# On the Syntheses of Thiophene Analogs of Practolol and "Reversed" Practolol



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The synthesis of the thiophene analogs of the cardio-selective β-adrenergic blocking agents Practolol and "reversed" Practolol has been attempted starting from 2-acetyl-5-bromothiophene. Although this synthesis worked for the second compound it was not possible to obtain the first one. From this and other results of this paper it can be deduced that the thiophene analog of Practolol must be an unstable compound.

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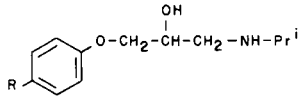
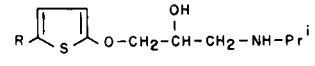
Practolol (**1**) had been a clinically useful cardioselective β-adrenergic-blocking agent until it was withdrawn from use because of serious side effects. On the other hand "reversed" Practolol (**2**) has been found to be also a highly selective β-blocker [1,2].



**1**, R = -NH-CO-CH$_3$
**2**, R = -CO-NH-CH$_3$

Our interest in thiophene analogs of clinical β-blocking agents, led us to consider the synthesis of compounds **3** and **4**.



**3**, R = -NH-CO-CH$_3$
**4**, R = -CO-NH-CH$_3$

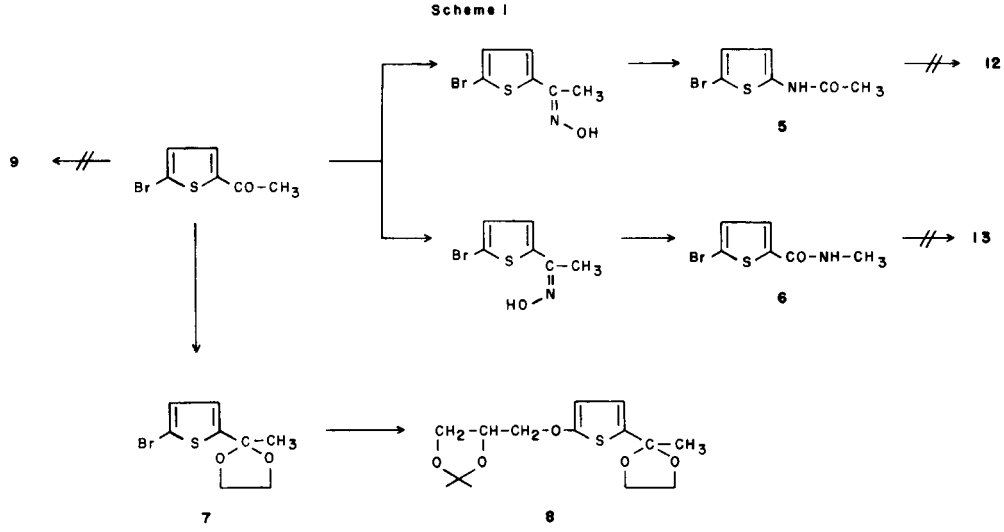
A suitable route, which could be applied to the synthesis of both compounds is the introduction of the oxypropanolamino side chain in thiophene ring by reaction of 5-acetyl-2-bromothiophene or derivatives with the sodium salt of 1,2-isopropylideneglycerol [3,4]. The conversion of the 5-acetyl group in the molecule in both acetylamino and methylcarbamoyl groups could be carried out after or before the insertion of the side chain by means of the Beckmann rearrangement of its *Z* and *E* oximes.

Since the reactions of 5-acetyl-2-bromothiophene as well as those of 5-acetylamino-2-bromothiophene and 2-bromo-5-methylcarbamoylthiophene with the sodium salt of 1,2-isopropylidene glycerol failed, the planned synthesis had to be lengthened by using the ketalic derivative of 5-acetyl-2-bromothiophene **7**, which did react with the sodium salt of 1,2-isopropylideneglycerol to give compound **8** in 65% yield (Scheme 1).

