Organic Heterocyclothiazenes. Part 8.[1] 7-Amino-1,3,5,2,4,6-trithiatriazepine and Related Compounds

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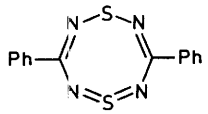
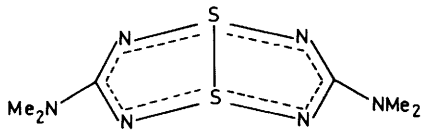
7-Aminotrithiatriazepine (**9**) is prepared from the 7-methoxycarbonyl derivative (**3**) through the corresponding hydrazide, acyl azide, and isocyanate. It is a stable crystalline compound, readily acylated and alkylated on the exocyclic nitrogen atom, but is very sensitive to aqueous acid. 7-Bromo- and 7-iodo-trithiatriazepine are prepared from the carboxylic acid by treatment with the halogen and mercuric oxide under u.v. irradiation; the halogen atoms are inert to nucleophilic displacement. The spectroscopic properties of trithiatriazepines, which are now fairly predictable, are summarised. Trithiatriazepine-7-carboxamide (**10**) is *N*-acetylated in high yield under mild neutral conditions with dinitrogen tetraoxide in acetonitrile.

In Part 7 of this series we reported the optimised formation of methyl 1,3,5,2,4,6-trithiatriazepine-7-carboxylate (**3**) from tetrasulphur tetranitride and dimethyl acetylenedicarboxylate, and conversion of the ester into the parent trithiatriazepine, a stable 10π aromatic system. Cycloaddition of alkynes to S_4N_4 remains the only route to trithiatriazepines. We now describe conversion of the ester (**3**) into the 7-amino compound (**9**) by the Curtius reaction, and conversion of the derived carboxylic acid into the 7-bromo and iodo derivatives by a modified Hunsdiecker reaction. Compound (**9**) is the first amine to be reported in this group of 10π heteroaromatic systems.

7-Aminotrithiatriazepine (**9**).—This compound was of particular interest since it would demonstrate the mutual interaction of a strongly electron releasing group and the electron rich heterocyclic ring. Electron releasing groups can destabilise such electron rich sulphur-nitrogen rings, as shown for example by replacement of the phenyl groups in the planar delocalised dithiatetrazocine (**1**) by dimethylamino groups to give the folded structure (**2**) with transannular S–S bonding.[2]



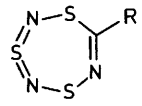
(**1**)



(**2**)

The 7-membered trithiatriazepine ring would clearly be much less able to achieve this compensating stabilisation.

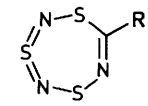
Since we wanted as mild a method as possible for conversion of the carboxylic acid derivatives into the amine, we chose a reaction *via* the acyl azide. Treatment of the methyl ester (**3**) with ethanolic hydrazine hydrate precipitated the analytically pure hydrazide (**4**) (90%), nitrosation of which with dinitrogen tetraoxide in acetonitrile [3] gave the acyl azide (**5**) as a crystalline solid, m.p. 75—76 °C (70%). Its i.r. spectrum exhibited characteristic absorptions at 2 145, 1 670, and 1 150 cm^{-1} for the azide, carbonyl, and N=S=N groups respectively. The azide (**5**) was sensitive to aqueous acid and to adsorption on silica but in spite of this it could be purified by rapid chromatography. In addition to the acyl azide (**5**), a small quantity of trithiatriazepine-7-carboxylic acid and two other minor products were isolated from the nitrosation reaction. These were the amide (**10**) (8%) and the imide (**11**) (8%). We suspected that the imide was



R

(**3**) CO_2Me
(**4**) $CONHNH_2$
(**5**) CON_3
(**6**) N=C=O
(**7**) $NHCONHCH_2Ph$
(**8**) $NHCO_2Me$
(**9**) NH_2

being formed *via* the amide; if the reaction was worked up as soon as all the hydrazide (**4**) had dissolved, very little imide was formed. If the reaction mixture was stirred for 10 min after complete dissolution of the hydrazide, the imide (15%) but virtually no amide was present. Both these minor products were prepared independently, the amide (**10**) by quantitative aminolysis of the ester (**3**) with methanolic ammonia, and the imide (**11**) (90%) by subjecting amide (**10**) to the nitrosation conditions (N_2O_4 in MeCN from −20 to +20 °C). This very



R

(**10**) $CONH_2$
(**11**) CONHAc
(**12**) $CO\overset{+}{N}{\equiv}C{-}Me$

mild acetylation of an amide, under neutral conditions, may have wider synthetic use. A possible reaction pathway is diazotisation of the primary amide and nucleophilic displacement of dinitrogen by the solvent to form the *N*-acyl nitrilium salt (**12**) which is hydrated on work up to give the imide (**11**).

Returning to our main theme, heating the acyl azide (**5**) for 1 h in refluxing benzene gave the isocyanate (**6**) quantitatively; this had a strong, characteristic isocyanate absorption at 2 240 cm^{-1} in the i.r. spectrum. Treatment of the benzene solution of the isocyanate with benzylamine caused immediate precipitation of the unsymmetrical urea (**7**) (92%). Heating the acyl azide in a refluxing mixture of equal volumes of methanol and benzene

gave the urethane (**8**) (83%) as expected. Hydrolysis of isocyanates to amines, *via* the carbamic acid, is usually best in concentrated acid or base as this reduces competing formation of the symmetrical urea.[4] As trithiatriazepines are base sensitive[5] we tried acidic hydrolysis (5M HCl, THF, 20 °C, 10 min) but this led to complete decomposition.

