Synthesis and Reactions of Pyrrolo[1,2-*a*][3,1,6]benzothiadiazocines

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A new synthesis of the thiadiazocine ring is reported together with an investigation of the diverse chemical reactions of pyrrolo[1,2-*a*][3,1,6]benzothiadiazocines.

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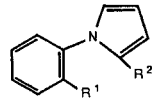
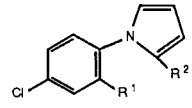
In a previous paper [1] we published two synthetic routes for the preparation of pyrrolo[1,2-*a*][3,1,6]benzothiadiazocines starting from *N*-(2-aminophenyl)pyrroles. We now report some experiments designed to lead to further syntheses of this novel 5,6,8-tricyclic ring system and also to investigate various aspects of the chemical reactivity of pyrrolobenzothiadiazocines.

We proposed to base an alternative synthesis of pyrrolobenzothiadiazocines on *N*-(2-toluene-*p*-sulphonamidophenyl)pyrrole **2**. Reaction of the sodium salt of this compound with ethyl bromoacetate readily gave the ester **3** and subsequent hydrolysis of the ester the acid **4**. We then hoped to prepare the thiadiazocine **17** from **4** by sequential thiocyanation and reduction to give **7** and ring closure [2]. Our efforts were frustrated by the difficulties we encountered in the thiocyanation step. The ester **3** was however smoothly thiocyanated and the resulting thiocyanate **5** reduced with sodium borohydride to the pyrrolyl thiol **6**. Since no satisfactory conditions were found for the hydrolysis of **6** to the acid **7**, this route to compound **17** had to be abandoned. Compound **6** was fully characterised by a variety of spectroscopic techniques and is one of the few pyrrolyl thiols reported in the literature [3].

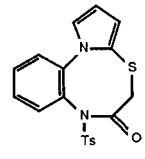
We also attempted to prepare a thiadiazocine from *N*-(2-nitrophenyl)-2-thiocyanatopyrrole **8** [4]. This was selectively reduced with sodium borohydride and the resulting thiol treated with phenacyl bromide to give the phenacylthiopyrrole **9**. The 4-chloro derivatives of **8** and **9**, compounds **15** and **16** were also prepared. We encountered unexpected difficulties in our attempts to reduce the nitro group in **9** with hydrogen and a palladium catalyst [5], iron and ethanolic hydrogen chloride [6], zinc and formic acid [1] and zinc and calcium chloride [7]. We were also unable to reduce nitro compound **16** either catalytically or by treatment with zinc and formic acid. *N*-(2-Aminophenyl)-2-phenacylthiopyrrole **12** was however prepared from *N*-(2-trifluoroacetamido)-2-thiocyanatopyrrole **11**. Sodium borohydride reduction of **11** effected both the cleavage of the trifluoroacetamido [8] and thiocyanato groups and subsequent reaction with phenacyl bromide furnished the





1, R^1 = NH_2, R^2 = H
2, R^1 = NHTs, R^2 = H
3, R^1 = $NTsCH_2CO_2C_2H_5$, R^2 = H
4, R^1 = $NTsCH_2CO_2H$, R^2 = H
5, R^1 = $NTsCH_2CO_2C_2H_5$, R^2 = SCN
6, R^1 = $NTsCH_2CO_2C_2H_5$, R^2 = SH
7, R^1 = $NTsCH_2CO_2H$, R^2 = SH
8, R^1 = NO_2, R^2 = SCN
9, R^1 = NO_2, R^2 = SCH_2COPh
10, R^1 = $NHCOCF_3$, R^2 = H
11, R^1 = $NHCOCF_3$, R^2 = SCN
12, R^1 = NH_2, R^2 = SCH_2COPh
13, R^1 = NH_2, R^2 = $SCH_2CO_2C_2H_5$
14, R^1 = NH_2, R^2 = $SCH_2CONHNH_2$

15, R^1 = NO_2, R_2 = SCN
16, R^1 = NO_2, R_2 = SCH_2COPh



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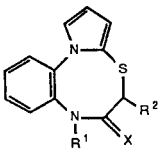
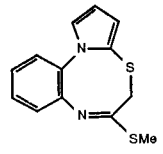
required pyrrolic intermediate **12**. We had anticipated by literature analogy [9] that **12** would cyclise on heating in toluene in the presence of *p*-toluenesulphonic acid, but no cyclisation could be effected under these conditions.

N-(2-Trifluoroacetamido)-2-thiocyanatopyrrole **11** was readily converted into the amino ester **13** by sequential sodium borohydride and ethyl bromoacetate treatment. The latter compound underwent ring closure on reaction with trimethylaluminium [6] to give the thiadiazocine **18** with identical characteristics to the 5,6-dihydro-6-oxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine prepared by an alternative route [1]. The terminal step in our latest synthesis thus involves ring closure by carbon-nitrogen bond formation whereas in our earlier syntheses ring closure was effected by carbon-sulphur bond fromation. The intermediate 2-thiocyanatopyrroles prepared in the course of this work were obtained by use of copper(II) thiocyanate as the thiocyanating reagent. Improved yields were obtained when the bulky precipitate of copper(I) thiocyanate formed as by-product was carefully extracted with hot ethanol.

