III. Dihydro-1-oxoindolizine Dyes. A. General Method 1. An appropriate active methylene compound dissolved in pyridine was treated with a pyridine solution of an equimolar amount of the desired triiodide B. The brightly colored solution was stirred at room temperature for 1 h and poured into water. The resulting precipitate was filtered off, washed with water, and air-dried to furnish good yields of product of good purity. In general, the use of other convenient solvents is not detrimetnal to the reaction if sufficient pyridine is present to react with the HI generated in the reaction. If the solvent is not water miscible, product is precipitated in ether or ligroin, filtered off, and washed with water to remove the pyridinium iodide.

If oxoindolizinium ions other than triiodides were used, an equivalent of benzoquinone or iodine was necessary to complete the reaction, although up to 50% yields of dye could be formed without additional oxidant.

B. General Method 2. The desired indolizinol, prepared by one of the previously described methods, was mixed with an equimolar amount of an appropriate active methylene compound and an excess of pyridine. The resulting solution was mixed with a dioxane solution of a molar equivalent of benzoquinone or iodine, stirred at room temperature for 1 h, and poured into water. The resulting dye was filtered off, washed thoroughly with water to remove hydroquinone or pyridinium hydroiodide, and air-dried to furnish 90–100% yields of product of good purity, as determined by thin-layer chromatography/silica gel.

C. A 20% solution of 2.06 g (10 mmol) of diphenyllcyclopropenone in 11 mL of quinoline was heated at 80 °C under argon for 50 min until IR indicated all of the cyclopropenone had reacted. The heat was removed, and the reaction mixture was treated sequentially with a 2-fold excess of Meldrum's acid and 4 equiv of iodine/12 mL of pyridine. After 40 min (590-nm absorption stops increasing) the reaction mixture was diluted with CH_2Cl_2 and washed five times with 1 N HCl. Evaporation of the organic layer furnished 5.8 g (>100% yield) of a crude blue solid shown by NMR to contain approximately 50% of the desired adduct. Crystallization from methanol gave pure product, as determined by microanalysis or thin-layer chromatography, as noted below.

IV. Dihydro-3-oxoindolizine Dyes. A. 5-(3,7-Dihydro-1,2-diphenyl-3-oxoindolizin-7-ylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5). Pyridine (10 mL) was thoroughly purged with argon, 2,3-diphenylcyclopropenone (0.41 g, 2 mmol) was added, and the mixture was stirred under argon for 0.5 h at room temperature. Addition of 2,2-dimethyl-1,3-dioxane-4,6-dione (0.32 g, 2.2 mmol) followed by a solution of I_2 (1.01 g, 4 mmol) in 10 mL of pyridine gave a red solution. The solution was poured into 200 mL of 1 N HCl, which precipitated the crude dye: 0.73 g (86%) after filtration, washing, and drying. This crude mixture of **5** and **6** was dissolved in a minimum of CH_2Cl_2 and poured into 100 mL of MeOH. The CH_2Cl_2 was boiled off, and 0.55 g (65%) of **5** was obtained after filtration and drying: mp 275–277 °C dec; $\lambda_{max}^{CH_2Cl_2}$ 442 nm; $\epsilon_{max}^{CH_2Cl_2}$ 4.30. Thin-layer chromatography indicated a trace of **6** as the only contaminant.

Acceptable micro analytical data were difficult to obtain on many of the tabulated compounds because of their tendency to tenaciously retain solvent. All materials gave correct m/z results and **6–14**, **19**, **20**, **25**, and **26** gave microanalytical results within 0.5% C, 0.2% H, N. Missing melting points and spectral properties for several compounds were not available since compounds were used as intermediates without obtaining the analytical data. The compounds were included in the table for comparative purposes.

