Novel Rearrangements of *N*-Arylpyrrolyl Sulphides (1)

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Base treatment of the pyrrolylthioacetate **2** and the pyrrolylthioacetonitrile **4** unexpectedly yielded a pyrrolo[2,1-*b*]thiazole **6** and 2-(α-cyano-2-nitrobenzyl)thiopyrrole (**7**), respectively.

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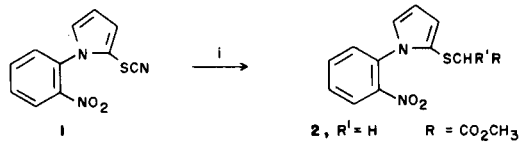
In an extension of our work on the synthesis of tricyclic ring systems from *N*-aryl-2-thiocyanatopyrroles (2) we decided to attempt the synthesis of pyrrolo[3,1,5]benzothiadiazepines.

Thiocyanation of aromatic amines in which the preferred *para* position is blocked affords *o*-thiocyanatoanilines. The latter compounds frequently spontaneously cyclise to 2-aminobenzothiazoles; alternatively heating with dilute hydrochloric acid is required (3). We had hoped to form an aminobenzothiadiazepine *via* the thiocyanation of *N*-(2-aminophenyl)pyrrole however this reaction gave erratic results. Several attempts to prepare the required *N*-(2-aminophenyl)-2-thiocyanatopyrrole by reduction of the readily available nitrophenylthiocyanatopyrrole **1** with ferrous sulphate in aqueous ammonia (4) or with stannous chloride in concentrated hydrochloric acid failed. Other reductive procedures which involved the use of iron powder in acetic acid, zinc and calcium chloride (5) or catalytic hydrogenation using platinum oxide (6) as a catalyst also proved unsuccessful. The difficulties in obtaining the amino compound might have been due to the presence of two reducible functionalities *i.e.*, the nitro and the thiocyanato group.

Scheme I



1

2, R^1 = H R = CO_2CH_3
3, R^1 = C_6H_5 R = CO_2CH_3
4, R^1 = H R = CN

i) $NaBH_4$, KOH and alkylating agent

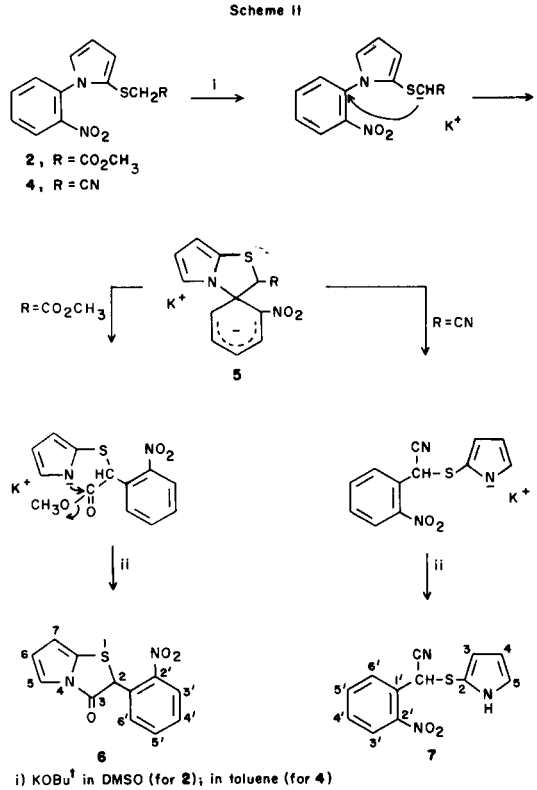
Yet another possible use of the nitrothiocyanato compound **1** as a precursor of the desired ring system, based on the known formation of hetero-aromatic *N*-oxides from nitrocompounds (7) was attempted. With this aim in mind methyl pyrrolylthioacetate **2** and phenylacetate **3** were prepared from thiocyanatopyrrole **1** (Scheme I).

As no reaction occurred upon treatment of compounds **2** and **3** with potassium *t*-butoxide in dry toluene at reflux temperature for about four hours, the cyclisation reactions were attempted with potassium *t*-butoxide in dimethylsulphoxide. An identifiable product was only obtained from methyl pyrrolylthioacetate **2**. With this substrate, starting material had disappeared after heating at 40° for about one hour. Work up of the reaction mixture afforded a yellow solid in 30% yield. The product is believed to be the pyrrolothiazole **6**. The spectroscopic and analytical data are in agreement with the proposed structure.

