Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Heterocycles With a Benzothiadiazepine Moiety. IV. Synthesis of Novel Tetracyclic Rings by Intramolecular Cyclization of 10-Bromoacetyl-10,11-dihydro-11-ethoxycarbonyl-pyrrolo[1,2-b] [1,2,5] Benzothiadiazepine 5,5-Dioxide and Its Derivatives

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Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 24(19), 2685-2695 (1994)

HETEROCYCLES WITH A BENZOTHIADIAZEPINE MOIETY. 4. SYNTHESIS OF NOVEL TETRACYCLIC RINGS BY INTRAMOLECULAR CYCLIZATION OF 10-BROMOACETYL-10,11-DIHYDRO-11-ETHOXYCARBONYLPYRROLO[1,2-b] [1,2,5] BENZOTHIADIAZEPINE 5,5-DIOXIDE AND ITS DERIVATIVES

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Abstract: Two novel tetracyclic derivatives, namely **5** and **8**, have been synthesized by intramolecular cyclization of the 10-bromoacetyl-10,11-dihydro-11-ethoxycarbonylpyrrolo[1,2-b] [1,2,5]benzothiadiazepine 5,5-dioxide (**3**) and, respectively, the bis-methylamide of 11-carboxy-10,11-dihydropyrrolo[1,2-b] [1,2,5]benzothiadiazepine-11-acetic acid 5,5-dioxide (**4**). The last compound formed when treating with an excess of methylamine either the lactam **5** or the diethyl ester of 11-carboxy-10,11-dihydropyrrolo[1,2-b] [1,2,5]benzothiadiazepine-11-acetic acid 5,5-dioxide (**7**). An unambiguous synthesis of the diester **7** was achieved to confirm the chemical structure of derivatives **4** and **5**.

During studies on new antidepressant agents related to aptazepine **1**[1-7] we attempted to synthesize the dioxoderivative **2** by treatment of **3** with an excess of methylamine. Contrary to our expectation instead of compound **2** we obtained as the sole product the diamide **4** , which could be presumably formed by the reaction of methylamine with the intermediate **5**.

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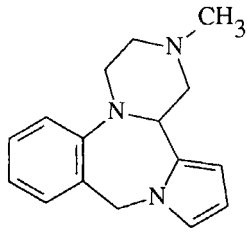
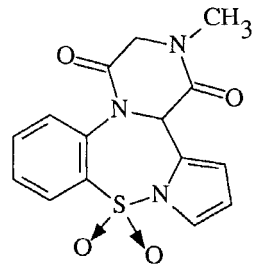