Registry No. **1**, 886-38-4; **4**, 105019-60-1; **5**, 86193-36-4; **6**, 86222-47-1; **7**, 86222-48-2; **8**, 86222-46-0; **9**, 121030-45-3; **10**, 86193-12-6; **11**, 86193-10-4; **12**, 86193-08-0; **13**, 121030-46-4; **14**, 121030-47-5; **15**, 121030-48-6; **16**, 121030-49-7; **17**, 121030-50-0; **18**, 121030-51-1; **20**, 86193-13-7; **21**, 121030-52-2; **22**, 121030-53-3; **23**, 121030-54-4; **24**, 121030-55-5; **25**, 121030-56-6; **26**, 121030-57-7; **27**, 121030-58-8; **28**, 121030-59-9; 5-cyano-2,3-diphenyl-1-indolizinol, 121030-41-9; 2-cyanopyridine, 100-70-9; 2,3-diphenyl-5-formyl-1-indolizinol, 121030-42-0; 2-pyridinecarboxaldehyde, 1121-60-4; 2,3-diphenyl-7-methyl-1-oxo(1*H*)-indolyimium tetrafluoroborate, 121030-44-2; 4-picoline, 108-89-4; pyridine, 110-86-1; 2,2-dimethyl-1,3-dioxane-4,6-dione, 2033-24-1.

Reaction of Carbamoyl-*S*-benzylcarbodithiolate with Dipolarophiles

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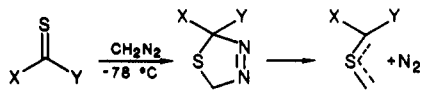
Tetrahydrothiophenes are obtained when dithiooxamide *S*-methylide is allowed to react with dipolarophiles. The reaction mechanism probably involves a nonconcerted pathway.

Introduction

Thiocarbonyl ylides can be successfully used in the synthesis of tetrahydrothiophenes.[1] There are several methods for obtaining thiocarbonyl ylides;[2] however, the mildest conditions are the ones used by Huisgen[3] in which a thiocarbonyl compound is treated with diazomethane to yield a thiadiazoline; this extrudes N_2 to yield the desired thiocarbonyl ylide (Scheme I).

However, only a few thioketones or thioaldehydes are readily available materials, owing to the instability of the C=S double bond. We have been searching for different stable thiocarbonyl compounds.

Scheme I



The easiest way to obtain stable thiocarbonyl compounds is to conjugate the C=S bond with heteroatoms. In fact, many of these compounds are stable, as thioesters or trithiocarbonates. However, conjugation of the C=S bond with the nonbonding electrons of the heteroatoms raises the LUMO of the thiocarbonyl compound, which turns the reaction with the diazoalkane into a slow process, and the rate of extrusion of N_2 is considerably enhanced. Under these conditions dithiolanes are the reaction products,[4] because the ylide undergoes cycloaddition with the

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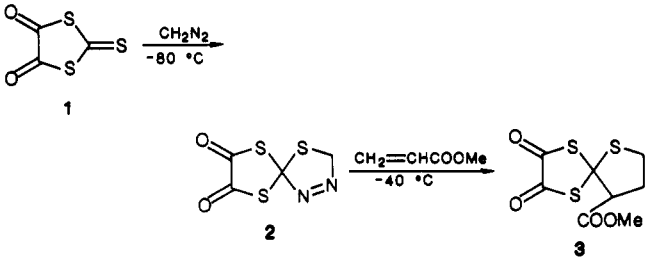
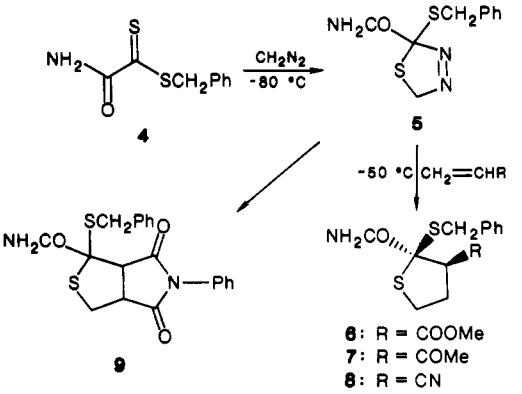
(2) Aono, M.; Hyodo, C.; Terao, V.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4039. Terao, V.; Tanaka, M.; Imai, N.; Achiwa, K. *Tetrahedron Lett.* **1985**, *26*, 3011.
(3) Kalwinsch, I.; Li, X.; Gottstein, J.; Huisgen, R. *J. Am. Chem. Soc.* **1981**, *103*, 7032. Kalwinsch, I.; Huisgen, R. *Tetrahedron Lett.* **1981**, *22*, 3941.
(4) Schönberg, A.; Cernik, D.; Urban, W. *Ber. Disch. Chem. Ges.* **1931**, *64*, 2577.

