Synthesis of Thio Analogues of Prostaglandin H_2 and Prostaglandin F_2 from Prostaglandin A_2[1]

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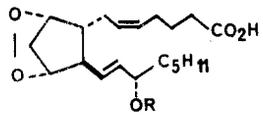
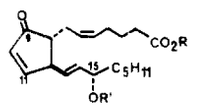
The prostaglandin endoperoxides PGG_2 (**1a**) and PGH_2 (**1b**) occupy a pivotal position in the biosynthesis of the primary prostaglandins, thromboxane A_2, and prostacyclin (PGI_2) from arachidonic acid.[2] The interesting spectrum of independent biological activity exhibited by the endoperoxides coupled with their lability has prompted the synthesis



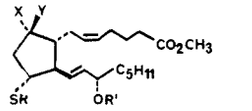
1 a) R = OH
b) R = H

of several potentially more stable analogues.[3,4] At the inception of a program in our laboratory aimed principally at the synthesis of the endo-disulfide analogue (6) of PGH_2, there was a surprising lack of C-9 and C-11 thio analogues of the prostaglandins in the literature. During the course of our work in this area, however, Hayashi et al.[3] reported a somewhat lengthy total synthesis of the endo-disulfide **6,** via the tetrahydropyranyl ether derivative of 9α,11α-dimercapto-9,11-dideoxyprostaglandin F_2 methyl ester (**5b**), and showed it to be a very effective biochemical mimic of PGH_2.

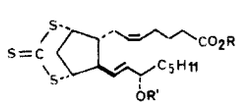
In this note we wish to present a short, stereoselective synthesis from (+)-PGA_2 (**2a**) of two endo-peroxide analogues, the novel *endo*-trithiocarbonate **4** and the endo-disulfide **6,** as well as 11α-mercapto-11-deoxyprostaglandin $F_{2\alpha}$ methyl ester (**3e**), 11α-mercapto-11-deoxyprostaglandin $F_{2\beta}$ methyl ester (**3d**), and 9α,11α-dimercapto-9,11-dideoxyprostaglandin F_2 (**5a**).[5]



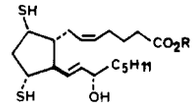
2 a) R = R' = H
b) R = CH_3, R' = Ac



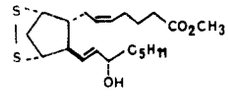
3 a) X, Y = O; R = R' = Ac
b) X = H; Y = OH; R = R' = Ac
c) X = OH; Y = H; R = R' = Ac
d) X = H; Y = OH; R = R' = H
e) X = OH; Y = H; R = R' = H
f) X = H; Y = OMs; R = R' = Ac



4 a) R = CH_3; R' = Ac
b) R = H; R' = H



5 a) R = H
b) R = CH_3



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(+)-PGA_2 (**2a**), readily obtained in quantity by enzymatic hydrolysis of the lipophilic extract of *Plexaura homomalla, homomalla* (Var. S, collected off the Cuban coast) was converted in 92% yield to the corresponding diester **2b** by treatment with diazomethane followed by acetic anhydride in pyridine. Kinetically controlled conjugate addition of thiolacetic acid to **2b** smoothly produced a single product **3a** in 85% yield, which was assigned the α configuration from ample precedent.[6] Treatment of thiolacetate **3a** with zinc borohydride in DME[7] then afforded a 4 to 1 mixture of 9β (**3b**) and 9α (**3c**) alcohols, respectively, in 85% yield. After chromatographic separation of the C-9 alcohols, methanolysis gave the new C-11 mercapto analogues of $PGF_{2\alpha}$ and $PGF_{2\beta}$, compounds **3e** and **3d,** respectively. The stereochemical assignments in alcohols **3b–e** were made on the basis of the generally observed greater mobilities[5,9] on silica gel and larger C-9 carbinolic proton downfield chemical shifts[10] for the 9α alcohols relative to the corresponding 9β alcohols. Further proof was secured through reduction of **3a** with lithium perhydro-9b-boraphenalylhydride, a reagent known to produce predominantly or exclusively PGF_α-type products from PGE derivatives,[6c,11] to afford the minor isomer **3c** as the major product.