Encouraged by our earlier success in converting the thiadiazocine **18** into its *N*-methyl derivative **19** by treatment with methyl iodide and sodium methoxide [1], we attempted to carry out a number of transformations which have been reported in the literature on related cyclic amides. Our attempts to *N*-phenylate **18** with diphenyl-



18, $R^1 = R^2 = H$, X = O
19, $R^1 = CH_3$, $R^2 = H$, X = O
20, $R^1 = R^2 = H$, X = S
21, $R^1 = CH_3$, $R^2 = H$, X = S
22, $R^1 = CH_3$, $R^2 = C(OH)(C_6H_5)_2$, X = O
23, $R^1 = R^2 = H$, $X = H_2$
24, $R^1 = COCH_3$, $R^2 = H$, $X = H_2$



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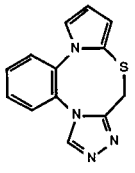

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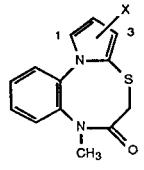

27, X = 1-(or 3)-Br
28, X = 1-(or 3)-CHO
29, X = 1-(or 3)-$CH_2N(CH_3)_2$

iodonium chloride [10,11] or obtain an imino-chloride using either a mixture of phosphorus pentachloride and phosphoryl chloride [5] or thionyl chloride [12] were however unsuccessful. Only starting material was isolated from the attempted reaction of **18** with *N*-methylpiperazine in the presence of titanium tetrachloride [13] and tarry material was obtained when **18** was treated with phosphorus pentasulphide in pyridine [14]. The hoped-for oxygen for sulphur exchange was achieved when 2,4-bis[phenylthio]-1,3-dithia-2,4-diphosphetane-2,4-disulphide was used as thionating agent and the thioamide **20** was obtained in 80% yield. The reagent is readily prepared from phosphorus pentasulphide and thiophenol [15]. Methylation of the sodium salt of the thioamide **20** gave the *S*-methyl derivative **25** [16]. The *N*-methyl derivative **21** was prepared by thionation of **19** under the same conditions established for the thioamide. The thioamide **20** was found to react readily with ammonia and hydrazine but the crystalline products of reaction have not so far been indentified. The thioamide did give the expected triazole **26** on treatment with formic acid hydrazide [17]. Our attempts to prepare a *N*-methylpiperazine derivative from **20** [16] or its *S*-methyl derivative **25** [13,16-18] failed.

In two other reactions the thiadiazocine **18** showed the reactivity which might be anticipated of a cyclic amide. Thus reduction of **18** with lithium aluminium hydride gave the corresponding amine **23** as an oil which was characterised by the preparation of a crystalline hydrochloride and *N*-acetyl derivative **24** [17]. Also on refluxing **18** with hydrazine hydrate, ring opening occurred and the hydrazide **14** was formed.

Analogy with thiazinone chemistry suggested that the methylene group in **19** might be reactive [19]. We found that the anion derived from **19** by proton abstraction with lithium diisopropylamide (LDA) gave on reaction with benzophenone the tertiary alcohol **22** [20]. On treatment with *N*-bromosuccinimide and dibenzoyl peroxide [19], bromination occurred not at the methylene group, but in the pyrrole ring to give either the 1- or 3-bromo derivative **27**. Pyrrolic substitution also took place when **19** was subjected to standard Vilsmeier [21] and Mannich [22] conditions. The ^1H nmr spectra of the resulting formyl **28** and dimethylaminomethyl **29**, derivatives and also of the bromo compound **27** showed clearly the presence of two coupled adjacent pyrrolic hydrogen atoms. The magnitude of the coupling (J = 3 - 4 Hz) does not enable a distinction between 1- or 3-substitution to be made. In the case of the Vilsmeier formylation of related compounds, examples of both α- and β-pyrrolic substitution has been reported [21,22]. It is hoped that spectroscopic measurements in progress will lead to an unambiguous assignment of structure.

EXPERIMENTAL

The ir spectra of solids were taken as Nujol mulls and liquids as thin films between sodium chloride discs. Nmr spectra were measured in deuteriochloroform unless otherwise stated. Mass spectral measurements were recorded on a Kratos MS 25 machine equipped with a DS 55 data system.

Ethyl *N*-[2-(1'-Pyrrolyl)phenyl]-*N*-toluene-*p*-sulphonylglycinate (**3**) (With S. A. Eccleshall).

