 6·3; N, 17·2; S, 19·4. $C_{11}H_{18}N_4S_2,HCl,H_2O$ requires C, 40·7; H, 6·45; N, 17·25; S, 19·7%), $\nu_{max.}$ 3370m, 1590s, 1538s, and 1495s cm.$^{-1}$.

2-*Mercapto*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine* (I; $R^1$ = Me, $R^2$ = $Pr^n$, $R^3$ = SH).—A mixture of 4-hydrazino-6-methyl-2-n-propylpyrimidine (8·3 g.), carbon disulphide (8 g.), and n-butanol (30 ml.) was heated and stirred in an autoclave at 130° for 15 hr. The crystalline precipitate (4·3 g.) of the crude *thiol* which formed was washed with methanol, dried at 50°, and recrystallised from acetic acid, m. p. 215—216° (Found: C, 52·4; H, 6·0; N, 26·9; S, 15·1. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·85; N, 26·9; S, 15·35%), $\nu_{max.}$ (KBr) 1650s, 1560s, 1520s, 1168s, and 985ms cm.$^{-1}$.

2-*Mercapto*-5-*n*-*propyl*-7-*trifluoromethyl*-s-*triazolo*[2,3-c]*pyrimidine*.—A mixture of 4-hydrazino-2-n-propyl-6-trifluoromethylpyrimidine (3·3 g.),[2] carbon disulphide (1·8 ml.), and n-butanol (6 ml.) was heated under reflux for 10 hr. The crystalline *mercaptotriazolopyrimidine* which precipitated on cooling (1·65 g.) recrystallised from butanol as very pale yellow plates, m. p. 112—113° (Found: C, 41·0; H, 3·5; N, 21·4. $C_9H_9F_3N_4S$ requires C, 41·2; H, 3·4; N, 21·4%), $\lambda_{max.}$ 201, 250, and 333 mμ (ε 9800, 20,800, and 3600).

2-*Methylmercapto*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—Dimethyl sulphate (2 ml.) was added to a stirred solution of the above thiol (4·2 g.) and sodium carbonate (4·3 g.) in water (45 ml.), at 20°. The crystalline precipitate which formed (4 g.) was recrystallised from light petroleum (b. p. 40—60°) to give the s-*methyl derivative* as colourless prismatic needles, m. p. 56—57° (Found: C, 54·0; H, 6·6; N, 24·7; S, 14·6. $C_{10}H_{14}N_4S$ requires C, 54·05; H, 6·3; N, 25·2; S, 14·4%), $\lambda_{max.}$ 237 and 285(infl.) mμ (ε 29,750 and 1900).

2-*Ethylmercapto*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—Similarly prepared from the thiol (2·9 g.) and diethyl sulphate (2 ml.), this product was obtained as colourless needles (3·05 g.), m. p. 41—42°. Distillation (b. p. 192°/21 mm.) gave material m. p. 42—43° (Found: C, 56·3; H, 6·9; N, 23·7. $C_{11}H_{16}N_4S$ requires C, 55·95; H, 6·8; N, 23·7%), $\lambda_{max.}$ 238 and 285(infl.) mμ (ε 32,330 and 2240).

7-*Methyl*-2-*methylsulphonyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—The above methylthio-compound (1·2 g.) was dissolved in concentrated sulphuric acid (5 ml.), and powdered ammonium persulphate (2·5 g.) was added gradually to the stirred solution kept at 20—25°. After 2½ hr. the acid mixture was poured on ice (30 g.). The crystalline *sulphone* (1·05 g.) crystallised from methanol in colourless needles (0·9 g.), m. p. 127—128° (Found: C, 47·0; H, 5·4; N, 22·0; S, 12·5. $C_{10}H_{14}N_4O_2S$ requires C, 47·25; H, 5·5; N, 22·05; S, 12·6%), $\lambda_{max.}$ 207 and 252 mμ (ε 14,700 and 7000), $\nu_{max.}$ (KBr) 1630vs, 1540ms, 1505ms, 1332vs, 1312vs, and 1151vs cm.$^{-1}$.

2-*Ethylsulphonyl*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—Similarly prepared from the ethylthio-derivative, the *product* crystallised from methanol in colourless prisms, m. p. 98—99° (Found: C, 49·0; H, 5·8; N, 20·8. $C_{11}H_{16}N_4O_2S$ requires C, 49·25; H, 5·95; N, 20·9%), $\lambda_{max.}$ 209, 255, and 283(infl.) mμ (ε 21,870, 7640, and 3560).

2-*Dimethylamino*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidine*.—The above methylsulphonyltriazolopyrimidine (0·25 g.) and dimethylamine (1·1 ml.; 20% sol. in ethanol) were heated together in a sealed tube at 120—130° for 16 hr. Water (2 ml.) was added to the cooled solution, and the *dimethylaminotriazolopyrimidine* (0·08 g.) crystallised as colourless needles, m. p. 92—93° (Found: C, 59·6; H, 8·0; N, 31·5. $C_{11}H_{17}N_5$ requires C, 60·4; H, 7·6; N, 32·0%), $\nu_{max.}$ (KBr) 2780s, 1575s, 1545vs, 1517s, 1505s, and 935s cm.$^{-1}$. A similar experiment using piperidine in place of dimethylamine gave the piperidinotriazolopyrimidine, m. p. 79—80° undepressed on admixture with the product described in Part II.[1]