The alcohol **3b** was also transformed to the corresponding mesylate **3f,** which underwent a smooth displacement reaction with attendant thiolacetate cleavage and cyclization upon treatment with sodium trithiocarbonate in aqueous methanol[12] to provide the bicyclic compound **4a** in 72% yield. Saponification of diester **4a** then gave the novel *endo*-trithiocarbonate analogue (**4b**) of PGH_2.[13]

The dimercapto derivative (**5a**) of PGF_2, which we had expected (as the triester) from the reaction of mesylate **3f** with sodium trithiocarbonate, could be obtained from trithiocarbonate **4b** using sodium in ethanol.[14] Esterification with diazomethane then produced **5b**.[3] Ester **5b** could also be secured by subjecting mesylate **3f** to treatment with potassium thiolacetate in DMF–Me_2SO,[3,5] followed by potassium carbonate in methanol.

The oxidative cyclization of the dimercaptan **5a,b** proved to be quite difficult. After numerous unsuccessful attempts to carry out this transformation, we found that the surprisingly simple method[15] of passing oxygen through a dilute methanolic solution of **5b** and 2.2 equiv of sodium methoxide effectively produced the thio analogue of PGH_2, endo-disulfide **6.**

Experimental Section

Isolation of the reaction products was accomplished by pouring the mixture into water, thoroughly extracting with the specified solvent, washing the combined extracts with a 10% aqueous HCl solution and/or a saturated aqueous sodium bicarbonate solution (if required), with water, and then with a saturated aqueous sodium chloride solution, drying the extracts over anhydrous sodium sulfate, filtering, and then concentrating under reduced pressure on a Buchi Rotovapor.

IR spectra were obtained using neat liquids between salt plates on a Beckman Acculab 4 spectrophotometer. A Beckman DBT recording spectrophotometer was used for the UV absorption spectra. NMR spectra were determined with a Jeol PMX-60 spectrometer using tetramethylsilane as the internal reference. Mass spectra were recorded on a MS-30AEI mass spectrometer generally at 70 eV using a direct insertion probe. Optical rotations were determined in $CHCl_3$ (C = 1) on a Perkin-Elmer 141 polarimeter. The circular dichroism (CD) curves were recorded on a Jouan 3 dichrograph instrument. Microanalyses were performed by the Central Service of the CNRS, Lyon. Thin layer chromatography was carried out using Merck $60F_{254}$ (0.25 mm) sheets. For column chromatography, Merck 230–400 mesh silica gel 60 and Mallinckrodt silicic acid silicar CC-4 and CC-7 were used.

(15*S*)-PGA_2 (2a) from *P. Homomalla* (Var. S).[15] *P. homomalla, homomalla* (Var. S) (1 kg), collected off Cuba and frozen within minutes of collection, was ground into a slurry. The slurry was stirred at room temperature for 24 h with 6–8 L of 0.1 M aqueous citric acid, and then 10 L of ethanol was added, the mixture was centrifuged and filtered, and the ethanol was evaporated in vacuo. A 1 M solution of citric acid was added to adjust the pH to 6.5–7 and the resulting solution was extracted with carbon tetrachloride. The aqueous solution was then acidified to pH 5–5.5 and the product was isolated with chloroform yielding 150–200 g of dark oil. This material was further purified by filtration column chromatography on silicic acid silicar

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CC-4 100–200 mesh eluting with a gradient of ethyl acetate in hexane, to afford a pale yellow oil containing 85–95% of PGA_2 (**2a**), having spectral (IR, NMR, UV) and biological characteristics identical with those reported in the literature.[16b,17] The purity of the PGA_2 was determined by TLC (system A IX).[9b]