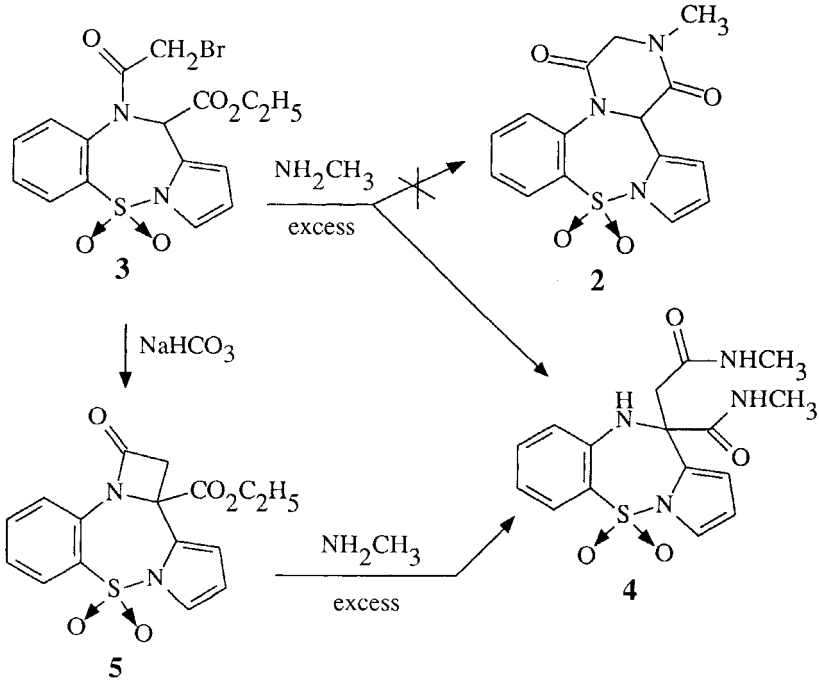
1



2

To confirm our supposition we prepared the tetracyclic lactam **5** by intramolecular cyclization of **3** in the presence of sodium bicarbonate. Subsequent reaction of **5** with an excess of methylamine afforded as expected the diamide **4** (Scheme 1).