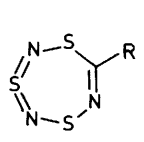
An attempt to record the u.v. spectrum of the isocyanate (**6**) in ethanol (for comparison with other trithiazepines) gave the spectrum of the urethane (**8**). This very rapid conversion of isocyanate into urethane at room temperature suggested the possibility of neutral hydrolysis of the isocyanate. Indeed, when the azide (**5**) was heated in a rapidly stirred mixture of benzene and water the amine (**9**) was formed (82%) as yellow crystals, m.p. 55—56 °C. Although the surface of the crystals darkened rapidly in air, the bulk material was stable at room temperature. The formula $CH_2N_4S_3$, from elemental analysis, was confirmed by the mass spectrum which also showed fragments for the loss of NS and at 46 (NS), 78 (NS_2), and 124 (N_2S_3), indicating that the heterocyclic ring was intact. The presence of the amino group was indicated by a broad resonance centred at 4.3 p.p.m. in the ^1H n.m.r. spectrum and by absorptions at 3 460 and 3 370 cm^{-1} in the i.r. spectrum, which also exhibited a band at 1 145 cm^{-1} assigned to the asymmetric N=S=N stretching vibration. The u.v. spectrum had a long wavelength absorption at $\lambda_{max.}$ 396 nm; the ring carbon atom resonated at 160.5 p.p.m., 15.5 p.p.m. downfield of the parent trithiatriazepine ^{13}C signal.

The amine (**9**) was very sensitive to aqueous acid, explaining its non-isolation from acidic hydrolysis of the isocyanate.

The best method for converting the hydrazide (**4**) into the amine (**9**) was to work up the nitrosation reaction mixture as soon as the hydrazide had dissolved. This gave a mixture of the azide (**5**) and the much less soluble amide (**10**); the azide could be preferentially dissolved in benzene and, with added water, converted directly into the amine, without involving chromatography of the sensitive azide.

Having found that amine (**9**) was isolable and stable, we could study the chemical interaction between the amino group and the electron-rich ring. The chemistry of 2-aminopyrimidine is dominated by its amidine reactivity.[6] Pyridines are less electron deficient than pyrimidines, and 2-aminopyridine reacts at the exocyclic nitrogen (*e.g.* in acylation) as well as at the ring nitrogen (*e.g.* in alkylation). If the trithiatriazepine ring is sufficiently electron-rich to suppress this amidine type delocalisation, electrophilic attack would occur exclusively at the exocyclic nitrogen, and so far this is what we have observed.

The amine was converted quantitatively into the acetamide (**13**) with a mixture of acetic acid and acetic anhydride. Structure (**13**) was based on elemental analysis, the mass



R

(**13**) NHAc
(**14**) NAc_2
(**15**) NMeR

spectrum, which showed the loss of ketene and the presence of fragments NS, NS_2, and N_2S_3, and its other spectroscopic properties which confirmed the retention of the trithiatriazepine ring. The u.v. spectra of the parent trithiatriazepine and the amine (**9**) exhibit long wavelength maxima at 327 and 396 nm respectively; the large shift caused by introduction of the amino group is almost nullified in the acetamido compound ($\lambda_{max.}$ 339 nm), as is to be expected. The same trend is observed with pyridine and its 2-amino and 2-acetamido derivatives. The u.v. and other spectroscopic properties of acetamide (**13**) are very similar to the closely related urethane (**8**).

Treatment of the acetamide (**13**) with acetyl chloride in pyridine, with 4-dimethylaminopyridine as catalyst, gave the diacetylimidotrithiatriazepine (**14**) (53%). Accurate mass measurement indicated the molecular formula $C_5H_6N_4O_2S_3$ and the low resolution spectrum showed the loss of ketene (twice) and the presence of NS, NS_2, and N_2S_3. Compared with the mono-acetyl derivative (**13**), the long wavelength u.v. absorption was shifted to slightly shorter wavelengths (329 nm) as expected. The 500 MHz ^1H n.m.r. spectrum showed that the two methyl groups were identical, thus confirming structures (**14**) and, by implication, (**13**).

Treatment of the amine (**9**) with iodomethane and potassium hydrogen carbonate in methanol at room temperature for 8 days gave the orange mono methyl derivative (**15**; R = H) (26%), which was less polar than the primary amine. Analysis of the u.v. spectrum indicated that substitutuion had again occurred on the exocyclic nitrogen. The u.v. absorption ($\lambda_{max.}$ 396 nm) for the starting amine was shifted to longer wavelengths (413 nm) on monomethylation, comparable to that observed with aniline and *N*-methylaniline and with 2-amino and 2-methylamino pyridine; in contrast, 2-imino-1-methylpyridine has a very different u.v. spectrum. The NH proton resonated at 4.45 p.p.m. in the n.m.r. and absorbed at 3 425 cm^{-1} in the i.r. spectrum.