It was then decided to study the effect of the activating group on the course of the reaction, namely by replacing the ester function with a nitrile group. The pyrrolylthioacetonitrile **4** was therefore prepared from nitrophenylthiocyanatopyrrole **1**. Reaction of the thioacetonitrile **4** with potassium *t*-butoxide in toluene at 50-70° for 3.5 hours afforded a product in 28% yield upon work up of the reaction mixture. It was assigned structure **7** on the basis of spectroscopic and analytical data.

A mechanism that accounts for the formation of compound **6** and **7** is shown in scheme II. It involves a

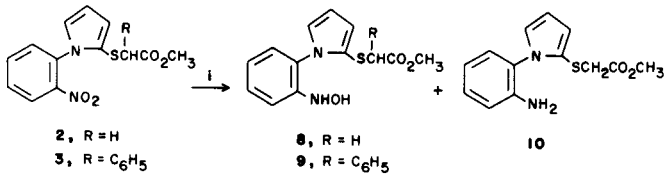
Scheme II



nucleophilic attack on the benzene ring by the generated carbanions to give Meisenheimer-type intermediates **5** (R = CO_2CH_3 or CN) which collapse to the corresponding pyrrolyl anions. When R = CO_2CH_3, the anion undergoes intramolecular acylation to give the pyrrolothiazole **6**. When R = CN, protonation of the intermediate anion yields the 2-substituted pyrrole **7**.

Preliminary work on a conventional route to benzothiadiazocines by reductive ring closure (8) of the pyrrolylthioacetates **2** and **3** failed to produce the desired compounds. Instead the corresponding hydroxylamines **8** and **9** were isolated. Prolonged reaction times resulted in the conversion of **8** to the amine **10**. The latter compound did not cyclise on heating in xylene (Scheme III).

Scheme III



2, R = H
3, R = C_6H_5

8, R = H
9, R = C_6H_5

10

i) Zn/$CaCl_2$ in CH_3OH

EXPERIMENTAL

The ir spectra of solids were taken as potassium bromide discs and liquids as thin films between sodium chloride plates. The nmr spectra were measured at 60 MHz in deuterochloroform on either a Perkin-Elmer R12B spectrometer or a Brücker WP60 unless otherwise specified. Mass spectral measurements were recorded on a Kratos MS25 machine equipped with a DS50S data system.

N-(2-Nitrophenyl)-2-thiocyanatopyrrole (**1**) was prepared by the published procedure (2).

2,3-Dihydro-2-(2-nitrophenyl)-3-oxopyrrolo[2,1-*b*]thiazole (**6**).

To a solution of *N*-arylthiocyanatopyrrole **1** (0.005 mole) in methanol (50 ml), kept under nitrogen, sodium borohydride (0.0075 mole) was added in portions and the mixture stirred at room temperature for 45 minutes. 85% Potassium hydroxide (0.0075 mole) in methanol (10 ml) was then added followed by methyl bromoacetate (0.0075 mole). The reaction mixture was heated under gentle reflux for 1.5 hours after which it was cooled, diluted with brine solution (50 ml) and extracted with chloroform (4 × 40 ml). The chloroform extracts were dried over magnesium sulphate, filtered and the solvent removed. The residue was passed through a silica gel column, and the oily product **2** eluted with chloroform (60% yield); ir: 1720 cm^{-1} (ester C=O); nmr: δ 3.10 (s, 2H, SCH_2), 3.60 (s, 3H, OCH_3), 6.35 (t, 1H, H-4), 6.65 (dd, 1H, H-3), 6.95 (dd, 1H, H-5), 7.4-8.3 (m, 4H, benzenoid); ms for $C_{13}H_{12}N_2O_4S$: 292 (M^+), 219 (292-$CH_2CO_2CH_3$), 187 (219-S), 173 (219-NO_2).