A mixture of *N*-(2-toluene-*p*-sulphonamidophenyl)pyrrole **2** [1] (14.8 g, 0.047 mole), sodium carbonate (14.79 g, 0.139 mole) and ethyl bromoacetate (8.35 g, 0.05 mole) in dry toluene (150 ml) was heated under reflux for 48 hours. After cooling, the precipitate of sodium bromide was filtered off, washed with toluene (50 ml) and the combined filtrate and washings evaporated. Ethanol (100 ml) was added to the residual oil and after cooling for several hours, the crystalline material was filtered off and recrystallised from ethanol to give colourless plates of the ester **3** (13.32 g, 71%), mp 115-116°; ir: 1740 cm^{-1} (C=O), 1330 (unsym SO_2), 1160 (sym SO_2); nmr: δ 1.08 (t, CH_3), 2.43 (s, CH_3), 3.89 (s, CH_2), 3.97 (q, CH_2), 6.28 (dd, H-3, H-4), 6.87 (dd, H-2, H-5), 7.06-7.80 (m, benzenoid); ms: 398 (M^+), 243 (398-$SO_2C_6H_4CH_3$).

Anal. Calcd. for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03. Found: C, 63.12; H, 5.62; N, 7.04.

N-[2-(1'-Pyrrolyl)phenyl]-*N*-toluene-*p*-sulphonylglycine (**4**) (With S. A. Eccleshall).

A solution of sodium hydroxide (2.84 g, 0.0071 mole) in water (15 ml) was added to a solution of the glycinate **3** (14.14 g, 0.0355 mole) in methanol (120 ml). The mixture was stirred at 45° for 16 hours and then concentrated to 50 ml. Acidification with 1*N* hydrochloric acid gave a solid which was extracted with chloroform (3 x 20 ml). The combined extracts were dried (magnesium sulphate), treated with charcoal and evaporated to 25 ml. The product was precipitated out by the addition of petroleum ether (bp 60-80°). The crude product was redissolved in aqueous base and re-precipitated by acidification. Finally crystallisation from a mixture of chloroform and petroleum ether (bp 60-80°) gave a sample of the acid **4** (8.0g, 61%), mp 173-174°; ir: 3200 cm^{-1} (OH), 1750 (C=O), 1340 (unsym SO_2), 1160 (sym SO_2); nmr (deuteriochloroform + acetone-d_6): δ 2.43 (s, CH_3), 3.90 (s, CH_2), 6.27 (dd, H-3, H-4), 6.82 (dd, H-2, H-5), 7.17-7.77 (m, benzenoid), 9.73 (s, OH); ms: 370 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_4S$: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.27; H, 4.86; N, 7.37.

N[2-*N'*-(Ethoxycarbonylmethyl)-*N'*-(toluene-*p*-sulphonyl)aminophenyl]-pyrrole-2-thiol (**6**).

To a solution of the ester **3** (4.5 g, 0.011 mole) in absolute ethanol (150 ml) at 0° and kept under nitrogen, copper(II) thiocyanate (6.0 g, 0.033 mole) was added portionwise. The mixture was stirred at 7° for 16 hours, filtered and the precipitate of copper(I) thiocyanate washed several times with hot ethanol. The combined filtrate and washings were evaporated to 70 ml before pouring into ice-water (200 ml). The oily precipitate was extracted with chloroform (3 x 20 ml), the combined extracts then dried (magnesium sulphate) and evaporated to give the thiocyanate **5** as an orange oil (4.38 g, 85%); ir: 2150 cm^{-1} (SCN), 1740 (C=O). A portion (1.37 g, 0.003 mole) was dissolved in ethanol (50 ml), cooled to 0-5° in a continuous stream of nitrogen and then treated portionwise with sodium borohydride (0.23 g, 0.006 mole). Stirring was continued at room temperature for 1 hour then water (50 ml) was added and the mixture left in a refrigerator overnight. The precipitated solid was filtered off, washed with water, air-dried and crystallised from propan-2-ol. Recrystallisation from the same solvent gave the thiol **6** (0.74 g, 57%), mp 158-160°; ir: 1740 cm^{-1} (C=O); nmr: δ 1.01 (t, CH_3), 2.44 (s, CH_3), 3.79-4.01 (m, NCH_2 and CH_2 ester), 6.32 (dd, H-4), 6.47 (dd, H-3), 7.13-7.78 (m, H-5 and benzenoid); ms: 430 (M^+), 357 (430-$CO_2C_2H_5$).

Anal. Calcd. for $C_{21}H_{22}N_2O_4S_2$: C, 58.58; H, 5.15; N, 6.51. Found: C, 58.64; H, 4.97; N, 6.64.

N-(2-Nitrophenyl)-2-phenacylthiopyrrole (**9**).

To a stirred solution of *N*-(2-nitrophenyl)-2-thiocyanatopyrrole **8** [4] (1.23 g, 0.005 mole) in dry methanol (50 ml), kept under nitrogen, sodium borohydride (0.28 g, 0.0075 mole) was added in portions and the mixture stirred at room temperature for 1 hour. A solution of potassium hydroxide (0.42 g, 0.0075 mole) in methanol (10 ml) was then added followed by phenacyl bromide (1.50 g, 0.0075 mole). The mixture was heated at 65° for 1.5 hours, cooled and then concentrated to 15 ml. The solid (0.73 g) was filtered off and washed with water. A second crop (0.37 g) was obtained from the filtrate. The combined crops were crystallised from ethanol to give yellow needles of product **9** (0.95 g, 56%), mp 97-98°; ir: 1660 cm^{-1} (C=O); nmr: δ 3.74 (s, CH_2), 6.28 (dd, H-4), 6.49 (dd, H-3), 6.84 (dd, H-5), 7.20-8.00 (m, benzenoid); ms: 338 (M^+), 187 (338-$SCH_2COC_6H_5$).

Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. Found: C, 63.93; H, 4.12; N, 8.34.

N-(2-Trifluoroacetamidophenyl)pyrrole (**10**).

To a solution of *N*-(2-aminophenyl)pyrrole **1** [23] (9 g, 0.057 mole) in glacial acetic acid (45 ml) under nitrogen, was added dropwise with cooling trifluoroacetic anhydride (12.06 ml, 0.085 mole). The mixture was stirred for 16 hours at room temperature and then poured into ice-water (200 ml). The crystalline product was filtered off washed well with water and recrystallised from ethanol-water to give white needles of **10** (9.5 g, 62%), mp 81-82°; ir: 3340 cm^{-1} (NH), 1760 (C=O); nmr: δ 6.41 (dd, H-3, H-4), 6.75 (dd, H-2, H-5), 7.20-7.70 (3H, m, benzenoid), 7.84 (s, br, NH), 8.20-8.40 (1H, m, benzenoid); ms: 245 (M^+), 185 (245-CF_3).

Anal. Calcd. for $C_{12}H_9F_3N_2O$: C, 56.70; H, 3.57; N, 11.02. Found: C, 56.64; H, 3.49; N, 11.02.

N-(2-Trifluoroacetamidophenyl)-2-thiocyanatopyrrole (**11**).

To a solution of *N*-(2-trifluoroacetamidophenyl)pyrrole **10** (9 g, 0.037 mole) in absoute ethanol (200 ml) at 0° under nitrogen, was added in portions, freshly prepared and dried copper(II) thiocyanate (20.3 g, 0.113 mole). The mixture was stirred vigorously for 24 hours at 7°. Copper(I) thiocyanate was filtered off and washed several times with hot ethanol. The combined filtrate and washings were evaporated to 70 ml before pouring into ice-water (200 ml). The resulting oil was extracted with dichloromethane (3 x 25 ml), the combined extracts dried (magnesium sulphate) and evaporated to give an orange oil which was absorbed onto a silica gel column. Elution with a 1:1-mixture of ethyl acetate and petroleum ether (bp 60-80°) gave an eluant which on evaporation and crystallisation of the residue from toluene yielded the product as fine white needles (7.5 g, 67%), mp 101-102°; ir: 3240 cm^{-1} (NH), 2160 (SCN), 1740 (C=O); nmr: δ 6.48 (dd, H-2), 6.90 (dd, H-3), 7.02 (dd, H-1), 7.20-7.78 (m, 3H, benzenoid and NH), 8.17-8.38 (m, 1H, benzenoid); ms: 311 (M^+), 285 (311-CN), 253 (311-SCN), 156 (253-$COCF_3$).

Anal. Calcd. for $C_{13}H_8F_3N_3OS$: C, 50.16; H, 2.59, N, 13.50. Found: C, 50.07; H, 2.64; N, 13.55.

N-(2-Aminophenyl)-2-phenacylthiopyrrole (**12**).

To a stirred solution of *N*-(2-trifluoroacetamidophenyl)-2-thiocyanatopyrrole **11** (1.0 g, 0.0034 mole) in absolute ethanol (40 ml), kept under nitrogen, sodium borohydride (0.5 g, 0.0134 mole) was added portionwise and the mixture stirred at room temperature for 1 hour. Acetone (15 ml) was then added and stirring was continued for another hour. To the resulting stirred, dark reaction mixture phenacyl bromide (0.76 g, 0.0038 mole) in absolute ethanol (15 ml) was added and the temperature raised to 65° for a further hour. The mixture was then concentrated to 20 ml and water (20 ml) was added. The product was extracted with dichloromethane (3 x 10 ml), and the combined extracts dried (magnesium sulphate) and evaporated. The residual oil was purified by chromatography on a silica gel column using a 1:1-mixture of ethyl acetate and light petroleum (bp 60-80°) as eluant. The phenacylthiopyrrole **12** (0.62 g, 60%) was obtained from the first fraction as an orange syrup; ir: 3400, 3320 cm^{-1} (NH_2), 1700 (C=O); nmr: δ 3.34 (s, br, NH_2), 3.73 (s, CH_2), 6.27 (dd, H-4), 6.41 (dd, H-3), 6.67-7.93 (m, H-5 and benzenoid); ms: 308 (M^+), 203 (308-COC_6H_5), 157 (308-$SCH_2COC_6H_5$).

N(4-Chloro-2-nitrophenyl)-2-thiocyanatopyrrole (**15**).