From the same methylation reaction another, less polar, product was isolated as a yellow oil, and shown by its mass spectrum to be a dimethyl compound (14%). Longer reaction times (15 days) gave more (28%) of this and less (10%) of the monomethylated amine. The dimethyl compound is tentatively assigned the tertiary amine structure (**15**; R = Me), mainly on the basis of its highfield ^1H n.m.r. spectrum (250 MHz) which showed only one resonance, at 2.95 p.p.m.; and the i.r. absorption at 1 140 cm^{-1} which is characteristic of the N=S=N stretching vibration in trithiatriazepines. However the u.v. spectrum was sufficiently different from that of the primary and secondary amines to cast some doubt on the dimethylamino structure.

Although the primary amine (**9**) was very sensitive to dilute aqueous acid, it was possible under rigorously dry conditions to prepare its hydrochloride salt. The salt was precipitated from ether with dry hydrogen chloride gas; it was instantly destroyed on contact with water, and it dissociated back to the amine when dissolved in organic solvents.

Attempted cyclisation of the amine (**9**) with oxalyl chloride, phenacyl bromide, and dimethyl acetylenedicarboxylate were unsuccessful, also indicating a lack of amidine reactivity.

We tried, unsuccessfully, to convert the amine into 7-hydroxytrithiatriazepine since it would be interesting to know whether the 7-hydroxy compound existed in this phenolic form or in the more usual oxo tautomer. 2-Aminopyridine is converted into 2-pyridone by diazotisation and hydrolysis, but this failed with the amine (**9**). Aqueous methods using sodium nitrite and mineral acids failed because of the instability of the amine to aqueous acid, and aprotic diazotisation gave recovered starting material (with N_2O_4 and triethylamine) or caused extensive decomposition (with $NO^+BF_4^-$ in MeCN or $MeCO_2H$).

7-Halogenotrithiatriazepines.—These compounds are not readily available from the parent ring since, unlike trithiadiazepine, this is resistant to electrophilic halogenation.[1] However they could be prepared from the carboxylic acid by modified Hunsdiecker reactions. The best method for the bromo compound proved to be that of Meyers and Fleming[7] for aromatic carboxylic acids, involving tungsten lamp irradiation of the acid, bromine, and mercuric oxide in tetrachloromethane. However, 7-bromotrithiatriazepine is

Table 1. U.v. absorption in ethanol of trithiatriazepines bearing electron withdrawing groups

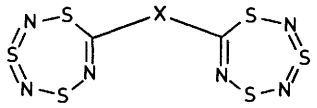
7-Substituent	$\lambda_{max.}$/ nm (log ε)	$\lambda_{max.}$/ nm (log ε)	$\Delta\lambda_{max.}$/ nm
O_2N	277 (3.75)	345 (3.11)	68
N_3CO	274 (4.08)	332 (3.49)	58
Ac	273 (4.10)	340 (3.40)	67
OHC	268 (—)	334 (—)	66
H_2NHNCO	267 (4.11)	332 (3.57)	65
MeO_2C	266 (4.09)	332 (3.40)	66
H_2NCO	266 (4.10)	331 (3.45)	65
AcNHCO	266 (4.25)	328 (3.56)	62
HO_2C	264 (4.27)	332 (3.60)	68

sensitive to irradiation and the best yield (52%) was obtained by regular extraction of the reaction mixture. Iodinative decarboxylation is much less well known, but simply replacing bromine by iodine in this procedure gave 7-iodotrithiatriazepine (33%).

With the bromo and iodo compounds available we wished to see if we could displace the halogen with nucleophiles, especially since it had just been found that the bromine in 6-bromotrithiadiazepine could be readily displaced by nucleophiles under mild conditions.[8] However, despite the (presumed) additional activation provided by the adjacent nitrogen atom, no displacement of the 7-halogenotrithiatriazepines was observed under the same or more vigorous conditions than those used with 6-bromotrithiadiazepine. The halogenotrithiatriazepines were recovered in high yield, for example, after treatment with silver acetate, silver benzoate, and copper benzoate in boiling xylene, with lithium di-isopropylamide or morpholide in THF from −78 to 20 °C, and with an excess of aqueous ammonia in THF at 20 °C. The inertness of these halogeno compounds compared with the reactive 6-bromotrithiadiazepine strongly suggests that the reactions of the latter do not proceed by direct nucleophilic aromatic displacement.

Since we could not prepare the acetoxy derivative in this way, we attempted to prepare it by Baeyer-Villiger oxidation of 7-acetyltrithiatriazepine, but this proved to be resistant to vigorous conditions [*m*-chloroperbenzoic acid (20 equiv.), boiling dichloromethane, 3 days; trifluoroperacetic acid, boiling 1,2-dichloroethane]. These reactions emphasise the stability of the heterocyclic ring towards oxidation.

Finally we prepared the symmetrical anhydride (**16**) in the hope that this could be converted into the ester (**17**) (and hence



(**16**) –CO–O–CO–
(**17**) –CO–O–

into 7-hydroxytrithiatriazepine) by a modification[9] of the Simonini reaction, analogous to the modified Hunsdiecker reaction above. Treatment of the carboxylic acid with a 1:1 mixture of trifluoroacetic anhydride and benzene gave the anhydride (**16**) (94%) as a crystalline solid; a reactive anhydride was needed to avoid the ready decarboxylation of the acid. The symmetrical anhydride structure was supported by i.r. and mass spectroscopic evidence. The compound rapidly hydrolysed on a silica plate, and treatment with an aqueous silica slurry cleanly regenerated the starting acid. However, treatment of the anhydride with mercuric oxide and iodine in boiling 1,2-dichloroethane[9] did not produce the required ester (**17**).