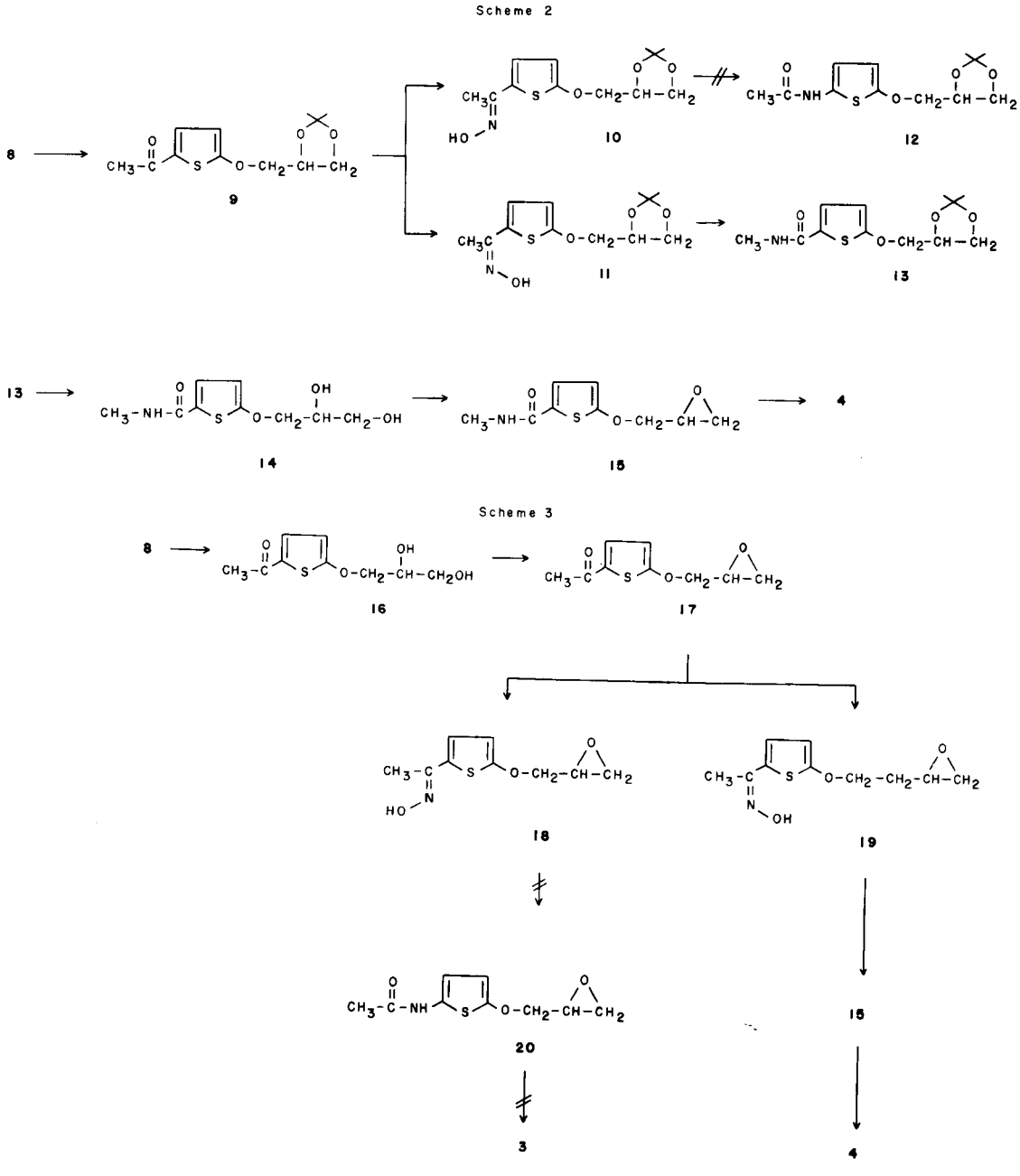
Starting from compound **8** two routes were followed as depicted in Schemes 2 and 3.