To a stirred solution of *N*-(4-chloro-2-nitrophenyl)pyrrole [1] (7.53 g, 0.033 mole) in dry methanol (150 ml) at 0° in a continuous stream of nitrogen, was added in portions freshly prepared, dry copper(II) thiocyanate (18.0 g, 0.10 mole). The mixture was stirred at 6° for 12 hours, copper(I) thiocyanate filtered off and washed with hot methanol (50 ml). The combined filtrate and washings were concentrated by vacuum distillation to 70 ml before pouring into ice-water (200 ml). The solid was filtered off and crystallised from ethanol to give the thiocyanate **15** as yellow needles (5.5 g, 58%), mp 102-103°; ir: 2160 cm^{-1} (SCN); nmr: δ 6.43 (dd, H-4), 6.86 (dd, H-3), 6.98 (dd, H-5), 7.47-8.18 (m, benzenoid); ms: 279 (M^+), 221 (279-SCN).

Anal. Calcd. for $C_{11}H_6ClN_3O_2S$: C, 47.23; H, 2.16; N, 15.02. Found: C, 47.23; H, 2.09; N, 15.10.

N-(4-Chloro-2-nitrophenyl)-2-phenacylthiopyrrole (**16**).

This was prepared from *N*-(4-chloro-2-nitrophenyl)-2-thiocyanatopyrrole **15** (1.5 g, 0.0054 mole) in an identical manner to that described for compound **9** above. The crude crystalline product (1.26 g) was purified by chromatography on silica gel using a 1:1-mixture of ethyl acetate and light petroleum (bp 60-80°) as eluant. After removal of the mobile impurity, the phenacylthiopyrrole **16** was obtained in the eluant. Crystallisation from ethanol gave yellow needles (1.14 g, 61%), mp 110-111°; ir: 1670 cm^{-1} (C=O); nmr: δ 3.75 (s, CH_2), 6.32 (dd, H-4), 6.54 (dd, H-3), 6.82 (dd, H-5), 7.20-7.92 (m, benzenoid); ms: 372 (M^+), 221 (372-$SCH_2COC_6H_5$).

Anal. Calcd. for $C_{18}H_{13}ClN_2O_3S$: C, 57.99; H, 3.51; N, 7.51. Found: C, 57.92; H, 3.46; N, 7.27.

5,6-Dihydro-6-oxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**18**).

To a solution of **11** (0.93 g, 0.003 mole) in absolute ethanol (40 ml) kept under nitrogen, sodium borohydride (0.47 g, 0.013 mole) was added portionwise. The mixture was stirred at room temperature for 1 hour, acetone (20 ml) was then added and stirring continued for a further hour. Ethyl bromoacetate (0.39 ml, 0.0035 mole) was added to the dark mixture and the temperature elevated to 65° for 45 minutes. The resulting orange solution was concentrated *in vacuo* to about 15 ml, aqueous sodium chloride solution (15 ml) added and the product extracted with dichloromethane (4 x 10 ml). The combined organic extracts were dried (magnesium sulphate) and evaporated to give ethyl [*N*-(2-aminophenyl)-2-pyrrolylthio]acetate **13** (0.73 g, 84%), as an oil which was purified by conversion into its hydrochloride by treatment of an ethereal solution with ethanolic hydrogen chloride and re-precipitation with aqueous

sodium carbonate; ir: 3440, 3360 cm^{-1} (NH_2), 1720 (C=O); nmr: δ 1.27 (t, CH_3), 3.05 (s, SCH_2), 3.65 (s, br, NH_2), 4.18 (q, CH_2 ester), 6.28 (dd, H-4), 6.55 (dd, H-3), 6.66-7.43 (m, H-5 and benzenoid); ms: 276 (M^+), 231 (276-OC_2H_5), 189 (276-$CH_2CO_2C_2H_5$), 157 (276-$SCH_2CO_2C_2H_5$).

A portion (0.62 g, 0.0022 mole) was dissolved in dichloromethane (15 ml) and while passing a continous stream of nitrogen, trimethylaluminium in hexane (2.0 ml, 0.004 mole, 2*M* solution) was added slowly. After stirring at room temperature for 1 hour the mixture was acidified to *p*H 5 by the dropwise addition of 1*N* acetic acid. Water (10 ml) was added, the organic phase separated and the aqueous phase extracted with dichloromethane (3 x 5 ml). The combined extracts were washed with saturated sodium chloride solution, dried (magnesium sulphate) and evaporated. The resulting residue was recrystallised from toluene to give thiadiazocine **18** (0.32 g, 62%), identical in all respects to a sample prepared by the alternative published method [1].

5,6-Dihydro-6-thioxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**20**).

A mixture of the thiadiazocine **18** (2.5 g, 0.011 mole), 2,4-bis[phenylthio]-1,3-dithia-2,4-diphosphetane-2,4-disulphide (2.25 g, 0.0055 mole) in dry tetrahydrofuran (50 ml) was stirred at room temperature for 2 hours. A further portion of the disulphide (0.55 g, 0.0013 mole) was added and the mixture stirred for 1 hour and then concentrated *in vacuo*. The resulting oil was absorbed on a silica gel column and the product was eluted with a 1:1-mixture of ethyl acetate and chloroform. The thiadiazocinethione **20** (2.15 g, 80%) was obtained as yellow plates, mp 163-164°, after crystallisation from ethanol-water; ir: 3080 cm^{-1} (NH); nmr: δ 3.71 (d, H-5a, J_{gem} = 9.9 Hz), 3.93 (d, H-5b, J_{gem} = 9.9 Hz), 6.25 (dd, H-2), 6.57 (dd, H-3), 6.84 (dd, H-1), 7.22-7.68 (m, benzenoid), 9.32 (s, NH); ms: 246 (M^+).