Spectroscopy of Trithiatriazepines.—Spectroscopic properties of the trithiatriazepines reported here and in Part 7[1] proved to be uniform and predictable, greatly assisting structure determination. There were also strong similarities with the spectral properties of the closely related trithiadiazepines.

In their u.v. spectra trithiatriazepines fall into two broad classes: (i) those bearing an electron withdrawing substituent and (ii) those bearing a substituent having a lone pair of electrons on the atom adjacent to the ring. The first has simple two peak spectra, with one maximum near 270 nm and log ε *ca.* 4, and other near 335 nm with log ε in the range 3.1—3.6 (see Table 1). The second group has more complex four band spectra, with $\lambda_{max.}$(log ε) of *ca.* 220 nm (4), 250 nm (4), 290 mn (3.5) often as a shoulder, and the longest wavelength absorption of very variable $\lambda_{max.}$ 330—410 nm (3.5) (see Table 2).

The mass spectra of trithiatriazepines almost always show a strong molecular ion and a simple characteristic fragmentation pattern. Like trithiadiazepines they give abundant ions of *m/z* 124 (N_2S_3). In contrast with the diazepines however the triazepines do not readily lose an NS fragment from the molecular ion; those with an electron withdrawing substituent show no trace of an (M^+ − NS) fragment, but those with lone pair substituents (NMe_2, NHMe, NH_2, I) adjacent to the ring do.

In the i.r. region all trithiatriazepines absorb in the range 1 150—1 135 cm^{-1} in $CHCl_3$ or CCl_4 solution, and this is attributed to asymmetric stretching vibration of the N=S=N unit; trithiadiazepines show the same absorption.[10]

The ring carbon atoms of the aromatic trithiatriazepines and trithiadiazepines resonate at low field (130—160 p.p.m.), indicative of a diamagnetic ring current. The former resonate at slightly lower field than the latter, presumably because of the deshielding effect of the extra imine type nitrogen atom.

Experimental

For general points see ref. 5. Light petroleum refers to the fraction, b.p. 40—60 °C.

1,3,5,2,4,6-*Trithiatriazepine-7-carbohydrazide* (**4**).—Methyl 1,3,5,2,4,6-trithiatriazepine-7-carboxylate (**3**) (1.51 g, 7.22 mmol) in ethanol (150 ml) was treated with hydrazine monohydrate (1.4 ml) and stirred at 30 °C for 1 h. 1,3,5,2,4,6-Trithiatriazepine-7-carboxyhydrazide (**4**) (1.355 g, 90%) was collected by filtration, washed with ethanol (2 × 20 ml), and dried *in vacuo*, m.p. 218—220 °C (Found: C, 11.3; H, 1.5; N, 33.4; S, 46.0. $C_2H_3N_5OS_3$ requires C, 11.5; H, 1.45; N, 33.5; S, 46.2%); $\lambda_{max.}$(EtOH) 244 (log ε 3.92), 267 (4.11), and 332nm (3.57); $\nu_{max.}$(KBr) 3 660—3 060br ($NHNH_2$), 1 710 and 1 670 (C=O and C=N), 1 435, 1 325, 1 300, 1 170, 1 140 (NSN), 1 070, 990, 960, 920, 800, 710, 660, and 640 cm^{-1}; δ_H[250 MHz; $(CD_3)_2SO$] 4.60 (br, $NHNH_2$); *m/z* (170 °C) 211 (M^+ + 2, 14%), 209 (M^+, 100), 178 (M^+ − $NHNH_2$, 14), 163 (M^+ − NS, 14), 150 (M^+ − $CONHNH_2$, 27), 124 (N_2S_3, 9), 78 (NS_2, 88), and 46 (NS, 58).

1,3,5,2,4,6-*Trithiatriazepine-7-carbonyl Azide* (**5**).—The hydrazide (**4**) (450 mg, 2.15 mmol) in acetonitrile (15 ml) was treated with dinitrogen tetraoxide (0.4 g, 4.35 mmol) in tetrachloromethane (2.8 ml) at −20 °C for 5 min. Ether (20 ml) was added and the solution obtained, was extracted twice with aqueous $NaHCO_3$, pre-adsorbed onto silica, and separated by dry flash chromatography on silica (60 g). Dichloromethane in light petroleum (60—80%) eluted the *title compound* (**5**) (330 mg, 70%) as needles, m.p. 75—76 °C (light petroleum) (Found: C, 11.5; N, 37.6%; M^+, 219.9297. $C_2N_6OS_3$ requires C, 10.9; N, 38.2%; *M*, 219.9296); $\lambda_{max.}$(EtOH) 274 (log ε 4.08) and 332 nm (3.49); $\nu_{max.}$(CCl_4) 2 145s (N_3), 1 670s (CO), 1 215s, 1 150m (NSN), 900m, 665w, and 630w cm^{-1}; *m/z* (80 °C) 222 (M^+ + 2, 10%), 220 (M^+, 71), 192 (M^+ − N_2, 12), 124 (N_2S_3, 3), 78 (NS_2,