0022-3263/89/1954-3664$01.50/0

Scheme II



Scheme III



thiocarbonyl compound. To overcome this drawback, highly electronegative heteroatoms can be used as substituents. In fact thiophosgene can be used as the starting thiocarbonyl compound.[5] Nevertheless, the chlorine-substituted tetrahydrothiophenes lose HCl in the reaction mixture, affording dihydrothiophenes in a low yield. We therefore tried a different possibility, namely, lowering the LUMO of a trithioester through conjugation of the nonbonding electrons of the sulfur atoms with carbonyl groups. The red dithiolane **1** rapidly reacts with diazomethane even at −80 °C, to yield the expected thiadiazoline **2**. Despite this we have been able to obtain good yields of the adducts **3** only with methyl acrylate as the dipolarophile. For unknown reasons, other dipolarophiles produced only mixtures (Scheme II).

Results and Discussion

In this work we turned our attention to thiocarbonyl groups substituted with both an activating and a deactivating group. The compound chosen was **4** previously reported by Viola and Mayer and referred to as dithiooxamide.[6] This compound is a stable readily available solid. Its deep red color allows titration with diazomethane at −80 °C, avoiding an excess of the diazoalkane. When the thiadiazoline **5** is heated to −50 °C N_2 is generated; the thiocarbonyl ylide is apparently formed and undergoes cycloaddition with the dipolarophile. The best yields were obtained when methyl acrylate was used as the dipolarophile (**6**, 80%); methyl vinyl ketone and acrylonitrile afforded somewhat lower yields (60%, 35%) of adducts **7** and **8**. Dipolarophiles can be used as the solvent in these reactions, due to the very high rate of diazomethane addition to the C=S bond compared to the pyrazoline formation from the dipolarophiles.

To improve the yields we tested doubly activated olefins, such as *N*-phenylmaleimide, maleic anhydride, and dimethyl fumarate. Whereas a medium yield of adduct **9** (42%) was achieved with *N*-phenylmaleimide, mixtures were obtained with maleic anhydride, and no adduct could be isolated from the reaction with dimethyl fumarate (Scheme III). Less reactive dipolarophiles such as methyl methacrylate or methyl crotonate also afforded negligible amounts of adducts; instead, a highly crystalline dimeric compound was obtained in high yield in these cases. Structure **10**, analogous to the dimer formed in the case of the benzophenone *S*-methylide reported by Huisgen[7] is highly probable. Workup under hydrolytic conditions then transformed the dimer **10** into the anhydride **11**, revealing the proximity of the methoxycarbonyl groups. Furthermore, the easy elimination of the benzylthio groups indicates a trans relationship (Scheme IV).

As pointed out by Huisgen,[7] the mechanism of this dimerization should not be concerted, a two-step pathway being much more likely. We have found that if the reaction is carried out in MeOH containing $ZnCl_2$, the zwitterionic intermediate **12** can be trapped to afford **13** in high yield.