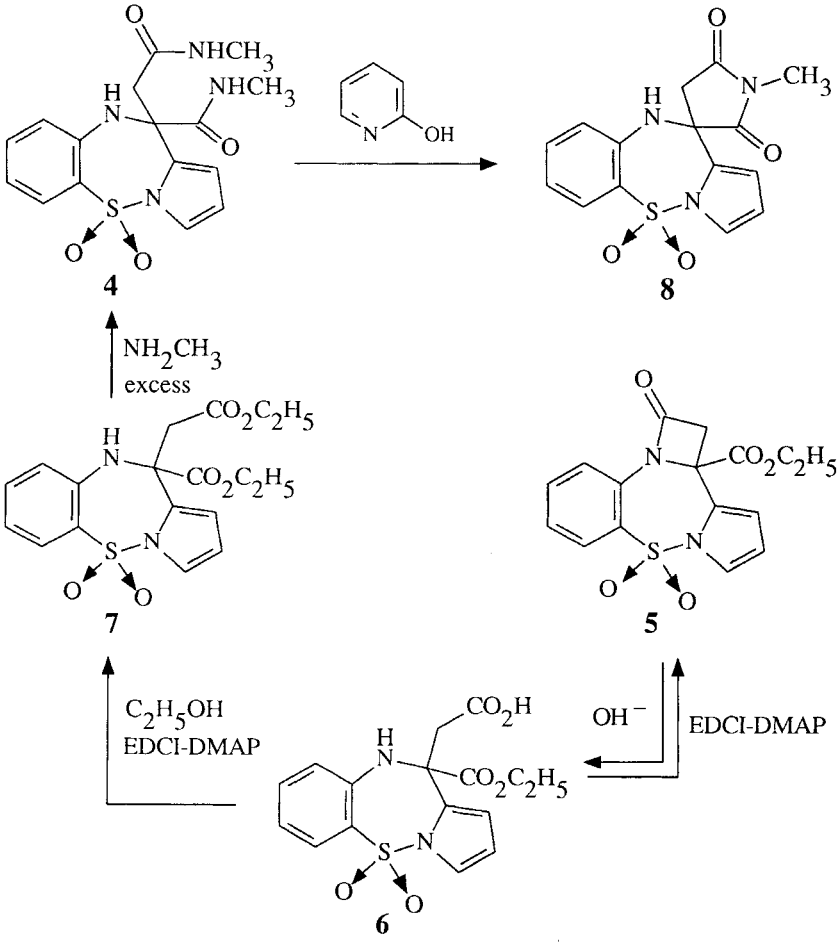
SCHEME 1



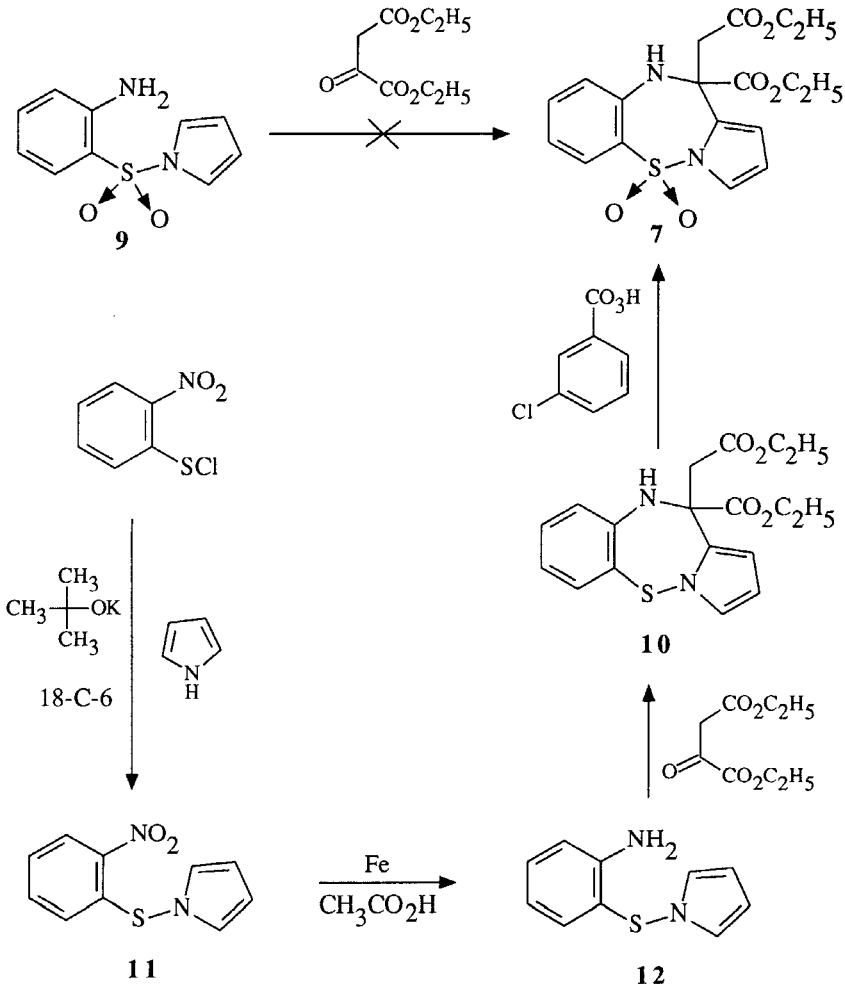
Intramolecular cyclization of **4** in the presence of 2-hydroxypyridine[8] led exclusively to the tetracyclic spiroderivative **8**, thus confirming the double substitution at the 11 position of the pyrrolobenzothiadiazepine ring.

Alkaline hydrolysis of the lactam **5** afforded the hemiester **6** , which in turn was esterified by treating with dry ethanol in the presence of N-(dimethylaminopro pyl)-N'-ethylcarbodiimidehydrochloride/4-dimethylaminopyridine (EDCI-DMAP)

SCHEME 2



SCHEME 3



to give the diester **7**. Treatment of this ester with an excess of methylamine gave the diamide **4** (Scheme 2). From **6** the lactam **5** formed again by intramolecular cyclization in the presence of EDCI-DMAP.

At this point we needed to obtain the diester **7** required for the synthesis of **4** by an unambiguous procedure.

A direct synthesis of **7** by reacting 1-(2-aminobenzenesulfonyl)-1*H*-pyrrole **9**[9] with diethyl oxalacetate was unsuccessful. However, we were able to prepare the diester **10**, which was then easily oxidized to the dioxide **7**.

Reaction of 2-nitrobenzenesulfenyl chloride with 1*H*-pyrrole in the presence of potassium *tert*-butoxide and 18-Crown-6 furnished 1-(2-nitrobenzenesulfenyl)-1*H*-pyrrole **11**, which was reduced to the corresponding amino derivative **12** with iron powder in acid medium. Condensation of **12** with diethyl oxalacetate with concomitant intramolecular cyclization led to the required diester **10** (Scheme 3).

In conclusion, novel tetracyclic structures can be easily prepared starting from compound **3** as proved by the synthesis of compounds **5** and **8**. The same derivative **3** was used by us in a recent work[10] as key intermediate for the preparation of the tetracyclic N-benzyl N-desmethyl derivative of compound **2**, which was then transformed in the benzothiadiazepine analog of aptazepine (**1**).