A solution of **2** (0.001 mole) in dimethyl sulphoxide (4-6 ml) was added to a stirred suspension of commercially available potassium *t*-butoxide (0.002 mole) in dry dimethyl sulphoxide (25 ml) kept under a continuous stream of dry nitrogen. The suspension, which turned dark in colour upon addition of the pyrrole, was stirred for one hour at 40°. The reaction mixture was then poured onto ice-water and acidified with 2*N* hydrochloric acid. The organic layer was separated and the aqueous layer extracted with chloroform (3 × 30 ml). The combined organic layers were dried over magnesium sulphate and the solvent removed. The residue, which consisted mainly of the cyclised product, was chromatographed on a silica gel column (chloroform) to give the crystalline product **6** in 30% yield. An analytical sample of mp 129-130° dec was obtained as a yellow powder by crystallisation from ethanol; ir: 1740 cm^{-1} (C=O); 1530 and 1370 (asym and sym NO_2 stretching); nmr: δ 6.0 (dd, 1H, H-7, $J_{7,6}$ = 3.3 Hz, $J_{7,5}$ = 1.1 Hz), 6.10 (s, 1H, H-2); 6.54 (t, 1H, H-6, $J_{6,5}$ = 3.3 Hz), 7.22 (dd, 1H, H-5), 7.44-8.13 (m, 4H, benzenoid); cmr (off resonance decoupled spectrum) δ 54.1 (d, C-2); 104.6 (d, C-7/C-6); 113.7 (d, C-7/C-6); 120.6 (d, C-5), 125.6, 130.1 (m, phenyl-C), 130.4 (s, phenyl C-2'), 131.2, 134.2 (m, phenyl-C), 167 (s, C=O); ms: 260 (M^+), 149, 146, 135 ($CHC_6H_4NO_2$), 119 (135-O), 98 (C_4H_4NS), 77 (Ph).

Anal. Calcd. for $C_{12}H_8N_2O_3S$: C, 55.37; H, 3.10; N, 10.76. Found: C, 54.93; H, 3.14; N, 10.70.

2-(α-Cyano-2-nitrobenzyl)thiopyrrole (**7**).

The reaction of *N*-arylthiocyanatopyrrole **1** with chloroacetonitrile was carried out as described above in the preparation of compound **2**. The oily product **4** was obtained in 45% yield. ir: 2240 cm^{-1} (C≡N); nmr: δ 3.10 (s, 2H, CH_2CN) 6.40 (t, 1H, H-4), 6.83 (dd, 1H, H-3), 6.95 (dd, 1H, H-5) 7.40-8.30 (m, 4H, benzenoid); ms for $C_{12}H_9N_3O_2S$: 259 (M^+), 219 (259-CH_2CN), 187 (259-SCH_2CN), 173 (219-NO_2).

A solution of **4** (0.001 mole) in dry toluene (4-6 ml) was treated with potassium *t*-butoxide (0.002 mole) in dry toluene (35 ml) for 3.5 hours at 50-70° under a nitrogen atmosphere. The reaction mixture was cooled and worked up as described in the preparation of **6** above to give the product **7** in 28% yield. An analytical sample of mp 99-100° was obtained as light brown needles by crystallisation from ether; ir: 3400 cm^{-1} (NH); 2300 (C≡N); 1530 and 1350 (asym and sym NO_2 stretching); nmr (200 MHz): δ 5.87 (s, 1H, CHCN), 6.20 (m, 1H, H-4), 6.29 (m, 1H, H-3, $J_{3,5}$ = 1.5 Hz, $J_{3,4}$ = 3.9 Hz, $J_{3,1}$ = 2.5 Hz), 6.95 (2 × t, 1H, H-5, $J_{5,4}$ = 2.9 Hz, $J_{5,1}$ = 2.8 Hz), 7.26 (m, 1H, benzenoid), 7.54 (m, 2H, benzenoid), 8.16 (m, 1H, benzenoid), 8.50 (s, br, 1H, NH, deuterium oxide exchangeable); cmr: δ 39.0 (*C*HCN), 110.8, 121.2, 123.7 (C-3, C-4, C-5), 126.1, 129.9, 130.2, 133.6 (C-3', C-4', C-5' and C-6'); ms: 259 (M^+), 135 ($CHC_6H_4NO_2$), 98 (C_4H_4NS), 77 (Ph).

Anal. Calcd. for $C_{12}H_9N_3O_2S$: C, 55.58; H, 3.50; N, 16.20. Found: C, 55.52; H, 3.56; N, 16.12.

Methyl [*N*-(2-Hydroxylaminophenyl)-2-pyrrolylthio]acetate (**8**).