In the first one, (Scheme 2), the acetyl group of compound **8** was selectively hydrolyzed and converted into the oximino group. The *E* and *Z* isomers thus obtained (**10** and **11**) were separated by hplc and their *p*-toluenesulfonic derivatives were subjected to a Beckmann rearrangement by elution through an activated alumina column [5]. Only the *p*-toluenesulfonic derivative of **11** could be thus transformed into compound **13** in 74% yield. In the case of

Scheme I



Scheme 2

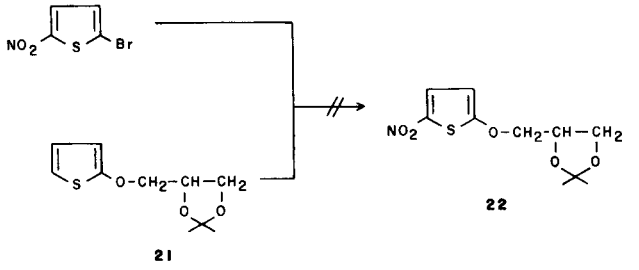


compound **10** although the starting material did disappear no identifiable compound could be isolated from the numerous compounds formed in the reaction. The thiophene analog of "reversed" Practolol (**4**) was then synthesized from compound **13** in three steps by a known procedure [3].

In the second procedure (Scheme 3) the side chain of compound **8** was first converted into the epoxide derivative **17** and then oximation of the acetyl group was performed under similar conditions. These *E* and *Z* oximes (**18** and **19**) were separated and subjected to the Beckmann rearrangement under the same conditions as mentioned above. Again, whereas the *E*-*p*-toluenesulfonyl oxime did rearrange to the expected compound **21** in 71% yield, the *Z* isomer did not yield the expected compound **20**. The thiophene analog of "reversed" Practolol was obtained as before from compound **15** which was identical in all respects to the compound synthesized by the first way.

All other attempts to obtain compound **3**, *"via"* compound **22**, such as etherification of 2-bromo-5-nitrothiophene or nitration of 1-(2-thienyloxy)-2,3-*O*-isopropylidenepropane (**21**) were not successful (Scheme 4).

Scheme 4



From the results of this work it could be deduced that Sicé's reaction [6] seems to be disfavoured by electron-attracting substituents and that thiophenic compounds with 5-acetylamino and 2-oxyalkyl groups in the same molecule are unstable.

## EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (90 MHz) spectrometer with TMS as internal reference. The separation of the oximes was made with a hplc Waters model 500 A. 2-Acetyl-5-bromothiophene [7], 2-acetamido-5-bromothiophene (**5**) [5,8], 2-bromo-5-*N*-methylcarboxamidothiophene (**6**) [5], and 1-(2-thienyloxy)-2,3-*O*-isopropylidenepropane (**21**) [3] were obtained according to the literature.

5-Bromo-2-(2-methyl-1,3-dioxolan-2-yl)thiophene (**7**).

2-Acetyl-5-bromothiophene (113.1 g, 0.55 mole) and a catalytic amount of *p*-toluenesulfonic acid were added to a stirred solution of ethyleneglycol (52.0 g, 0.84 mole) in benzene (330 ml). The reaction mixture was refluxed for 3 days until the water was separated. The organic layer was washed with a 5% aqueous sodium bicarbonate solution and with water, dried over sodium sulfate and evaporated to dryness yielding 128.5 g (94%) of compound **7** as a colourless solid, mp 62-63° (ethanol); nmr (deuteriochloroform): δ 1.71 (s, 3H, $CH_3$), 4.02 (m, 4H, -$CH_2$-$CH_2$-), 6.83 (d, 1H, J = 3.6 Hz, thiophene proton), 6.96 (d, 1H, J = 3.6 Hz, thiophene proton).

*Anal.* Calcd. for $C_8H_9O_2BrS$: C, 38.56; H, 3.64; S, 12.84. Found: C, 38.46; H, 3.62; S, 12.95.

1-[5-(2-Methyl-1,3-dioxolan-2-yl)-2-thienyloxy]-2,3-*O*-isopropylidenepropane (**8**).