Knowing that dimer formation occurs through a polar pathway, we carried out the cycloadditions in apolar solvents such as hexane/CH_2Cl_2. Despite this, the yields of the adducts could not be significantly improved. The use of MeOH as solvent did not lead to any appreciable change in the dimer–cycloadduct competition. This, together with the lack of reactivity of well recognized dipolarophiles such as maleic anhydride or dimethyl fumarate, could indicate a zwitterionic pathway for these cycloadditions. Huisgen has already reported on nonconcerted cycloadditions of thiocarbonyl ylides[8] (Scheme IV).

Further evidence on this point was gained by studying the stereochemistry of the acrylate adduct **6**. From the "maximum secondary overlap" rule one would expect a cis relationship between the carboxamide and the carboxymethyl group if in fact a concerted reaction does take place. The ^1H NMR spectrum of **6** shows coupling constants between the C-3 proton and the C-4 neighboring protons of 6.7 Hz and 7.1 Hz. This points to a trans structure, provided that the carbonyl functions adopt a pseudoequatorial position. Moreover, when this compound was hydrolyzed at room temperature with KOH/MeOH, elimination of the thiobenzyl group took place to yield the dihydrothiophene **14**. This rapid elimination also points to a trans relationship between the thiobenzyl group and the H-3 proton (Scheme V).

So far we have been unsuccessful in our attempts to intercept the zwitterion. When the ylide was allowed to react with methyl acrylate in MeOH/CF_3COOH, only complex mixtures were produced. This is surprising for a concerted pathway, because if methyl acrylate is absent from the reaction mixture, protonation leads to trapping of the dimer to yield **13** and trapping of the ylide to yield **15**, the latter compound with a regiochemistry contrary to that reported for the capture of benzophenone ylide.

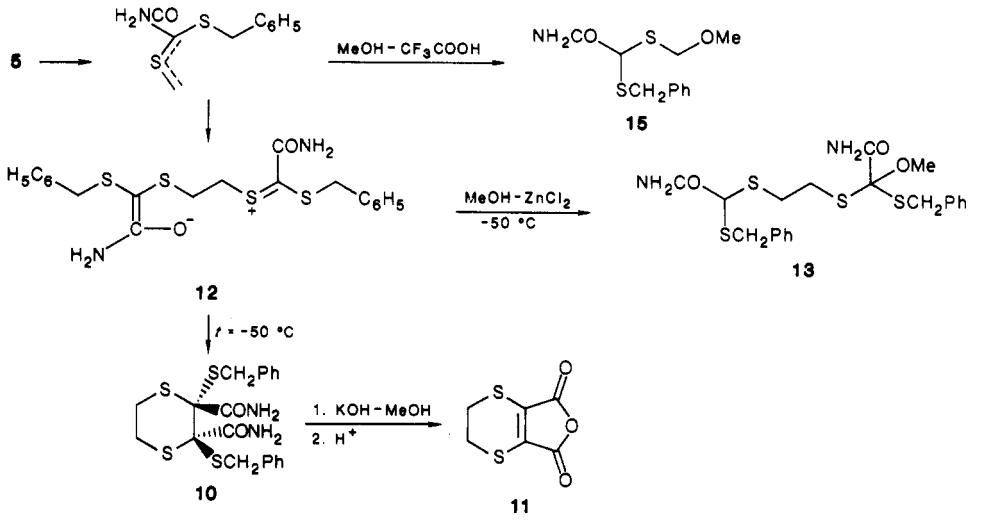
Experimental Section

Melting points were obtained in a Kofler apparatus and are uncorrected. IR spectra were recorded on a Beckman Acculab II. NMR spectra were recorded on a Bruker WP 200 SY instrument (200 MHz ^1H, 50.3 MHz ^{13}C). Mass spectra were obtained with a VG TS250 spectrometer at 70 eV.