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 apparatus and are uncorrected. IR spectra were run on a Perkin-Elmer 1310 spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian EM-390 (90 MHz) specrometer using tetramethylsilane as internal standard. ^{1}H-NMR and ^{13}C-NMR-APT spectra of compounds **4** and **8** were obtained on a Varian Gemini 200 MHz spectrometer. Column chromatographies were performed on alumina Merck (70-230 mesh) and silica gel Merck (70-230 mesh). Aluminum oxide/TLC-cards Fluka (aluminum oxide precoated aluminum cards with fluorescent indicator 254 nm) and Silica gel/TLC-cards Fluka (silica gel precoated aluminum cards with fluorescent indicator 254 nm) were used for thin layer chromatography. Developed plates were visualized by UV light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure (approx. 20 bar). Elemental analyses were performed by laboratories of Prof. A Pietrogrande, University of Padova (Italy).

11-Carboxy-10,11-dihydropyrrolo[1,2-b][1,2,5]benzothiadiazepine-11-acetic acid bis-methylamide 5,5-dioxide (4). From **3**. A solution of **3** (0.54 g, 1.27 mmol) and 40% aqueous methylamine (20 ml) in ethanol (50 ml) and tetrahydrofuran (50 ml) was heated under stirring at 45°C for 2 hours. After concentration to a small volume the mixture was extracted with ethyl acetate. Organic layer was separated, washed with brine and dried. Removal of the solvent gave 0.23 g of **4** (50%), mp 268-270°C (after crystallization from aqueous N,N-dimethylformamide); IR (nujol): ν 1645 (CO), 3240 and 3360 cm^{-1} (NH); ^{1}H-NMR (DMF-d7): δ 2.68 (d, 3H, J = 4.6 Hz, CH_3), 2.74 (d, 3H, J = 4.8 Hz, CH_3), 2.93 and 3.27 (2d, 2H, ABq, J = 14 Hz, CH_2), 6.34 (t, 1H, $J_{1-2} = J_{2-3}$ = 3.2 Hz, H_2), 6.43 (dd, 1H, J_{1-2} = 3.2 Hz, J_{1-3} = 1.6 Hz, H_1), 6.96 and 7.02 (overlapped t and d, 2H, $J_{6-7} = J_{7-8}$ = 7.5 Hz, H_6 and H_8), 7.31 (dd, 1H, J_{2-3} = 3.2 Hz, J_{1-3} = 1.6 Hz, H_3), 7.53 (t, 1H, $J_{6-7} = J_{7-8}$ = 7.5 Hz, J_{7-9} = 1.4 Hz, H_7), 7.72 (d, 1H, J_{8-9} = 7.5 Hz, J_{7-9} = 1.4 Hz, H_9), 7.94 (m broad, 1H, CONH), 8.14 (s, 1H, NH), 8.39 ppm (m broad, 1H, CONH); ^{13}C-NMR-APT (DMF-d7): δ 25.83 and 26.51 (CH_3), 43.25 and 45.00 (aliphatic), 111.52, 115.13, 119.08, 121.91 and 122.65 (CH), 124.46 (C), 126.30 (CH), 130.16 (C), 135.64 (CH), 144.30 (C), 171.41 and 171.65 ppm (carbonyl).

From **5.** Starting from **5** compound **4** (68% yield) was prepared as above reported.

From **7**. Starting from **7** compound **4** (70% yield) was prepared as above reported.

Anal. Calcd. for $C_{16}H_{18}N_4O_4S$: C, 53.02; H, 5.00; N, 15.46; S, 8.84. Found: C, 52.93; H, 5.03; N, 15.28; S, 8.86.