Zinc powder (3.27 g, 0.05 mole) was added to a stirred solution of methyl [*N*-(2-nitrophenyl)-2-pyrrolylthio]acetate (**2**) (1.0 g, 0.0034 mole) and calcium chloride (0.555 g, 0.005 mole) in 80% aqueous methanol (60 ml). The suspension was heated under reflux for 1.5 hours, cooled to room temperature and filtered. The filtrate was diluted with water and extracted with chloroform. The chloroform extracts were dried over magnesium sulphate, filtered and the solvent removed. The thick oily residue was absorbed on a silica gel column and methyl [*N*-(2-aminophenyl)-2-pyrrolylthio]acetate (**10**) eluted with chloroform in the first fraction. Evaporation of the solvent afforded a thick oil (0.09 g, 10%), which solidified on standing; ir: 3500, 3400 cm^{-1} (NH_2); 1720 (ester C=O); nmr: δ 3.1 (s, 2H, SCH_2), 3.35-3.67 (s, br, 2H, NH_2, deuterium oxide exchangeable), 3.57 (s, 3H, OCH_3), 6.3 (dd, 1H, H-4), 6.57 (dd, 1H, H-3), 6.7-7.3 (m, 5H, H-5 and benzenoid); ms for $C_{13}H_{14}N_2O_2S$: 262 (M^+), 189 (262-$CH_2CO_2CH_3$), 157 (262-$SCH_2CO_2CH_3$), 156 (189-SH).

Methyl [*N*-(2-hydroxylaminophenyl)-2-pyrrolylthio]acetate (**8**) was eluted with chloroform as the second fraction (0.35 g, 37%). An analytical sample of mp 81-83° was obtained as off-white needles by crystallisation from *n*-hexane; ir: 3500-2500 cm^{-1} (OH, br), 3300 (NH), 1725 (ester C=O); nmr: δ 3.05 (s, 2H, SCH_2), 3.55 (s, 3H, OCH_3), 5.5-6.4 (v br, s, 2H, NHOH, deuterium oxide exchangeable), 6.3 (t, 1H, H-4); 6.65 (dd, 1H, H-3), 6.8 (dd, 1H, H-5), 7.0-7.6 (m, 4H, benzenoid): ms: 278 (M^+), 262 (278-O), 260 (278-H_2O), 189 (262-$CH_2CO_2CH_3$), 187 (260-$CH_2CO_2CH_3$), 173 (189-NH_2).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06. Found: C, 56.19; H, 5.24; N, 9.99.

Methyl α-[*N*-(2-Hydroxylaminophenyl)-2-pyrrolylthio]phenylacetate (**9**).

The reaction of *N*-arylthiocyanatopyrrole **1** with methyl α-bromo-

phenyl acetate (**9**) was carried out as described above in the preparation of compound **2**. The oily product **3** was obtained in 85% yield; ir: 1740 cm^{-1} (br, ester C=O); nmr: δ 3.50 (s, 3H, OCH_3), 4.4 (s, 1H, SCH), 6.3 (dd, 1H, H−4), 6.5 (dd, 1H, H−3), 6.9 (dd, 1H, H−5), 7.0-8.2 (m, 9H, benzenoid); ms for $C_{19}H_{16}N_2O_4S$: 368 (M^+), 219 (368-CHPhCO_2CH_3), 186 (219-S), 173 (219-NO_2), 77 (Ph).

Zinc powder (3.27 g, 0.05 mole) was added to a stirred solution of methyl α-[*N*-(2-nitrophenyl)-2-pyrrolylthio]phenyl acetate (**3**) (1.06 g, 0.0028 mole) and calcium chloride (0.555 g, 0.005 mole) in 80% aqueous methanol (50 ml). The suspension was heated under reflux for 1.5 hours, cooled to room temperature and filtered. The filtrate was diluted with water and extracted with chloroform. The chloroform extracts were dried over magnesium sulphate, filtered and the solvent removed. The thick oily residue was absorbed on a silica gel column. The hydroxylaminophenylpyrrole **9**, the major product of the reaction, was eluted with chloroform (0.973 g, 50.3%). An analytical sample of mp 97-99° was recrystallised from n-hexane as tan needles; ir: 3350-2500 cm^{-1} (br, OH), 3350 (NH), 1740 (ester C=O); nmr: δ 3.6 (s, 3H, OCH_3), 4.5 (s, 1H, SC*H*Ph), 5.5-6.2 (s, br, 2H, NHOH, deuterium oxide exchangeable), 6.3 t, 1H, H−4), 6.55 (t, 1H, H−3), 6.9 (t, 1H, H−5), 7.0-7.6 (m, 9H, benzenoid); ms: 354 (M^+), 338 (354-0), 203, 189 (338-$CH_2C_6H_4CO_2CH_3$), 173 (189-NH_2), 157 (189-S), 156 (189-SH), 77 (Ph).

Anal. Calcd. for $C_{19}H_{18}N_2O_3S$: C, 64.38; H, 5.12; N, 7.90. Found: C, 64.44; N, 5.08; N, 7.91.

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REFERENCES AND NOTES

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