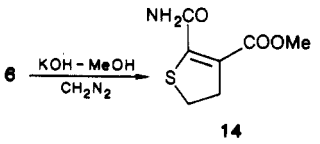
9-(Methoxycarbonyl)-2,3-dioxo-1,4,6-trithiaspiro[4.4]nonane (3). 1[9] (364 mg) in methyl acrylate at −80 °C under nitrogen was treated with diazomethane until a colorless solution was

(5) To be published elsewhere.
(6) Thiel, W.; Viola, H.; Mayer, R. *Z. Chem.* **1977**, *17*, 366.
(7) Huisgen, R.; Fulka, C.; Kalwinsch, I.; Li, X.; Mloston, G.; Moran, J. R.; Probstl, A. *Bull. Soc. Chim. Belg.* **1984**, *93*, 511.
(8) Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6401.
(9) Krebs, B.; Gattow, G. *Angew. Chem.* **1963**, *75*, 978.

Scheme IV



Scheme V



obtained. The reaction mixture was then heated to −50 °C and nitrogen began to be generated. When extrusion of nitrogen had finished, the solution was allowed to warm to room temperature, the solvent was removed by concentration in vacuo, and 400 mg (65%) of **3** was obtained. ^{1}H NMR ($CDCl_3$): δ 3.67 (3 H, s), 3.58 (1 H, m), 3.26–3.19 (2 H, m), 2.80–2.70 (1 H, m), 2.50–2.28 (1 H, m). ^{13}C NMR ($CDCl_3$): δ 187.9 (s), 187.7 (s), 167.9 (s), 62.2 (d), 52.2 (q), 32.3 (t), 31.1 (t).

2-(Benzylthio)-2-carbamoyl-3-(methoxycarbonyl)tetrahydrothiophene (6). An ethereal solution of diazomethane was added dropwise to a stirred solution of the dithiooxamide **4** (340 mg) in methyl acrylate (15 mL) under a nitrogen atmosphere at −78 °C until the red color of the reaction mixture had vanished. The solution was then allowed to warm to −50 °C and a slow extrusion of N_2 took place. When the generation of nitrogen has ceased, the reaction was considered to have finished. The excess of methyl acrylate was removed by concentration in vacuo and the residue was purified by crystallization from methanol, affording 380 mg (80%) of **6**. When the reaction was carried out in a 1:1 hexane–methylene chloride mixture and the dipolarophile was added when diazomethane titration had finished, **6** was isolated in a yield of 55%. If the solvent was methanol, yield was nearly the same, 52%; mp 142 °C. IR (Nujol): 3440, 3150 (NH), 1735 (C=O), 1680 (C=O amide), 1205 (C—O), 780, 760, 705 (monosubstituted aromatic ring) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.24 (5 H, s), 4.12 (1 H, t, J = 6.8 Hz), 3.92 (2 H, AB system, J_{AB} = 11.6 Hz), 3.71 (3 H, s), 3.22 (1 H, m), 3.00 (1 H, m), 2.47 (2 H, m). ^{13}C NMR ($CDCl_3$): δ 172.3 (s), 170.9 (s), 136.6 (s), 129.1 (d, 2 C), 128.5 (d, 2 C), 127.3 (d), 69.6 (s), 54.6 (d), 51.6 (q), 38.1 (t), 33.4 (t), 31.7 (t) MS, m/e (rel intensity): 3.11 (M^+, 5), 267 (M^+ − $CONH_2$, 40), 188 (M^+ − SC_7H_7, 80), 91 (C_7H_7, 100).

3-Acetyl-2-(benzylthio)-2-carbamoyltetrahydrothiophene (7). The dithiooxamide **4** (400 mg) was dissolved in a 1:1 methylene chloride–methyl vinyl ketone mixture at −78 °C under a nitrogen atmosphere. According to the same procedure as above, the solution was titrated with diazomethane, the mixture reaction heated to −50 °C, and the nitrogen extruded. After the usual workup, the crude residue was purified by column chromatography (silica gel), affording 331 mg (60%) of the adduct **7**, mp 135 °C. IR (Nujol): 3420, 3210 (NH), 1715 (C=O), 1690 (C=O amide), 1600, 775, 710 (aromatic ring) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.26 (5 H, m), 4.16 (1 H, dd, J = 10.8 Hz), 3.93 (2 H, AB system, J = 11.5 Hz), 3.00 (2 H, m), 2.57 (1 H, m), 2.39 (1 H, m), 2.29 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 205.5 (s), 172.4 (s), 136.3 (s), 129.3 (d, 2 C), 128.6 (d, 2 C), 127.4 (d), 69.6 (s), 61.5 (d), 37.8 (t), 33.1 (t), 31.6 (t), 31.3 (q). MS, m/e (rel intensity): 295 (M^+, 5), 251 (M^+ − $CONH_2$, 50), 172 (M^+ − SC_7H_7, 90), 91 (C_7H_7, 100).