12,12a-Dihydro-12a-ethoxycarbonyl-11-oxo-11*H*-azeto[2,1-d]rolo[1,2-b][1,2,5]benzothiadiazepine 5,5-dioxide (5). From **3**. A mixture of **3** (7.00 g, 16 mmol), $NaHCO_3$ (1.44 g, 17 mmol), ethanol (300 ml), tetrahydrofuran (300 ml) was refluxed for 24 hours. After cooling the mixture was filtered and the solvent evaporated to a residue which was dissolved in chloroform, dried and concentrated. The residue was purified by chromatography on silica gel column eluting with chloroform. First fractions were collected and evaporated to give 5.5 g of **5** (98%) as an oil which solidified by trituration with carbon tetrachloride, mp 160-161°C (after crystallization from toluene/cyclohexane); IR (nujol): ν 1735 (CO ester), 1770 cm^{-1} (CO β-lactam); ^{1}H-NMR ($CDCl_3$): δ 1.21

(t, 3H, $COOCH_2CH_3$), 3.56 and 3.76 (ABq, 2H, J = 15 Hz, methylene of β-lactam), 4.25 (q, 2H, $COOCH_2CH_3$), 6.35 (m, 1H, pyrrole), 6.46 (m, 1H, pyrrole), 7.15-7.45 (m, 2H, pyrrole and benzene), 7.55-7.68 (m, 1H, benzene), 7.98-8.15 (m, 1H, benzene), 8.51-8.61 ppm (m, 1H, benzene).

From **6**. A solution of **6** (0.63 g, 1.7 mmol), N-(dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.33 g, 1.7 mmol) and 4-dimethylaminopyridine (0.21 g, 1.7 mmol) in dichloromethane (30 ml) was stirred at room temperature for 48 hours, then diluted with water and acidified with 10% HCl. The organic layer was separated, washed with brine and dried. Removal of the solvent gave a residue which was purified on silica gel column eluting with chloroform. First fractions were collected and evaporated to afford 0.36 g of oily **5** (42%) which solified by treatment with carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{14}N_2O_5S$: C,55.48; H,4.07; N, 8.08; S, 9.25. Found: C, 55.44; H, 4.09; N, 8.12; S, 9.46.

10,11-Dihydro-11-ethoxycarbonylpyrrolo[1,2-b][1,2,5]benzothia diazepine-11-acetic acid 5,5-dioxide (6). A mixture of **5** (1.00 g 2.9 mmol), 1N aqueous KOH (3.0 ml), ethanol (10 ml) and tetrahydrofuran (10 ml) was stirred at room temperature for 1 hour. The solution was treated with crushed ice and made acid (pH 2) with 1N HCl. After extraction with chloroform the organic layer was separated, washed with brine and evaporated to afford **6** in quantitative yield (1.04 g) as an oil which solidified by trituration with carbon tetrachloride, mp 168-171°C (after crystallization from toluene/cyclohexane); IR (nujol): ν 1690 (CO acid), 1720 (CO ester), 3350 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ 1.31 (t, 3H, $COOCH_2CH_3$), 3.36 and 3.86 (2d, 2H, ABq, J = 18 Hz, methylene), 4.31 (q, 2H, $COOCH_2CH_3$), 6.18 (m, 2H, pyrrole), 6.88-7.61 (m, 4H, pyrrole and benzene), 7.71-7.91 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{16}H_{16}N_2O_6S$: C, 52.73; H, 4.42; N, 7.68; S, 8.80. Found: C, 52.53; H, 4.30; N, 7.58; S, 8.89.

Ethyl 10,11-dihydro-11-ethoxycarbonylpyrrolo[1,2-b][1,2,5] benzothiadiazepine-11-acetic acid 5,5-dioxide (7). From **6**. N-(Dime thylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.52 g, 2.7 mmol) was added while stirring to an ice-cooled solution of **6** (1.00 g, 2.7 mmol), 4-dime thylaminopyridine (0.16 g, 1.35 mol) and absolute ethanol (0.15 ml) in