Anal. Calcd. for $C_{12}H_{10}N_2S_2$: C, 58.51; H, 4.09; N, 11.37. Found: C, 58.51; H, 4.10; N, 11.43.

6-Methylthio-5*H*-pyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**25**).

To a stirred suspension of sodium hydride (0.13 g, 0.0058 mole; prewashed with dry petroleum ether) in dry tetrahydrofuran (20 ml) was added dropwise a solution of the thione **20** (1.35 g, 0.0055 mole) in dry tetrahydrofuran (30 ml). The mixture was stirred at room temperature for 1 hour. To the resulting solution, methyl iodide (1.54 g, 0.011 mole) was added, the mixture was stirred for 2 hours at room temperature, filtered evaporated *in vacuo* and the residue extracted with dichloromethane. After drying with magnesium sulphate, the solvent was evaporated to give an oil which quickly solidified. Crystallisation from ethanol-water gave the product (0.99 g, 70%) as colourless microcrystals mp 92.5-93.5°; nmr: δ 2.13 (s, SCH_3), 3.18 (d, H-5a, J_{gem} = 11.7 Hz), 3.66 (d, H-5b, J_{gem} = 11.7 Hz), 6.17 (dd, H-2), 6.43 (dd, H-3), 6.80 (dd, H-1), 6.90-7.50 (m, benzenoid); ms: 260 (M^+), 213 (260-SCH_3).

Anal. Calcd. for $C_{13}H_{12}N_2S_2$:, C, 59.97; H, 4.65; N, 10.76. Found: C, 59.84; H, 4.59; N, 10.77.

5,6-Dihydro-7-methyl-6-thioxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**21**).

A mixture of thiadiazocine **18** (0.44 g, 0.0018 mole), 2,4-bis[phenylthio]-1,3-dithia-2,4-diphosphetane-2,4-disulphide (0.45 g, 0.0011 mole) in dry tertahydrofuran (15 ml) was stirred for 2 hours. A further 0.2 g portion of disulphide was added and the mixture was stirred for 8 hours. The resulting solution was filtered and evaporated *in vacuo* leaving an oil which was chromatographed on a silica gel column. The fraction obtained by elution with a 1:1-mixture of ethyl acetate-petroleum ether (bp 60-80°) gave after crystallisation from ethanol, the product as pale yellow microcrystals (0.25 g, 53%), mp 160-161°; nmr: δ 3.25 (s, NCH_3), 3.80 (d, H-5a, J_{gem} = 9.9 Hz), 4.03 (d, H-5b, J_{gem} = 9.9 Hz), 6.26 (dd, H-2), 6.53 (dd, H-3), 6.88 (dd, H-1), 7.25-7.83 (m, benzenoid); ms: 260 (M^+), 227 (260-SH), 186 (260-CH_3NCSH).

Anal. Calcd. for $C_{13}H_{12}N_2S_2$: C, 59.97; H, 4.65; N, 10.76. Found: C, 60.20; H, 4.66; N, 10.86.

Pyrrolo[2,1-*e*]*sym*.-triazolo[1,2-*a*][3,1,6]benzothiadiazocine (**26**).

Thiolactam **20** (0.5 g, 0.002 mole) and formic acid hydrazide (1.20 g, 0.02 mole) were refluxed in toluene (20 ml) for 72 hours. After cooling, charcoal was added. The mixture was boiled for 5 minutes, filtered and the filtrate refrigerated overnight. The crystalline product was filtered off, washed with toluene and recrystallised from the same solvent to afford white plates of the triazole **26** (0.32 g, 62%), mp 219-220°; nmr: δ 3.79 (d, H-4a, J_{gem} = 14.0 Hz), 4.56 (d, H-4b, J_{gem} = 14.0 Hz), 6.19 (dd, H-7), 6.55 (dd, H-6), 6.99 (dd, H-8), 7.50-7.83 (m, benzenoid), 7.97 (s, H-1); ms: 254 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.01; H, 3.83; N, 22.21. Found: C, 61.21; H, 3.89; N, 22.14.

5,6-Dihydropyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**23**).

Thiadiazocine **17** (1.0 g, 0.0043 mole) and lithium aluminium hydride (0.66 g, 0.0174 mole) were refluxed in dry tetrahydrofuran (50 ml) under nitrogen for 18 hours. After cooling and the sequential addition of water (1 ml), 15% sodium hydroxide solution (1 ml) and water (1 ml), the reaction mixture was filtered. The solid was washed with dichloromethane (3 x 15 ml) and to the combined filtrate and washings water (15 ml) was added. The organic layer was separated, dried (magnesium sulphate), treated with charcoal, filtered and concentrated to give the crude product as an oil (0.55 g, 59%); ir (neat): 3375, 3325 cm^{-1} (NH); nmr: δ 2.48-2.80 (m, SCH_2), 2.92 (s, br, NH), 3.10-3.50 (m, NCH_2), 6.30 (dd, H-2), 6.58 (dd, H-3), 6.77-7.40 (m, H-1 and benzenoid): ms: 216 (M^+).