Table 2. U.v. absorption [$\lambda_{max.}$/nm (log ε)] values for trithiatriazepines in ethanol bearing an atom with a lone pair of electrons

7-Substituent	Band 1	Band 2	Band 3	Band 4
MeNH	215 (—)[a]	262 (3.92)	290sh (3.61)	413 (3.49)
H_2N	217 (—)[a]	258 (4.01)	290sh (3.67)	396 (3.69)
AcNH[b]	227 (3.86)	265 (3.92)	290sh (3.31)	339 (3.41)
BnNHCONH	obscured	254 (3.98)	290sh (3.29)	337 (3.45)
MeOCONH	225 (4.07)	250 (4.05)	293 (3.45)	335 (3.69)
Ac_2N	229 (4.01)	248 (4.01)	295 (3.29)	329 (3.62)
Br	223 (4.13)	252 (3.84)	280 (3.60)	339 (3.60)
I	230 (4.32)	253 (4.00)	288 (3.53)	343 (3.58)

[a] U.v. data in ethanol are unreliable below 220 nm. [b] Also exhibits a shoulder at 355 nm (log ε 3.35).

100), and 46 (NS, 73). Ethyl acetate in dichloromethane (60—80%) eluted the *imide* (**11**) (32 mg, 8%) as needles, m.p. 151.5—153.5 °C (dichloromethane) (Found: C, 20.5; H, 1.6; N, 23.5. $C_4H_4N_4O_2S_3$ requires C, 20.3; H, 1.7; N, 23.7%); $\lambda_{max.}$(EtOH) 266 (log ε 4.25) and 328 nm (3.56); $\nu_{max.}$($CHCl_3$) 3 360w (NH), 1 720m (CO), 1 698s (CO), 1 478s, 1 378w, 1 264m, 1 179w, 1 155w (NSN), 1 017w, and 989w cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.59 (3 H, s, CH_3CO) and 9.67 (1 H, s, br, NH); *m/z* (150 °C) 238 (M^+ + 2, 4.4%), 236 (M^+, 30), 124 (N_2S_3, 99), 78 (NS_2, 100), 46 (NS, 33), and 43 (Ac, 94). Ethyl acetate in dichloromethane (90—100%) eluted 1,3,5,2,4,6-*trithiatriazepine*-7-*carboxamide* (**10**) (33 mg, 8%), m.p. 180 °C (ethyl acetate–dichloromethane) (Found: C, 12.6; H, 1.0; N, 28.6. $C_2H_2N_4OS_3$ requires C, 12.4; H, 1.0; N, 28.8%); $\lambda_{max.}$(EtOH) 266 (log ε 4.10) and 331 nm (3.46); $\nu_{max.}$($CHCl_3$) 3 519w and 3 402w (NH), 1 680s (CO), 1 563m, 1 369w, 1 153w (NSN), and 974w cm^{-1}; δ_H(250 MHz; $CDCl_3$) 5.62 (s, br, NH_2); *m/z* (170 °C) 196 (M^+ + 2, 14.5), 194 (M^+, 100), 124 (N_2S_3, 17), 78 (NS_2, 97), and 46 (NS, 41).

1,3,5,2,4,6-*Trithiatriazepine*-7-*carboxamide* (**10**).—Methyl trithiatriazepine-7-carboxylate (**3**) (50 mg, 0.24 mmol), methanol (15 ml), and saturated methanolic ammonia (10 ml) were stirred for 1.5 h at 20 °C. Evaporation of the solvent gave the title compound (45 mg, 97%) identical with material described above.

N-*Acetyl*-1,3,5,2,4,6-*trithiatriazepine*-7-*carboxyimide* (**11**).—The amide (**10**) (10 mg, 0.052 mmol) in acetonitrile (1 ml) was treated with dinitrogen tetraoxide (15 μl, 0.103 mmol) and stirred at −20 °C. After 10 min t.l.c. indicated the reaction was 70% complete. The mixture was stirred for 20 min at 20 °C. Ether (10 ml) was added and the solution washed with aqueous sodium hydrogen carbonate (twice), followed by water, dried (Na_2SO_4), and evaporated to give the imide (**11**) (11.0 mg, 90%) identical with that obtained above.

7-*Isocyanato*-1,3,5,2,4,6-*trithiatriazepine* (**6**).—The acyl azide (**5**) (20 mg, 0.091 mmol) was heated in refluxing benzene (5 ml) for 1 h. Evaporation of the benzene gave the *isocyanate* (**6**) (18 mg, 100%) as a low melting solid (Found: M^+, 191.9233. $C_2N_4OS_3$ requires *M*, 191.9234); $\lambda_{max.}$(EtOH) 265 and 330 nm; $\nu_{max.}$(CCl_4) 2 240s (NCO), 1 505w, 1 145w (NSN), 1 020w, 960m, and 940w cm^{-1}; *m/z* (100 °C) 194 (M^+ + 2, 12%), 192 (M^+, 84), 124 (N_2S_3, 14), 78 (NS_2, 100), and 46 (NS, 100).