(+)-Prostaglandin A_2 15-Acetate Methyl Ester (2b). A solution of 5 g (15.0 mmol) of PGA_2 (**2a**) in ether was treated with an ethereal solution of diazomethane to afford after filtration column chromatography on silicic acid silicar CC-7, 5 g of PGA_2 methyl ester as a pale yellow oil: $[\alpha]_D$ +148°; IR λ_{max} (film) 3450, 1730, 1705, 1580, 970 cm^{-1}; UV λ_{max} (MeOH) 217 nm (10 200); NMR δ_{Me_4Si} (CCl_4) 7.33 (dd, J = 2, 5 Hz, 1 H), 6.03 (dd, J = 2, 5 Hz, 1 H), 5.40 (m, 4 H), 3.95 (m, 1 H), 3.60 (s, 3 H), 3.12 (m, 1 H), 0.93 (t, J = 5 Hz, 3 H).

The above prostaglandin A_2 methyl ester (5 g, 14.4 mmol) was dissolved in 12.5 mL of pyridine and treated with 7.5 mL of acetic anhydride. After 2 h at room temperature, ice chips were added followed by 125 mL of cold water. After the reaction mixture was stirred for an additional 15 min, the product was isolated with ethyl acetate and then purified by filtration column chromatography on silicic acid silicar CC-7. Elution with 10% ethyl acetate in hexane gave fractions homogeneous by TLC (hexane–ethyl acetate, 7:3), affording 5.25 of prostaglandin A_2 acetate methyl ester (**2b**):[16b] 90%; $[\alpha]_D$ +102°; IR λ_{max} (film) 1735, 1705, 1590, 1240, 970 cm^{-1}; UV λ_{max} (MeOH) 217 nm (9980); NMR δ_{Me_4Si} (CCl_4) 7.33 (dd, J = 2, 6 Hz, 1 H), 6.03 (dd, J = 2, 6 Hz, 1 H), 5.3 (m, 5 H), 3.58 (s, 3 H), 3.15 (m, 1 H), 1.97 (s, 3 H), 0.89 (t, J = 5 Hz, 3 H).

(−)-11α-Thiolacetoxy-11-deoxyprostaglandin E_2 15-Acetate Methyl Ester (3a). To a stirred solution of 5 g (12.8 mmol) of **2b** in 25 mL of methanol at −78 °C under nitrogen was added 1.4 g of potassium thiolacetate dissolved in 50 mL of methanol and 9.2 mL of thiolacetic acid, and the resulting suspension was stirred for 30 min. The reaction mixture was then treated with aqueous sodium bicarbonate to neutral pH and diluted with 100 mL of water. The methanol was evaporated under reduced pressure and the product was isolated with methylene chloride and purified by filtration column chromatography on silicic acid silicar CC-7. Elution with 10% ethyl acetate–hexane gave fractions homogeneous by TLC (hexane–ethyl acetate, 7:3) affording 4.9 g (82%) of **3a** as a colorless oil:[6c] $[\alpha]_D$ −50°; IR λ_{max} (film) 1735, 1690, 1240, 970, 630 cm^{-1}; UV λ_{max} (MeOH) 232 nm (5030); NMR δ_{Me_4Si} (CCl_4) 5.33 (m, 5 H), 3.59 (s, 3 H), 3.10–2.60 (m, 1 H), 2.27 (s, 3 H), 1.97 (s, 3 H), 0.90 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{38}O_6S$: C, 64.35; H, 8.21. Found: C, 63.94; H, 8.25.