Sodium (11.5 g, 0.50 mole) was added to 309 g (2.34 mole) of 2,3-*O*-isopropylideneglycerol in order to obtain the sodium salt, whereupon compound **7** (41.5 g, 0.17 mole), potassium iodide (0.2 g, 0.001 mole) and cupric oxide (6.7 g, 0.08 mole) were added. The reaction mixture was heated at 90° for 3 days and after cooling the isopropylideneglycerol was distilled (80-81° at 11 mm). The residue was extracted with carbon tetrachloride, washed repeatedly with water, dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was distilled at reduced pressure and a colourless oil (33.1 g, 65%) was obtained, bp 148-151° (0.5 mm); nmr (deuteriochloroform): δ 1.39 (s, 3H, -$CH_3$-), 1.45 (s, 3H, -$CH_3$), 1.71 (s, 3H, -$CH_3$), 3.60-4.72 (m, 9H, -O-$CH_2$-CH-$CH_2$ and -$CH_2$-$CH_2$-), 6.18 (d, 1H, J = 4 Hz, thiophene proton), 6.75 (d, 1H, J = 4 Hz, thiophene proton).

*Anal.* Calcd. for $C_{14}H_{20}O_5S$: C, 55.79; H, 6.71; S, 10.69. Found: C, 55.51; H, 6.42; S, 10.98.

1-(5-Acetyl-2-thienyloxy)-2,3-*O*-isopropylidenepropane (**9**).

*p*-Toluenesulfonic acid (4.2 g, 0.02 mole) was added to a stirred solution of 26.2 g (0.09 mole) of compound **8** in 1000 ml of anhydrous acetone. The reaction mixture was refluxed for 18 hours and after cooling neutralized with sodium bicarbonate and stirred another half hour. The inorganic solid so formed was filtered off and the solvent was evaporated to dryness. The oil obtained crystallized spontaneously and was purified by a silica-gel column chromatography using ethyl acetate-*n*-hexane (1:4) as eluent, yielding as main fraction a colourless solid, which was recrystallized from *n*-hexane (17.0 g, 76%), mp 57-58° (*n*-hexane); ir (nujol, ν): 1640 (C=O); nmr (deuteriochloroform): δ 1.40 (s, 3H, $CH_3$), 1.46 (s, 3H, $CH_3$), 2.47 (s, 3H, -CO-$CH_3$), 3.77-4.68 (m, 5H, -O-$CH_2$-CH-$CH_2$-), 6.39 (d, 1H, J = 4 Hz, thiophene proton), 7.54 (d, 1H, J = 4 Hz, thiophene proton).

*Anal.* Calcd. for $C_{12}H_{16}O_4S$: C, 56.24; H, 6.29; S, 12.50. Found: C, 56.12; H, 6.43; S, 12.62.

Oximation Reaction of Compound **9**.

Hydroxylamine hydrochloride (8.5 g, 0.12 mole) was added to a stirred solution of compound **9** (8.5 g, 0.03 mole) in 33 ml of triethylamine and the reaction mixture was refluxed for 1 hour. After cooling water was added and the organic layer was separated. The aqueous layer was extracted twice with ethyl acetate and all the organic layers were washed with water, dried over sodium sulfate and the solvent was removed, yielding a solid, which was a mixture of compounds **10** and **11**. These two isomers were separated by hplc using ethyl acetate-*n*-hexane (1:2) as eluent.

*E*-Isomer.

This isomer was obtained in a yield of 38% (3.4 g), Rf = 0.45; mp 112° (*n*-heptane); ir (nujol): ν 3300-3200 (-OH); nmr (deuteriochloroform): δ 1.41 (s, 3H, $CH_3$), 1.47 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$-C=N), 3.7-4.7 (m, 5H, -O-CH{-CH-CH{-), 6.24 (d, 1H, J = 4 Hz, thiophene proton), 6.96 (d, 1H, J = 4 Hz, thiophene proton), 8.0-8.5 (s, 1H, OH).