N-*Benzyl*-N′-1,3,5,2,4,6-*trithiatriazepin*-7-*ylurea* (**7**).—Benzylamine (10 μl, 0.092 mmol) was added to a solution of the isocyanate (**6**) (17.5 mg, 0.091 mmol) in benzene (13 ml). The *title compound* (**7**) (25 mg, 92%) was collected by filtration and washed with benzene, m.p. 196 °C (ethanol) (Found: C, 35.7; H, 2.9. $C_9H_9N_5OS_3$ requires C, 36.1; H, 3.0%); $\lambda_{max.}$(EtOH) 254 (log ε 3.98), 290sh (3.29), and 337 nm (3.45); $\nu_{max.}$(KBr) 3 316s and 3 241m (NH), 1 646s (CO), 1 565s, 1 499s, 1 466m, 1 456m, 1 248m, 1 190m, 1 133m, 1 072m, 966m, 935m, 746m, 696s, 656s, and 605m cm^{-1}; δ_H[250 MHz; $(CD_3)_2CO$] 4.42 (2 H, s, CH_2), 6.74 [1 H, s br, NH], 7.33 (5 H, m, Ph), and 8.80 [1 H, s br, NH]; *m/z* (200 °C) 299 (M^+, 1%), 192 (13), 166 (23), 133 (51), 124 (N_2S_3, 21), 107 (26), 106 (53), 91 (100), 78 (NS_2, 90), and 46 (NS, 71).

Methyl 1,3,5,2,4,6-*Trithiatriazepin*-7-*ylcarbamate* (**8**).—The acyl azide (**5**) (20 mg, 0.091 mmol), benzene (5 ml), and methanol (1 ml) were heated at reflux for 1 h. The reaction mixture was pre-adsorbed onto silica and separated by dry flash chromatography. Dichloromethane eluted the *title compound* (**8**) (17 mg, 83%) as pale yellow needles, m.p. 111 °C (Found: C, 16.1; H, 1.7; N, 24.8. $C_3H_4N_4O_2S_3$ requires C, 16.1; H, 1.8; N, 25.0%); $\lambda_{max.}$(EtOH) 225 (log ε 4.07), 250 (4.05), 293 (3.45), and 335 nm (3.69); $\nu_{max.}$(CCl_4) 3 496m (NH), 2 958w, 1 756s, 1 743s, 1 724m, 1 532m, 1 459m, 1 424w, 1 316w, 1 224s, 1 141w (NSN), 1066w, and 665w cm^{-1}; δ_H(250 MHz; $CDCl_3$) 3.80 (3 H, s, CH_3) and 6.98 [1 H, s br, NH]; *m/z* (170 °C) 224 (M^+, 20), 124 (N_2S_3, 20), 78 (NS_2, 100), and 46 (NS, 43).

7-*Amino*-1,3,5,2,4,6-*trithiatriazepine* (**9**).—The acyl azide (**5**) (400 mg, 1.82 mmol), benzene (40 ml), and water (10 ml) were heated at reflux with rapid stirring for 3 h. The layers were separated and the aqueous layer extracted with benzene (3 × 20 ml). The combined benzene portions were filtered, dried (Na_2SO_4), and evaporated to give 7-*amino*-1,3,5,2,4,6-*trithiatriazepine* (**9**) (250 mg, 82%) as a yellow crystalline solid, m.p. 55—56 °C (Found: C, 7.2; H, 1.2; N, 33.3. $CH_2N_4S_3$ requires C, 7.2; H, 1.2; N, 33.7%); $\lambda_{max.}$(EtOH) 258 (log ε 4.01), 290sh (3.67), and 396 nm (3.62); $\nu_{max.}$(CCl_4) 3 460 and 3 370 (NH_2), 1 590, 1 520, 1 230, 1 145 (NSN), and 660 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 4.3 [s br, NH_2]; δ(62.9 MHz; $CDCl_3$) 160.5; *m/z* (80 °C) 168 (M^+ + 2, 3.5%), 166 (M^+, 25), 124 (N_2S_3, 53), 120 (M^+ − NS, 18), 78 (NS_2, 100), and 46 (NS, 80).

7-*Acetamido*-1,3,5,2,4,6-*trithiatriazepine* (**13**).—7-Aminotrithiatriazepine (**9**) (10 mg, 0.06 mmol), acetic acid (1 ml), and acetic anhydride (1 ml) were stirred at 20 °C for 10 min after which time the yellow colour of the starting amine had disappeared. The reaction mixture was evaporated and either recrystallised (light petroleum–dichloromethane) or pre-adsorbed onto silica and subjected to dry flash chromatography on silica (5 g). Ethyl acetate in dichloromethane (40—50%) eluted the highly crystalline 7-*acetamido*-1,3,5,2,4,6-*trithiatriazepine* (**13**) (12.8 mg, 100%), m.p. 168.5—169 °C (light petroleum–dichloromethane) (Found: C, 17.6; H, 1.9; N, 26.6. $C_3H_4N_4OS_3$ requires C, 17.3; H, 1.9; N, 26.9%); $\lambda_{max.}$(EtOH) 227 (log ε 3.86), 265 (3.92), 295sh (3.31), 339 (3.41), and 355sh nm (3.35); $\nu_{max.}$($CHCl_3$) 3 408m and 3 248br (NH), 1 704s and 1 684s (C=O and C=N), 1 531s, 1 470m, 1 370m, 1 254m, 1 150m (NSN), 1 022w, and 974w cm^{-1}; $\nu_{max.}$(KBr) 3 453br, 3 215sh, 3 184s, 3 084m, 3 025m, 1 635s, 1 567s, 1 497m, 1 435m, 1 375m, 1 289s, 1 171m, 1 146s, 1 027s, 979m, 868m, 778m, 689m, 667s, 621m, and 604m cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.27 (3 H, s, Ac) and 7.93 [1 H, s br, NH]; *m/z* (150 °C) 210 (M^+ + 2, 8.4%), 208 (M^+, 60), 166 (M^+ − ketene, 8), 124 (N_2S_3, 20), 78 (NS_2, 100), 46 (NS, 33), and 43 (Ac, 73).