(−)-11α-Thiolacetoxy-11-deoxypostaglandin $F_{2\alpha+\beta}$ 15-Acetate Methyl Ester (3b,c). A solution of 4.6 g (9.9 mmol) of **3a** in 40 mL of dry dimethoxyethane (DME) was stirred at room temperature under nitrogen. A solution of 30 mL (1.5 equiv) of zinc borohydride (0.5 M, freshly prepared)[18] in DME was added dropwise over 5 min and stirring was continued for 30 min after which a saturated sodium hydrogen tartrate solution was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the resulting suspension was filtered through a coarse porosity sintered glass funnel. Isolation of the product with methylene chloride afforded 4.3 g of a mixture of alcohols. Analysis of the mixture by TLC (hexane–ethyl acetate, 1:1) showed only the two C-9 epimers, R_f 5.1 (9α) and R_f 4.5 (9β). The mixture was separated by column chromatography on silicic acid silicar CC-7. Elution with hexane–ethyl acetate, 9:1, gave 840 mg (18%) of the 9α-isomer **3c** as a colorless oil: $[\alpha]_D$ −31°; IR λ_{max} (film) 3500, 1740, 1690, 1240, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 5 H), 4.10 (m, 1 H), 3.62 (s, 3 H), 2.60 (m, 1 H), 2.27 (s, 3 H), 2.00 (s, 3 H), 0.85 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{40}O_6S$: C, 64.07; H, 8.60; S, 6.84. Found: C, 63.92; H, 8.62; S, 6.76.

Further elution with hexane–ethyl acetate, 85:15, gave 3.2 g (70%) of the 9β-isomer **3b** as a colorless oil: $[\alpha]_D$ −45°; IR λ_{max} (film) 3500, 1740, 1690, 1250, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.30 (m, 5 H), 3.90 (m, 1 H), 3.62 (s, 3 H), 2.67 (m, 1 H), 2.28 (s, 3 H), 2.00 (s, 3 H), 0.88 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{40}O_6S$: C, 64.07; H, 8.60; S, 6.84. Found: C, 64.08; H, 8.37; S, 6.70.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\alpha+\beta}$ Methyl Ester (3d,e). Methanolysis of the thiolacetate and acetate groups in **3b,c** (230 mg, 0.5 mmol) was effected using 20 mL of anhydrous methanol and 5 equiv of potassium carbonate at 20 °C for 30 min, followed by acidification with 1 N HCl (to pH 4–5) and isolation of the product with ether. Mercaptans **3d** (175 mg, 93%) and **3e** (168 mg, 89%) could be purified by column chromatography on silicic acid silicar CC-4 using hexane–ethyl acetate as the eluent.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\beta}$ Methyl Ester (3d): $[\alpha]_D$ +2.08°; IR λ_{max} (film) 3400, 2560, 1730, 1240, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.42 (m, 4 H), 4.00 (m, 2 H), 3.63 (s, 3 H), 3.0 (m, 1 H), 0.87 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{21}H_{36}O_4S$: C, 65.59; H, 9.44; S, 8.34. Found: C, 65.49; H, 9.43; S, 8.06.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\alpha}$ Methyl Ester (3e): $[\alpha]_D$ +11.19°; IR λ_{max} (film) 3450, 2560, 1730, 1240, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 4 H), 4.06 (m, 2 H), 3.59 (s, 3 H), 2.70 (m, 1 H), 0.87 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{21}H_{36}O_4S$: C, 65.59; H, 9.44; S, 8.34. Found: C, 65.89; H, 9.45; S, 8.14.

(−)-11α-Thiolacetoxy-11-deoxyprostaglandin $F_{2\beta}$ 9-Mesylate 15-Acetate Methyl Ester (3f). A stirred solution of 1.0 g (2.1 mmol) of alcohol **3b** in 10 mL of dry pyridine was cooled to 0 °C and 0.50 mL (6.3 mmol) of methanesulfonyl chloride was added dropwise. After 1 h at 0 °C the mixture was poured onto crushed ice and the product was isolated with ether to give 1.0 g of colorless oil (86%): $[\alpha]_D$ −41.3°; IR λ_{max} (film) 1740, 1695, 1250, 1180, 970, 630 cm^{-1}; UV λ_{max} (MeOH) 233 nm (5000); NMR δ_{Me_4Si} (CCl_4) 5.43 (m, 4 H), 5.15 (m, 1 H), 4.80 (m, 1 H), 3.63 (s, 3 H), 2.96 (s, 3 H), 2.26 (s, 3 H), 2.00 (s, 3 H), 0.93 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{26}H_{42}O_8S_2$: C, 57.12; H, 7.74. Found: C, 57.41; H, 7.84.