2-(Benzylthio)-2-carbamoyl-3-cyanotetrahydrothiophene (8). Diazomethane was added dropwise to an acrylonitrile solution (30 mL) of **4** (400 mg) at −78 °C under nitrogen until a colorless solution was obtained. The reaction mixture was allowed to warm to −50 °C, at which temperature bubbles of nitrogen could be observed. When the reaction had finished, the solvent was evaporated off to give a residue that was chromatographed on SiO_2, yielding 180 mg (35%) of **8**. When the reaction was carried out in a 1:1 hexane–methylene chloride mixture as solvent, yield was significantly lower, 18%; mp 156 °C (IR (Nujol): 3400, 3200 (NH), 2260 (CN), 1680 (C=O), 1500, 790, 710 (aromatic ring) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.30 (5 H, m), 4.04 (1 H, t, J = 6 Hz), 4.02 (2 H, AB system, J_{AB} = 12 Hz), 3.17 (1 H, m), 3.08 (1 H, m), 2.61 (2 H, m). ^{13}C NMR ($CDCl_3$) δ 171.1 (s), 135.8 (s), 129.4 (d, 2 C), 128.7 (d, 2 C), 127.7 (d), 118 (s), 66.5 (s), 42.4 (d), 38.8 (t), 34.7 (t), 31.6 (t) MS, m/e (rel intensity): 278 (M^+, 10), 234 (M^+ − $CONH_2$, 17), 187 (9), 155 (M^+ − SC_7H_7, 100), 91 (C_7H_7, 100).

6-(Benzylthio)-6-carbamoyl-2-phenyl-2-aza-5-thiaperhydropentalene-1,3-dione (9). 400 mg of the dithiooxamide **4** (400 mg) was dissolved in a 1:2 hexane-methylene chloride mixture at −78 °C under a nitrogen atmosphere. Diazomethane was added dropwise until the red color of the solution had vanished; when the titration had been completed the thiadiazoline **5** appeared precipitated as a white solid. Following this, 400 mg of *N*-phenylmaleimide in a methylene chloride solution was added and the reaction mixture was heated to −50 °C. After the extrusion of nitrogen, the reaction was worked up as usual and **9** (42%) was obtained by crystallization, mp 128 °C. IR (Nujol): 3410, 3190 (NH), 1800 (C=O imide), 1690 (C=O amide), 1510 (aromatic rings), 1200 (CN), 750, 710 (aromatic rings) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.33 (10 H, m), 4.45 (1 H, d, J = 8.7 Hz), 4.17 (1 H, m), 3.97 (2 H, AB system, J_{AB} = 11.6 Hz), 3.22 (2 H, m). ^{13}C NMR (DMSO-d_6): δ 176.4 (s), 173.8 (s), 170.1 (s), 135.8 (s), 132.0 (s), 129.2 (d, 2 C), 129.0 (d, 2 C), 128.8 (d, 2 C)8 128.5 (d, 2 C), 127. 0 (d), 126.7 (d), 71.6 (s), 54.8 (d), 51.4 (d), 36.7 (t), 31.7 (t). MS, m/e (rel intensity): 398 (M^+, 12), 354 (M^+ − $CONH_2$, 65), 275 (M^+ − SC_7H_7, 100), 91 (C_7H_7, 100).