7-(*Diacetylamino*)-1,3,5,2,4,6-*trithiatriazepine* (**14**).—7-Acetamidotrithiatriazepine (**13**) (7.2 mg, 0.035 mmol), acetyl chloride (5 μl, 0.07 mmol), pyridine (1 ml), and 4-(dimethylamino)pyridine (1 crystal) were stirred at room temperature for 2.5 h. Acetyl chloride (5 μl, 0.07 mmol) was added and the mixture stirred for a further 3 h. The solvents were evaporated and the residue pre-adsorbed onto silica (5 g) and separated by

dry flash column chromatography. Dichloromethane in light petroleum (90—100%) eluted 7-(*diacetylamino*)-1,3,5,2,4,6-*trithiatriazepine* (**14**) (4.6 mg, 53%) as a colourless oil (Found: M^+, 249.9648. $C_5H_6N_4O_2S_3$ requires M, 249.9652); $\lambda_{max.}$(EtOH) 229 (log ε 4.01), 248 (4.00), 300sh (3.29), and 329 nm (3.62); $\nu_{max.}$(CCl_4) 2 928w, 1 734s (CO), 1 507w, 1 419w, 1 368m, 1 249m, 1 211s, 1 145w (NSN), 1 039w, 1 001w, 974w, and 932w cm^{-1}; δ_H(500 MHz; $CDCl_3$) 2.396; *m/z* (150 °C) 250 (M^+, 18%), 208 (M^+ − ketene, 84), 166 [M^+ − (2 × ketene), 8], 162 [M^+ − (ketene + NS) 9], 124 (N_2S_3, 28), 120 [M^+ − (2 × ketene + NS), 5], 78 (NS_2, 100), 46 (NS, 21), and 43 (Ac, 99). Ethyl acetate in dichloromethane eluted unchanged starting material (3.00 mg, 42%).

Treatment of 7-Aminotrithiatriazepine (**9**) *with Iodomethane.*—7-Aminotrithiatriazepine (**9**) (25 mg, 0.15 mmol), potassium hydrogen carbonate (0.2 g), iodomethane (0.2 ml), and methanol (2 ml) were stirred at 20 °C for 4 days. Potassium hydrogen carbonate (0.2 g), iodomethane (0.2 ml), and methanol (2 ml) were added and the reaction mixture was stirred for a further 4 days. It was then filtered and the solid washed with dichloromethane. The filtrate and washings were combined, pre-adsorbed onto silica and separated by dry flash chromatography on silica (10 g). Dichloromethane in light petroleum (30—35%) eluted 7-*dimethylamino*-1,3,5,2,4,6-*trithiatriazepine* (**15**; R = Me) (4 mg, 14%) as a yellow oil; $\lambda_{max.}$(EtOH) 285 and 350 nm; $\nu_{max.}$(CCl_4) 2 960—2 800m, 1 510m, 1 450m, 1 140m (NSN), 1 080s, 965m, 930m, 880m, and 660s cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.95 (s); *m/z* (130 °C) 196 (M^+ + 2, 4.1%), 194 (M^+, 29), 148 (M^+ − NS, 6), 124 (N_2S_3, 39), 78 (NS_2, 100), and 46 (NS, 40). Dichloromethane in light petroleum (45—50%) eluted 7-*methylamino*-1,3,5,2,4,6-*trithiatriazepine* (**15**; R = H) (7.0 mg, 26%) as orange needles, m.p. 73—73.5 °C (Found: C, 13.6; H, 2.0; N, 30.8. $C_2H_4N_4S_3$ requires C, 13.3; H, 2.2; N, 31.1%); $\lambda_{max.}$(EtOH) 262 (log ε 3.92), 290sh (3.61), and 413 nm (3.49); $\nu_{max.}$(CCl_4) 3 425s (NH), 2 960—2 820m, 1 530s, 1 480s, 1 420s, 1 200s, 1 140s (NSN), 920s, and 660s cm^{-1}; δ_H(250 MHz; $CDCl_3$) 2.95 (3 H, s, CH_3N) and 4.45 (1 H, s br, NH); *m/z* (100 °C) 182 (M^+ + 2, 10%), 180 (M^+, 69), 134 (M^+ − NS, 10), 124 (N_2S_3, 35), 78 (NS_2, 100), and 46 (NS, 38). Dichloromethane in light petroleum (65—70%) eluted the unchanged amine (**9**) (4 mg, 16%).

A repeat of the above procedure but with stirring for 16 days gave 7-methylaminotrithiatriazepine (10%) and 7-dimethylaminotrithiatriazepine (28%).