(−)-9α,11α-Trithiocarbonate of 9,11-Dideoxyprostaglandin F_2 15-Acetate Methyl Ester (4a). Mesylate **3f** (900 mg, 1.65 mmol) in 10 mL of methanol was added dropwise to a stirred solution of aqueous sodium trithiocarbonate (33%, 8 mL)[12] under nitrogen. After stirring at 60 °C for 1 h, the mixture was carefully acidified with 0.5 M sulfuric acid to pH 4–5 and the product was isolated with ether and purified by filtration on silicic acid to afford 652 mg (82%) of **4a** as a viscous yellow oil: $[\alpha]_D$ −72°; CD (c 1; CH_3OH); $[\theta]_{455}$ −490; $[\theta]_{400}$ 0; $[\theta]_{350}$ +420; $[\theta]_{338}$ 0; $[\theta]_{319}$ −630; $[\theta]_{310}$ 0; $[\theta]_{294}$ +4110; $[\theta]_{275}$ +1230 (shoulder); $[\theta]_{262}$ 0; $[\theta]_{238}$ −9800; $[\theta]_{226}$ 0; IR λ_{max} (film) 1735, 1245, 1030, 980 cm^{-1}; UV λ_{max} (MeOH) 339 (12 300) 298 nm (7780); NMR δ_{Me_4Si} ($CDCl_3$) 5.35 (m, 5 H), 3.68 (s, 3 H), 3.6–2.9 (m, 2 H), 2.06 (s, 3 H), 0.90 (t, J = 5 Hz, 3 H); mass spectrum m/e 484 M^+ (39.88), $M^+ - OCH_3$ (13.19), $M^+ - S$ (21.88), $M^+ - HS$ (89.58), $M^+ - HOAc$ (43.25); molecular ion at m/e 484.1776, calcd, 484.1776.

(−)-9α,11α-Trithiocarbonate of 9,11-Dideoxyprostaglandin F_2 (4b). A 300-mg (0.62 mmol) sample of **4a** was saponified using 5 equiv of 1 M sodium hydroxide in methanol under nitrogen at 20 °C for 1 h. Acidification with 0.5 M sulfuric acid to pH 4–5 was followed by isolation of the crude product with ether. Purification by filtration on silicic acid then afforded 215 mg (81%) of **4b** as a viscous yellow oil: $[\alpha]_D$ −45°; IR λ_{max} (film) 3300, 1720, 1040, 980 cm^{-1}; UV λ_{max} (MeOH) 340 (12 500), 299 nm (8040); NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 6 H), 4.15 (m, 1 H), 3.6–2.9 (m, 2 H), 0.86 (t, J = 5 Hz, 3 H).

(−)-9α,11α-Dimercapto-9,11-dideoxyprostaglandin F_2 (5a) and Methyl Ester (5b): From Trithiocarbonate 4b. To a stirred solution of 250 mg (0.58 mmol) of **4b** in 10 mL of methanol at 0 °C under nitrogen was added sodium metal (667 mg, 29 g-atom) and stirring was continued for 30 min. After dilution with 50 mL of water, the solution was carefully acidified with 0.5 M sulfuric acid to pH 4–5 and the product was isolated with ethyl acetate to give 150 mg of crude **5a,** which was rapidly[5,15] purified by column chromatography on silicic acid silicar CC-4. Elution with 40% ethyl acetate in hexane gave fractions homogeneous by TLC (system A IX),[9b] affording 98 mg (43%) of **5a** as a pale yellow oil: $[\alpha]_D$ −22°; IR λ_{max} (film) 3400, 2570, 1700, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.69 (s, 2 H), 5.40 (m, 4 H), 4.15 (m, 1 H), 3.50 (m, 1 H), 2.80 (m, 1 H), 0.85 (t, J = 5 Hz, 3 H).