To a solution of amine **23** (1.0 g, 0.0046 mole) in dry ether (25 ml) was added dropwise an ethanolic hydrogen chloride solution until the *p*H was 2. The reaction mixture was left in the refrigerator overnight and then filtered. The precipitate was washed with ether and dried to give the hydrochloride as a colourless solid (0.63 g, 54%), mp 249-251°.

Anal. Calcd. for $C_{12}H_{12}N_2S.HCl$: C, 57.02; H, 5.18; N, 11.08. Found: C, 56.99; H, 5.12; N, 11.10.

7-Acetyl-5,6-dihydropyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**24**).

Amine **23** (0.55 g, 0.0025 mole) was stirred with a mixture of acetic anhydride and pyridine (2:1, 9 ml) at room temperature for 18 hours. The solvents were removed *in vacuo*, water (15 ml) was added and the residue extracted into dichloromethane (15 ml). The extract was dried (magnesium sulphate) and evaporated to give a crude solid (0.42 g). Crystallisation from ethanol-water gave the product as colourless plates (0.39 g, 59%), mp 169-170°; ir: 1645 cm^{-1} (C=O); nmr: δ 1.54 (s, CH_3), 2.48-2.60 (m, H-6a),3.02-3.30 (m, H-5a and H-5b), 4.83-4.95 (m, H-6b), 6.29 (dd, H-2), 6.59 (dd, H-3), 6.91 (dd, H-1), 7.33-7.56 (m, benzenoid); ms: 258 (M^+), 217 (258-CH_3CO).

Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84. Found: C, 64.91; H, 5.39; N, 10.83.

[*N*-2-Aminophenyl-2-pyrrolylthio]acetylhydrazide (**14**).

A mixture of thiadiazocine **18** (0.8 g, 0.003 mole) and 98% hydrazine hydrate (6 ml) was heated under reflux for 5 hours. Excess of hydrazine hydrate was removed by vacuum distillation and water (10 ml) added to the oily residue. The resulting crude solid (0.48 g) gave on crystallisation from ethanol colourless needles of the hydrazide **14** (0.45 g, 49%), mp 156-157°; ir: 3460, 3345, 3300 and 3260 cm^{-1} (NH), 1675 (C=O); nmr: (DMSO-d_6 + deuteriochloroform): δ 3.09 (s, CH_2) 4.05 (s, br, 2 x NH_2), 6.26 (dd, H-4), 6.46-7.29 (m, H-3, H-5 and benzenoid), 8.82 (s, br, NH); ms: 262 (M^+), 230 (262-N_2H_4), 189 (262-$CH_2CONHNH_2$).

Anal. Calcd. for $C_{12}H_{14}N_4OS$: C, 54.94; H, 5.38; N, 21.36. Found: C, 54.71; H, 5.38; N, 21.33.

5,6-Dihydro-5-(diphenylhydroxymethyl)-7-methyl-6-oxopyrrolo[1,2-*a*]-[3,1,6]benzothiadiazocine (**22**).

To dry tetrahydrofuran (25 ml), kept under a continuous stream of nitrogen, was added (0.8 g, 0.008 mole) of diisopropylamine. The solution was cooled to -70° and 1.55 *M* *n*-butyl lithium solution in hexane (5.2 ml, 0.008 mole) was added with a syringe. The mixture was stirred for 15 minutes, warmed to room temperature during 45 minutes, and then cooled to -60°. A solution of the thiadiazocine **19** (0.98 g, 0.004 mole) in dry tetrahydrofuran (15 ml) was added with a syringe and the reaction mix-

ture brought to room temperature over 45 minutes. To the resulting orange solution at -30° was added benzophenone (0.73 g, 0.004 mole) in dry tetrahydrofuran (10 ml) and the reaction mixture allowed to come to room temperature and then stirred for a further 4 hours. Saturated aqueous sodium chloride was added and the mixture extracted with dichloromethane (3 x 20 ml). The combined extracts were dried (magnesium sulphate) and evaporated *in vacuo*. The resulting oil was chromatographed on silica gel using ethyl acetate-light petroleum (bp 60-80°) (1:1) as eluant. The third fraction contained the crude product (0.56 g) and the fourth fraction gave unchanged thiadiazocine (0.2 g). The product crystallised from toluene as white clusters (0.5 g, 37%), mp 233-235°; ir: 3280 cm^{-1} (OH), 1640 (C=O); nmr: δ 2.69 (s, NCH_3), 5.04 (s, H-5), 6.23 (dd, H-2), 6.58 (dd, H-3), 6.76 (s, OH), 7.01 (dd, H-1), 7.05-7.75 (m, benzenoid); ms: 426 (M^+).

Anal. Calcd. for $C_{26}H_{22}N_2O_2S$: C, 73.21; H, 5.20; N, 6.57. Found: C, 73.28; H, 5.16; N, 6.48.