dichloromethane (50 ml). Stirring was continued at 0°C for 2 hours and then at room temperature overnight. The solution was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was separated, washed with 5% $NaHCO_3$, then with brine and dried. Removal of the solvent gave a residue which was purified on silica gel column eluting with chloroform. First fractions were collected and evaporated to give 0.95 g of **7** (90%) as an oil which solidified on standing, mp 96-97°C (after crystallization from cyclohexane); IR (nujol): ν 1720 and 1730 (CO esters), 3360 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 6H, $COOCH_2CH_3$), 3.35 and 3.77 (2d, 2H, ABq, J = 15 Hz, methylene), 4.18 and 4.26 (2q, 4H, $COOCH_2CH_3$, overlapped signals), 5.88 (s, 1H, NH, disappeared on treatment with D_2O), 6.15 (m, 2H, pyrrole), 6.78-7.13 (m, 2H, benzene), 7.18-7.55 (m, 2H, pyrrole and benzene), 7.81 ppm (m, 1H, benzene).

From **10**. A solution of **10** (0.35 g, 1.00 mmol) in benzene (10 ml) was added dropwise onto a solution of 55% 3-chloroperoxybenzoic acid (0.80 g, 2.5 mmol), then the mixture was stirred at room temperature for 2 hours. Water and ethyl acetate were added. After shaking the organic layer was separated, washed with brine and dried. Removal of the solvent gave a residue which was purified by passing through an alumina column (chloroform as eluent). First eluates were collected and evaporated to give 0.10 g of oily **7** (26%) which solidified on standing.

Anal. Calcd. for $C_{18}H_{20}N_2O_6S$: C, 55.08; H, 5.13; N, 7.14; S, 8.17. Found: C, 55.15; H, 5.11; N, 7.05; S, 8.27.

Spiro[1-methyl-2,5-dioxopyrrolidine-3,11'-[10'H]pyrrolo[1,2-b][1,2,5]benzothiadiazepine 5',5'-dioxide] (8). A solution of **4** (0.54 g, 1.5 mmol) and 2-hydroxypyridine (0.14 g, 1.5 mmol) in diphenylether (8 ml) was heated at 180°C for 20 hours. After cooling the mixture was treated with *n*-hexane (60 ml). The solid which formed was filtered, dissolved in chloroform and chromatographed on alumina column (chloroform as eluent). The central eluates after evaporation of the solvent gave 0.25 g of **8** (50%), mp 247-248°C (after crystallization from toluene); IR (nujol): ν 1690 and 1770 (CO), 3320 cm^{-1} (NH); ^{1}H-NMR (DMF-d7): δ 3.07 (s, 3H, CH_3), 3.37 and 3.52 (2d, 2H, ABq, CH_2), 6.18 (dd, 1H, J_{1-2} = 3.3 Hz, J_{1-3} = 1.5 Hz, H_1), 6.33 (t, 1H, $J_{1-2} = J_{2-3}$ = 3.3 Hz, H_2), 6.98 (t, 1H, J = 7.5 Hz, H_8), 7.10 (d, 1H, J = 7.5 Hz, H_6), 7.43 (s, 2H, H3 and NH), 7.55 (t, 1H, J = 7.5 Hz, H_7), 7.74 ppm (d, 1H, J = 7.5 Hz,

H9); ^{13}C-NMR-APT (DMF-d7): δ 25.26 (CH_3), 4.41 and 64.49 (aliphatic), 112.06, 115.06, 119.84, 122.51 and 123.30 (CH), 125.43 (C), 126.72 (CH), 128.68 (C), 136.13 (CH), 145.13 (C), 174.21 and 176.52 ppm (carbonyl).

Anal. Calcd. for $C_{15}H_{13}N_3O_4S$: C, 54.36; H, 3.95; N, 12.68; S, 9.67. Found: C, 54.37; H, 4.15; N, 12.38; S, 9.93.