A 125-mg (0.32 mmol) sample comparable to that above was dissolved in ether and esterified with ethereal diazomethane. Rapid[5,15] purification of the ester by filtration column chromatography on silicic acid silicar CC-7 using increasing concentrations of ethyl acetate in hexane afforded 118 mg (91%) of **5b** as a pale yellow oil.[3] $[\alpha]_D$ −7.2°; IR λ_{max} (film) 3400, 2560, 1730, 970 cm^{-1}; NMR δ_{MeSi_4} ($CDCl_3$) 5.39 (m, 4 H), 4.07 (m, 1 H), 3.61 (s, 3 H), 3.5 (m, 1 H), 2.80 (m, 1 H), 0.86 (t, J = 5 Hz, 3 H); mass spectrum m/e 400 M^+ (2.24), $M^+ - H_2O$ (9), $M^+ - SH$ (4), $M^+ - SH_2$ (10.52), $M^+ - (H_2O + SH)$ (14.52), $M^+ - (H_2O + SH_2)$ (16.68).

From Mesylate 3f. Mesylate **3f** (500 mg, 0.91 mmol) was treated with sodium thiolacetate (450 mg, 4.6 mmol) in Me_2SO–DMF (1:1) at 50 °C for 14 h.[3,5] The product was isolated with methylene chloride and purified by filtration column chromatography on silicic acid silicar CC-7 using hexane–ethyl acetate, 9:1, to afford 310 mg (64%) of 9α,11α-dithiolacetoxy-9,11-dideoxyprostaglandin F_2 15-acetate methyl ester as a colorless oil: IR λ_{max} (film) 1740, 1690, 1250, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.30 (m, 5 H), 4.03 (m, 1 H), 3.65 (s, 3 H), 2.33 (s, 3 H), 2.28 (s, 3 H), 2.03 (s, 3 H), 0.87 (t, J = 5 Hz, 3 H).

Methanolysis of the acetates (300 mg) was done as before (MeOH, K_2CO_3). The product **5b** (190 mg, 83%) was identical by NMR, IR,

and MS with that obtained by the method described above. Because of the observed instability[5,15] of mercaptans **5a,b,** the crude products were generally used without any chromatographic purification.

Disulfide Analogue of Prostaglandin H_2 Methyl Ester (6). To a stirred solution of 130 mg (0.32 mmol) of **5b** in 10 mL of methanol at room temperature was added 38 mg (0.70 mmol) of sodium methoxide, and then O_2 was bubbled through the resulting suspension.[15] After 1 h, the reaction mixture was diluted with 50 mL of H_2O and neutralized with 0.1 N HCl. The methanol was evaporated under reduced pressure, and the product was isolated with methylene chloride to afford 112 mg (87%) of nearly pure **6,** which was further purified by filtration column chromatography on silicic acid silicar CC-7. Elution with ethyl acetate–hexane, 1:3, gave fractions homogeneous by TLC (system A IX)[9b] affording 51 mg of **6** as a pale yellow oil:[3] $[\alpha]_D$ +8.81°; CD (*c* 1; CH_3OH); $[\theta]_{375}$ +1180; $[\theta]_{330}$ 0; $[\theta]_{256}$ +6500; $[\theta]_{242}$ 0; $[\theta]_{234}$ −5580; $[\theta]_{230}$ 0; IR λ_{max} (film) 3450, 1735, 970 cm^{-1}; Raman (neat) 520 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.40 (m, 4 H), 4.00 (m, 1 H), 3.60 (s, 3 H), 0.87 (t, J = 5 Hz, 3 H); mass spectrum *m/e* (electron impact) 398 M^+ (95.34), $M^+ - H_2O$ (6.47), $M^+ - OCH_3$ (13.91), $M^+ - S$ (9.42), $M^+ - SH$ (5.54), $M^+ - (H_2O + OCH_3)$ (7.62), $M^+ - (H_2O + S)$ (13.66), $M^+ - (H_2O + SH)$ (13.60), $M^+ - C_5H_{11}$ (7.02), $M^+ - (OCH_3 + H_2O + SH_2)$ (47.68); mass spectrum (chemical ionization) 455 ($M^+ + C_4H_9$), 437 ($M^+ + C_4H_9 - H_2O$), 399 ($M^+ + 1$), 381 ($M^+ + 1 - H_2O$) base peak, 349 ($M^+ + 1 - H_2O - S$ or CH_3OH). Although the NMR spectrum shows some discrepancies with that of the reported compound[3] (identical IR), the clean chemical ionization mass spectrum (through *m/e* 800) would appear to preclude any alternative dimeric or polymeric structure:[5,15] *m/e* 398.1940, calcd, 398.1949.