1-(or 3)-Bromo-5,6-dihydro-7-methyl-6-oxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine (**27**).

A suspension of the thiadiazocine **19** (0.5 g, 0.002 mole), *N*-bromosuccinimide (0.365 g, 0.002 mole) and dibenzoyl peroxide (0.0026 g, 0.008 mole) in dry carbon tetrachloride (50 ml) was stirred at 50° for 15 hours, filtered and evaporated to 10 ml. Upon cooling a solid (0.58 g) separated. Crystallisation from ethanol gave the product as white needles (0.54 g, 82%), mp 162-163°; ir: 1655 cm^{-1} (C=O); nmr: δ 2.88 (s, NCH_3), 3.21 (d, H-5a, J_{gem} = 9.9 Hz), 3.45 (d, H-5b, J_{gem} = 9.9 Hz), 6.27 (d, pyrrolic-H, $J_{vicinal}$ = 3.7 Hz), 6.55 (d, pyrrolic-H, $J_{vicinal}$ = 3.7 Hz), 7.20-7.70 (m, benzenoid); ms: 324/322 (M^+).

Anal. Calcd. for $C_{13}H_{11}BrN_2OS$: C, 48.31; H, 3.43; N, 8.67. Found: C, 48.13; H, 3.41; N, 8.70.

5,6-Dihydro-7-methyl-6-oxopyrrolo[1,2-*a*][3,1,6]benzothiadiazocine-1-(or 3)-carboxaldehyde (**28**).

To cold dimethylformamide (0.54 g, 0.0075 mole) was added phosphorus oxychloride (1.14 g, 0.0075 mole) dropwise. The mixture was stirred at room temperature for 15 minutes, then diluted with 1,2-dichloromethane (20 ml), cooled, and a solution of thiadiazocine **19** (0.8 g, 0.0032 mole) in 1,2-dichloromethane (15 ml) was added slowly. The mixture was then stirred and heated under reflux for 4 hours, cooled, a solution of anhydrous sodium acetate (3.7 g, 0.045 mole) in water (25 ml) was added, and the mixture stirred at 85° for 30 minutes. After cooling, the mixture was extracted with chloroform (3 x 15 ml). The combined extracts were washed with saturated sodium bicarbonate solution (2 x 10 ml), saturated aqueous sodium chloride (2 x 10 ml), dried (magnesium sulphate) then evaporated to give an oily residue which was triturated with ethanol. The resultant solid was filtered off washed with cold ethanol and crystallised from toluene to give colourless clusters of microcrystals of the carboxaldehyde (0.28 g, 32%), mp 184-185°; ir: 1660 cm^{-1} (C=O); nmr: δ 2.94 (s, NCH_3), 3.30 (d, H-5a, J_{gem} = 10.4 Hz), 3.62 (d, H-5b, J_{gem} = 10.4 Hz), 6.80 (d, pyrrolic-H, $J_{vicinal}$ = 3.2 Hz), 6.87 (d, pyrrolic-H, $J_{vicinal}$ = 3.2 Hz), 7.44-7.68 (m, benzenoid), 9.99 (s, CHO); ms: 272 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.96; H, 4.38; N, 10.30.

5,6-Dihydro-1-(or 3)-dimethylaminomethyl-7-methyl-6-oxopyrrolo[1,2-*a*]-[3,1,6]benzothiadiazocine (**29**).

A mixture of thiadiazocine **19** (0.5 g, 0.002 mole), paraformaldehyde (0.2 g) and dimethylamine hydrochloride (0.285 g, 0.0035 mole) in ethanol (15 ml), was heated under reflux for 16 hours. The ethanol was removed under vacuum and the residue stirred with water (15 ml) for a few minutes and then the solution basified to *p*H 9 with 1*N* sodium hydroxide and extracted with dichloromethane (3 x 5 ml). The organic extracts were dried (magnesium sulphate) and the solvent evaporated. The residue was absorbed on a silica gel column, elution with ethyl acetate-dichloromethane (1:1) gave an eluate which contained unchanged starting material (0.08 g). Further elution with ethyl acetate gave an eluate which contained the product. This was recrystallised from ethanol-water as colourless needles, (0.26 g, 50%), mp 128-129°; ir: 1665 cm^{-1} (C=O); nmr: δ 2.06 [s, $N(CH_3)_2$], 2.85 (s, NCH_3), 2.99 (d, a-H, NCH_2, J_{gem} = 13.6 Hz), 3.16 (d, b-H, NCH_2, J_{gem} = 13.6 Hz), 3.22 (d, H-5a, J_{gem} = 10 Hz), 3.47 (d, H-5b, J_{gem} = 10 Hz), 6.14 (d, pyrrolic-H, $J_{vicinal}$ = 3.4 Hz), 6.48 (d, pyrrolic-H, $J_{vicinal}$ = 3.4 Hz), 7.27-7.68 (m, benzenoid); ms: 301 (M^+), 257 [301-$N(CH_3)_2$].

Anal. Calcd. for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94. Found: C, 63.83; H, 6.23; N, 13.98.

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