7-*Amino*-1,3,5,2,4,6-*trithiatriazepine Hydrochloride.*—Hydrogen chloride gas was passed through a solution of 7-aminotrithiatriazepine (**9**) (16.6 mg, 0.1 mmol) in dry ether (10 ml). The hydrochloride (12.0 mg, 59%) was collected by filtration, m.p. 140 °C (decomp.); $\lambda_{max.}$(EtOH) identical with that of the starting amine; $\nu_{max.}$(KBr) 3 700—2 400 (NH), 1 650, 1 610, 1 400, 1 140, 895, and 660 cm^{-1}.

Treatment of 7-Aminotrithiatriazepine (**9**) *with Hydrochloric Acid.*—7-Aminotrithiatriazepine (16.6 mg, 0.1 mmol) in THF (1 ml) was treated with hydrochloric acid (4M; 0.05 ml). After 20 s a white solid started to precipitate and after 2 h all the starting amine (**9**) had disappeared (t.l.c.). The white solid was collected by filtration and found to be ammonium chloride (8.0 mg, 37% based on all four nitrogen atoms).

7-*Bromo*-1,3,5,2,4,6-*trithiatriazepine.*—Trithiatriazepine-7-carboxylic acid (74 mg, 0.37 mmol), red mercury(II) oxide (81 mg, 0.37 mmol), and tetrachloromethane (10 ml) were stirred at 50 °C for 0.2 h. Bromine (29 μl, 0.56 mmol) was added and the mixture was irradiated under reflux with a 150 W tungsten lamp for 1.5 h. The tetrachloromethane solution containing trithiatriazepinecarboxylic acid and 7-bromotrithiatriazepine was decanted off, the solvent removed by evaporation, and the 7-bromotrithiatriazepine extracted from the residue with light petroleum. The residue was redissolved in tetrachloromethane (10 ml), combined with the reaction mixture and mercury(II) oxide (81 mg), and bromine (29 μl) added. The reaction mixture was irradiated for 1.5 h as above. The extraction, replenishment of reagents, and irradiation procedure was repeated for a third time.

The reaction mixture and all of the light petroleum extracts were combined, pre-adsorbed onto silica, and purified by flash chromatography on silica (15 g). Elution with light petroleum gave 7-bromotrithiatriazepine (0.044 g, 52%), m.p. 49 °C, identical with that described earlier.[1]

7-*Iodo*-1,3,5,2,4,6-*trithiatriazepine.*—Trithiatriazepine-7-carboxylic acid (68 mg, 0.35 mmol), red mercury(II) oxide (76 mg, 0.35 mmol), and tetrachloromethane (10 ml) were heated at 50 °C for 0.2 h. Iodine (89 mg, 0.35 mmol) was added and the reaction mixture irradiated at reflux for 1.5 h. The reaction mixture was twice subjected to the same extraction, replenishment of reagents, and further irradiation by the procedure used in the above preparation of 7-bromotrithiatriazepine.

The reaction mixture and the light petroleum extracts were combined and the solid collected by filtration. Treatment of this solid with HCl (4M; 20 ml), extraction with dichloromethane (3 × 5 ml), and evaporation of the dichloromethane portions gave unchanged trithiatriazepine-7-carboxylic acid (8 mg, 12%). The filtrate was pre-adsorbed onto silica and separated by flash chromatography on silica (15 g). Light petroleum eluted 7-*iodotrithiatriazepine* (32 mg, 33%) as prisms, m.p. 97—98 °C (light petroleum) (Found: C, 4.6; N, 15.1; S, 35.0. CIN_3S_3 requires C, 4.3; N, 15.2; S, 34.7%); $\lambda_{max.}$(EtOH) 230 (log ε 4.32), 253 (4.00), 288 (3.53), and 348 nm (3.58); $\nu_{max.}$(CCl_4) 1 551m, 1 492s, 1 482s, 1 216w, 1 139s, 983w, and 866s cm^{-1}; *m/z* (150 °C) 279 (M^+ + 2, 14%), 277 (M^+, 100), 231 (4), 185 (2), 150 (M^+ − I, 75), 127 (I^+, 15), 124 (N_2S_3, 3), 78 (NS_2, 68), and 46 (NS, 65). Light petroleum eluted 1,3,5,2,4,6-trithiatriazepine and methanol–ethyl acetate (1:1) eluted unchanged trithiatriazepine-7-carboxylic acid (4 mg, 6%).

Treatment of Trithiatriazepine-7-carboxylic Acid with Trifluoroacetic Anhydride.—The acid (10 mg, 0.051 mmol), trifluoroacetic anhydride (0.1 ml), and benzene (2 ml) were heated at reflux for 1 h. The reaction mixture was evaporated and benzene (1 ml) added and the solution heated at reflux for a further 1 h. Evaporation of the solvent gave 1,3,5,2,4,6-trithiatriazepine-7-carboxylic anhydride (**16**) (9.0 mg, 94%), m.p. 120—125 °C; $\nu_{max.}$ 1 796m, 1 776m, 1 747m, 1 724m, 1 487w, 1 325w, 1 137s, 1 012w, and 970s cm^{-1}; *m/z* (140 °C) 372 (M^+, 0.5%), 223 (44), 149 (38), 78 (NS_2, 100), and 46 (NS, 40).

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