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Registry No.—**2a,** 13345-50-1; **2a** methyl ester, 31753-19-2; **2b,** 36323-03-2; **3a,** 67452-66-8; **3b,** 67452-67-9; **3c,** 67452-68-0; **3d,** 67452-42-0; **3e,** 67452-43-1; **3f,** 67452-44-2; **4a,** 67452-45-3; **4b,** 67452-46-4; **5a,** 67452-47-5; **5b,** 61955-20-2; **6,** 61955-22-4; methanesulfonyl chloride, 124-63-0; sodium trithiocarbonate, 534-18-9; 9α,11α-dithiolacetoxy-9,11-dideoxypostaglandin F_2 15-acetate methyl ester, 67452-48-6.

References and Notes

(1) Contribution no. 30 from the Laboratoire de Chimie Organique, C.E.R.M.O.

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Addition of Cyclic Secondary Amines to Benzo[*b*]thiophene and 3-Methylbenzo[*b*]thiophene

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Metal-catalyzed addition of primary and secondary amines to conjugated hydrocarbons is well documented,[1] and a general method of ethylating amines with ethylene using an alkali metal salt of the amine as catalyst has been described.[2] More recently, Eisenbraun and co-workers have shown that, in addition to reduction products, naphthalene and methylnaphthalenes undergo reductive amination in the presence of sodium and secondary amines.[3] We wish to report the addition of cyclic secondary amines to the C_2–C_3 bond of benzo[*b*]thiophene (**1**) and 3-methylbenzo[*b*]thiophene (**2**) in the presence of an alkali metal salt of the amine. A definite assignment for the position of attachment of nitrogen on C_2 for the adducts can be made using NMR data. 2-Alkylaminobenzo[*b*]thiophenes are readily obtained by aromatization of the adducts.

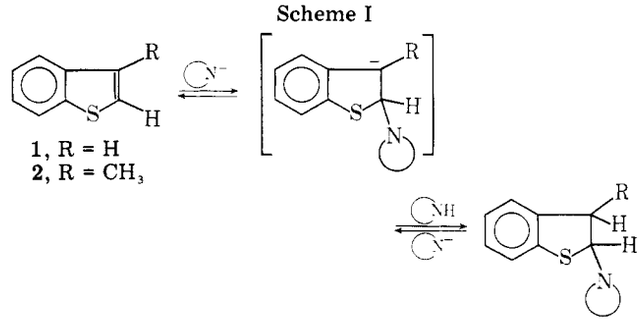
On stirring (18 h, 40 °C) benzo[*b*]thiophene **1** or **2** in a cyclic secondary amine in the presence of dispersed sodium, an adduct is obtained in high yield (see Table I). Similar addition is performed using an alkali metal salt of the amine instead of dispersed sodium. In this case, the anion of the amine is formed by reaction of the amine with *n*-butyllithium or sodium hydride.

We suggest nucleophilic addition of the anion of the amine as the first step of the reaction. The amine is needed for the protonation of the intermediate carbanion, as supported by the failure of addition of sodamide in toluene or the lithio salt of piperidine in hexane on **1** (Scheme I).

When similar reactions are performed on 2-methylbenzo[*b*]thiophene, 2,3-dimethylbenzo[*b*]thiophene, benzo[*b*]furan, or benzo[*b*]selenophene, no addition has been detected. Heterocycles are recovered unreacted except benzo[*b*]selenophene, which is reduced to ethylbenzene.

When a low molecular weight primary amine, e.g., propylamine,[4] is substituted for a cyclic secondary amine in reac-

Scheme I



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