Ethyl 10,11-dihydro-11-ethoxycarbonylpyrrolo[1,2-b][1,2,5] benzothiadiazepine-11-acetic acid (10). A solution of **12** (4.56 g, 24 mmol), diethyl oxalacetate (6.77 g, 36 mmol) and maleic acid (1.16 g, 10 mmol) in absolute ethanol (100 ml) was refluxed for 3.5 hours. The mixture was concentrated and the residue partitioned between water and chloroform. The organic layer was separated, washed with 5% $NaHCO_3$, then with brine and dried. Removal of the solvent gave a crude product which was purified on silica gel column (dichloromethane as eluent). First fractions were discarded and central eluates were collected and evaporated to give 8.3 g of **10** (96%) as an oil which solidified on standing, mp 69-70°C (after crystallization from *n*-hexane); IR (nujol): ν 1720 (CO), 3320 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 6H, $COOCH_2CH_3$), 3.30 and 3.52 (2d, 2H, ABq, J = 15 Hz, methylene), 4.20 and 4.30 (2q, 4H, $COOCH_2CH_3$, overlapped signals), 5.80 (s, 1H, NH, disappeared on treatment with D_2O), 6.03 (m, 2H, pyrrole), 6.51-6.88 (m, 3H, pyrrole and benzene), 6.98-7.31 ppm (m, 2H benzene).

Anal.. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77; S, 8.89. Found: C, 59.87; H, 5.55; N, 7.66; S, 9.12.

1-(2-Nitrobenzenesulfenyl)pyrrole (11). A solution of pyrrole (5.00 g, 74 mmol) in dry tetrahydrofuran (75 ml) was added dropwise to a well stirred mixture of potassium *tert*-butoxide (9.95 g, 90 mmol) and 18-crown-6 (2.08 g, 8 mmol) in the same solvent (75 ml). The mixture was stirred at room temperature for 15 minutes, then cooled to 0°C while a solution of 2-nitrobenzenesulfenyl chloride (14.00 g, 74 mmol) in dry tetrahydrofuran (75 ml) was dropped onto. Reaction was stirred at room temperature for 18 hours, then concentrated to a small volume. The residue was extracted with dichloromethane, washed with brine and dried. After removal of the solvent crude product was purified on alumina column eluting with chloroform/petroleum ether 1:1. First eluates were collected and evaporated to give 8.9 g of **11** (55%), mp 71°C (after crystallization from ligroin); ^{1}H-NMR ($CDCl_3$):

δ 6.10-6.23 (m, 1H, benzene), 6.43 (m, 2H, pyrrole), 6.86 (m, 2H, pyrrole), 7.23-7.66 (m, 2H, benzene), 8.30-8.43 ppm (m, 1H, benzene).

Anal. Calcd. for $C_{10}H_8N_2O_2S$: C, 54.53; H, 3.66; N, 12.72; S, 14.56; Found: C, 54.45; H, 3.68; N, 12.82; S, 14.52.

1-(2-Aminobenzenesulfenyl)pyrrole (12). Iron powder (6.8 g) was added over a period of 30 minutes to a water-cooled solution of **11** (5.00 g, 23 mmol) in glacial acetic acid (60 ml) and the mixture was stirred for 3.5 hours. Water and ethyl acetate were added with shaking and the organic layer was separated, washed with 5% $NaHCO_3$, then with brine and dried. Removal of the solvent gave a residue which was purified by passing through an alumina column eluting with dichloromethane. First fractions were collected and evaporated to afford 3.4 g of **12** (78%) as an oil which solidified on standing, mp 50-51°C (after crystallization from ligroin); IR (nujol): ν 3280 and 3340 cm^{-1} (NH_2); ^{1}H-NMR ($CDCl_3$): δ 4.33 (s, broad, 2H, NH_2, disappeared on treament with D_2O), 6.16 (m, 2H, pyrrole), 6.41-6.48 (m, 4H, pyrrole and benzene), 7.03-7.50 ppm (m, 2H, benzene).

Anal. Calcd. for $C_{10}H_{10}N_2S$: C, 63.12; H, 5.30; N, 14.72; S, 16.85. Found: C, 63.27; H, 5.31, N, 14.63; S, 16.77.

Acknowledgements. Authors are grateful to Italian MURST for grants (60% and 40%).

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(Received in the UK 7 March 1994)