2,3-Bis(benzylthio)-2,3-dicarbamoyl-1,4-dithiacyclohexane (10). The dithiooxamide **4** (300 mg) was dissolved in a methylene chloride–hexane (16 mL/12 mL) mixture at −78 °C under nitrogen and with constant sitrring. The solution was treated with diazomethane, affording a suspension from which the thiadiazoline **5** precipitated. The reaction was allowed to warm to −50 °C, the generation of nitrogen began, and when the reaction had finished, white solid **10** (85%) was removed from the solution by filtration, mp 220 °C dec. IR (Nujol): 3440, 3320 (NH), 1690, 1650 (C=O), 1600, 1500, 790 (aromatic rings) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.29 (10 H, m), 3.77 (4 H, AB system, J_{AB} = 12 Hz), 3.0 (4 H, AB system, J_{AB} = 11.6 Hz). ^{13}C NMR (DMSO-d_6) δ 167.6 (s, 2 C), 136.2 (s, 2 C), 129.0 (d, 4 C), 128.1 (d, 4 C), 126.8 (d, 2 C), 72.3 (s, 2 C), 38.3 (t, 2 C), 27.9 (t, 2 C). MS, m/e (rel intensity): E.I.

359 ($M^+ - C_7H_7$, 20), 91 (C_7H_7, 100). C.I. (isobutane): 451 ($M^+ + 1$, 35).

5,6-Dihydro-2-oxa-4,7-dithiaindan-1,3-dione (11). The dimer **10** (200 mg) was dissolved by heating in a methanolic solution of KOH (2 N). The solvent was evaporated off and the residue was extracted with ethyl acetate and water. The aqueous layer was acidified with 2 N HCl and extracted with ethyl acetate to yield, after the usual workup, 150 mg (71%) of the anhydride **11**; mp 108 °C IR (Nujol) 1835, 1755 (C=O anhydride), 1220 (C—O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.38 (4 H, s). ^{13}C NMR ($CDCl_3$) δ 163.8 (s, 2 C), 132.9 (s, 2 C), 26.2 (t, 2 C). MS, *m/e* (rel intensity): 188 (M^+, 75), 144 ($M^+ - CO_2$, 15), 116 ($M^+ - C_2O_3$, 50), 88 (100).

2-(Benzylthio)-7-carbamoyl-2-methoxy-9-phenyl-3,6,8-trithianonanamide (13). Diazomethane was added dropwise to a methanol solution of **4** (500 mg) at −78 °C under nitrogen until a colorless solution was obtained. Following this, 470 mg of $ZnCl_2$ in methanol was added, the temperature was slowly raised, and at −60 °C the first bubbles of nitrogen were observed. When the generation of nitrogen had ceased, the reaction mixture was poured into an aqueous solution affording 450 mg (80%) of **13** by filtration; mp 147 °C. IR (Nujol) 3400, 3200 (NH), 1680 (C=O), 1500 (aromatic rings), 1100 (C—O) cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.29–7.27 (10 H, m), 4.40 (1 H, s), 3.85 (2 H, AB system, J_{AB} = 12 Hz), 3.75 (2 H, AB system, J_{AB} = 12 Hz), 3.38 (3 H, s), 2.84 (4 H, m). ^{13}C NMR (DMSO-d_6) δ 169.7 (s), 168.2 (s), 137.3 (s), 136.6 (s), 128.7 (d, 4 C), 128.2 (d, 4 C), 126.8 (d, 2 C), 98.3 (s), 51.8 (q), 51.8 (d), 34.5 (t), 34.3 (t), 30.0 (t, 2 C). MS, *m/e* (rel intensity): 270 (10), 210 (35), 91 (100).