7-*Methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidin*-2-*ylsulphonyl Chloride and the Corresponding Sulphonamide*.—2-Mercapto-7-methyl-5-n-propyl-*s*-triazolo[2,3-*c*]pyrimidine (10 g.) was suspended in a mixture of chloroform (100 ml.) and water (100 ml.). Chlorine (12 g.) was passed into the mixture with stirring at 10—15°. The chloroform layer was separated, dried over calcium chloride, and evaporated to dryness under reduced pressure. A little of the residual solid (14·5 g.) was crystallised from light petroleum (b. p. 80—100°) to give the *sulphonyl chloride* as colourless needles, m. p. 78—79° (Found: Cl, 13·0. $C_9H_{11}ClN_4O_2S$ requires Cl, 12·9%). A further sample of the sulphonyl chloride was warmed in dilute aqueous sodium carbonate until it dissolved. Addition of cetyltrimethylammonium bromide gave a precipitate of the base sulphonate, which was crystallised from water and used for spectroscopic investigation $\lambda_{max.}$ 206 and 260 mμ (ε 25,800 and 6300), $\nu_{max.}$ 1625vs, 1541ms, 1495s, 1227vs, 1050vs, and 664s cm.$^{-1}$. The remainder of the acid chloride was pulverised and added in portions to aqueous ammonia (*d* 0·88) (25 ml.) at 20—25°. Water (25 ml.) was added to the paste, followed by sufficient concentrated hydrochloric acid to give an acid reaction. The crude *sulphonamide* (9·5 g.), washed with water and recrystallised from water (charcoal), formed colourless glistening

plates, m. p. 176—177° (Found: C, 42·2; H, 5·2; N, 26·7. $C_9H_{13}N_5O_2S$ requires C, 42·35; H, 5·1; N, 27·45%), $\lambda_{max.}$ 208 and 257 mμ (ε 24,000 and 5900).

The NN-*dimethyl-sulphonamide* was precipitated when excess acetic acid was added to the solution formed by warming a suspension of the crude sulphonyl chloride (2 g.) in aqueous dimethylamine (40%; 20 ml.) and methanol (15 ml.). It crystallised from methanol as colourless needles, m. p. 144—145° (Found: C, 46·6; H, 5·5; N, 24·5. $C_{11}H_{17}N_5O_2S$ requires C, 46·65; H, 6·0; N, 24·75%), $\lambda_{max.}$ 207 and 254 mμ (ε 17,200 and 6600). Similarly prepared, the corresponding N-*methyl derivative* crystallised from methanol as colourless prisms, m. p. 158—159° (Found: C, 44·2; H, 5·5; N, 26·2. $C_{10}H_{15}N_5O_2S$ requires C, 44·6; H, 5·5; N, 26·0%), $\lambda_{max.}$ 207 and 256 mμ (ε 20,400 and 5900). Similarly, the corresponding *sulphonanilide* was formed by shaking the sulphonyl chloride (3 g.) with aniline (4·1 g.) in benzene (15 ml.). The residue (2·8 g.) left after evaporation of the solvent from the benzene layer and treatment with 5N-hydrochloric acid crystallised from butanol as cream coloured prisms, m. p. 195—196° (Found: C, 54·2; H, 5·3; N, 21·4. $C_{15}H_{17}N_5O_2S$ requires C, 54·4; H, 5·15; N, 21·15%).

7-*Methyl*-5-*n*-*propyl*-s-*triazolo*[2,3-c]*pyrimidin*-2-*ylsulphonyl Bromide*.—Prepared as was the sulphonyl chloride, from the thiol (1 g.) and bromine (1 ml. in 3 ml. chloroform) in chloroform and water, this *product* crystallised from light petroleum (b. p. 60—80°) as colourless prismatic needles, m. p. 82—83° (Found: C, 33·7; H, 3·6; N, 16·8. $C_9H_{11}BrN_4O_2S$ requires C, 33·85; H, 3·45; N, 17·55%).

3-*Mercapto*-7-*methyl*-5-*n*-*propyl*-s-*triazolo*[4,3-c]*pyrimidine* (II; $R^1$ = Me, $R^2$ = $Pr^n$, $R^3$ = SH).—Carbon disulphide (25 ml.) in n-butanol (12·5 ml.) was added to a hot solution of 6-hydrazino-4-methyl-2-n-propylpyrimidine (10 g.) in n-butanol (50 ml.). Triethylamine (17 ml.) was added rapidly and the mixture was heated under reflux on a steam-bath for 6 hr. The resulting yellow solution was evaporated under reduced pressure until precipitation commenced, and the suspension was cooled at 0°. The yellow solid was filtered off, washed with ethanol, and dried at 60°, to yield the *product* (2·55 g.), yellow needles, m. p. 204—206° (from ethanol) (Found: C, 51·6; H, 6·0; N, 26·9; S, 14·8. $C_9H_{12}N_4S$ requires C, 51·9; H, 5·8; N, 26·9; S, 15·35%), $\lambda_{max.}$ 238, 298, 347(infl.) mμ (ε 6000, 11,000, and 4000).

IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION,
ALDERLEY PARK, MACCLESFIELD, CHESHIRE. [*Received, December 31st,* 1964.]