2-Carbamoyl-4,5-dihydro-3-(methoxycarbonyl)thiophene (14). The adduct **6** (200 mg) was treated with KOH/MeOH (2.5 N) at room temperature with constant stirring for 2 h. The reaction mixture was then quenched with water and extracted with ethyl acetate. The aqueous layer was acidified with HCl (2 N) and extracted with ethyl acetate. The organic layer was concentrated and the residue was esterified with diazomethane to afford after chromatography **14** (20%); mp 73–75 °C. IR (Nujol): 3300 (NH), 1700 (COOMe), 1680 ($CONH_2$) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.79 (3 H, s), 3.4–3.1 (4 H, m). ^{13}C NMR ($CDCl_3$) δ 164.6 (s), 163.2 (s), 155.1 (s), 123.9 (s), 52.2 (q), 39.6 (t), 28.8 (t). MS, *m/e* (rel intensity): C.I. (isobutane), 188 ($M^+ + 1$, 80), 171 ($M^+ - NH_2$, 60), 129 (($M^+ + 1$) − COOMe, 100).

5-Carbamoyl-7-phenyl-2-oxa-4,6-dithiaheptane (15). Diazomethane was added to a methanol solution of the dithioxamide **4** (300 mg) at −78 °C under nitrogen until the red color had vanished. Two drops of CF_3COOH were added and the reaction mixture was allowed to warm to −50 °C. When the generation of nitrogen had ceased, the reaction was assumed to have finished. The usual workup gave 110 mg of **13** and 150 mg (41%) of **15**, mp 64 °C. IR (Nujol) 3400, 3200 (NH), 1690, 1650 (C=O), 1500 (aromatic ring), 1200 (C—O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.25 (5 H, m), 4.72 (2 H, AB system, J_{AB} = 12 Hz), 4.30 (1 H, s), 3.83 (2 H, AB system, J_{AB} = 12 Hz), 3.29 (3 H, s). ^{13}C NMR ($CDCl_3$) δ 171.4 (s), 136.5 (s), 129.0 (d, 2 C), 128.5 (d, 2 C), 127.3 (d), 74.5 (t), 56.3 (q), 50.5 (d), 36.2 (t). MS, *m/e* (rel intensity). 257 (M^+, 20), 226 ($M^+ - OCH_3$, 20), 213 ($M^+ - CONH_2$, 40), 180 ($M^+ - C_2H_5OS$, 35), 134 ($M^+ - SC_7H_7$, 95), 91 (C_7H_7, 100).

Synthesis of Nitroxyl (Aminoxyl) Labeled Probes for Studies of Intracellular Environment by EPR and MRI

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Syntheses are delineated for the following three classes of nitroxyl (aminoxyl) labeled active esters: (1) phosphoric acid derivatives containing phenyl and *p*-nitrophenyl moieties, (2) EDTA and DTPA containing acetoxymethyl and (pivaloyloxy)methyl as protecting groups, and (3) several amino acid derivatives containing the acetoxymethyl group. These compounds are expected to be of interest as potential probes in studies of intracellular environments by ESR spectroscopy and magnetic resonance imaging (MRI).

Introduction

The nitroxyl radicals originally were developed as biophysical probes for studies of motion in physical and biophysical model systems,[1-6] but now have become employed increasingly in functional biological systems. This development not only has introduced potential new limitations and requirements, especially in regard to solubility and stability, for the properties of nitroxyl probes but also has made possible a broader range of applications of nitroxyl-labeled compounds. In addition to their utilization as probes of motion, nitroxyl radicals also have been employed in biological systems in studies aimed at their use as contrast agents[7-22] for NMR imaging (MRI) and spectroscopy (MRS), agents[23,24] for electron spin resonance imaging (ESRI or EPRI), in vivo ESR spectroscopy,[25] radiosensitizers,[26-28] anticancer agents,[29-35] and probes in metabolism.[20] The latter applications are based on the effect of oxygen on the ESR spectra,[36] on the reduction by cells of nitroxyl radicals to the hydroxylamines[18,37] and the oxidation of hydroxylamines to nitroxyl radicals,[22] including the effect of oxygen on these reactions.

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