*Anal.* Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.31; N, 5.15. Found: C, 52.91; H, 6.36; N, 5.40.

*Z*-Isomer.

This compound was obtained in a yield of 35% (3.1 g), Rf = 0.22, mp 104-105° (*n*-heptane); ir (nujol): ν 3300-3200 (-OH); nmr (deuteriochloroform): δ 1.42 (s, 3H, $CH_3$), 1.47 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$-C=N), 3.7-4.7 (m, 5H, -$CH_2$-CH-$CH_2$-), 6.37 (d, 1H, J = 4.5 Hz, thiophene proton), 7.25 (d, 1H, J = 4.5 Hz, thiophene proton), 8.4-8.7 (s, 1H, OH).

*Anal.* Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.31; N, 5.15. Found: C, 53.14; H, 6.11; N, 5.38.

1-(5-Methylcarbamoyl-2-thienyloxy)-2,3-*O*-isopropylidenepropane (**13**).

To a stirred solution of compound **11** (1.36 g, 0.005 mole) in acetone (8 ml) cooled at 0° a solution of sodium hydroxide (0.2 g, 0.005 mole) in water (3 ml) was added. This suspension was treated with *p*-toluenesulfonylchloride (0.95 g, 0.005 mole) and the mixture was stirred for 3 hours. The solution was evaporated to dryness and the residue was extracted with benzene, dried over sodium sulfate and applied to an alumina (50 g) column deactivated with water (0.7 ml). This column was eluted with portions of 100 ml of benzene/chloroform gradually increasing the amount of chloroform (5:0, 4:1, 3:2, 2:3, 1:4, 0:5). The intermediate fraction 2:3 afforded mainly a chromatographically pure solid, which was crystallized from benzene (1.0 g, 74% yield), mp 137-138°; ir (nujol): ν 3310 (-NH), 1620 (C=O); nmr (deuteriochloroform): δ 1.45 (s, 3H, -$CH_3$), 1.52 (s, 3H, $CH_3$), 3.02 (d, 3H, -$CH_3$-NH), 3.80-4.74 (m, 5H, -$CH_2$-CH-$CH_2$-), 5.70-6.30 (m, 1H, NH), 6.35 (d, 1H, J = 2.3 Hz, thiophene proton), 7.35 (d, 1H, J = 2.3 Hz, thiopene proton).

*Anal.* Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.31; N, 5.16. Found: C, 53.33; H, 6.37; N, 5.42.

(5-Methylcarbamoyl-2-thienyl)glycerol (**14**).

A solution of compound **13** (1.5 g, 0.005 mole) and 10 ml of an 80% acetic acid solution was heated at 70° for 30 minutes and the solvent was evaporated *in vacuo*. The syrup obtained was recrystallized from ethyl acetate, yield 83%, mp 119-120°; ir (nujol): ν 3440 (-NH-), 3350 (-OH), 1605 (-C=O); nmr (dimethylsulfoxide-$d_6$): δ 2.78 (d, 3H, $CH_3$), 3.32-4.28 (m, 5H, -$CH_2$-CH-$CH_2$), 4.36 (t, 1H, J = 5.6 Hz, -$CH_2$-O*H*), 5.11 (d, 1H, J

= 5.6 Hz, -CH-O*H*), 6.41 (d, 1H, J = 4.0 Hz, thiophene proton), 7.51 (d, 1H, J = 4.0 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{13}NO_4S$: C, 46.75; H, 5.66; N, 6.05. Found: C, 46.78; H, 5.65; N, 6.19.

1-(5-Methylcarbamoyl-2-thienyloxy)-2,3-epoxypropane (**15**) (From Compound **14**).

*p*-Toluenesulfonyl chloride (1.06 g, 0.005 mole) was added at −10° to a stirred solution of compound **14** (1.2 g, 0.005 mole) in 12 ml of anhydrous pyridine, the reaction mixture was stirred at room temperature for 1 day and then a solution of 1.5 *N* sulfuric acid was added cooling with an ice-bath. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic extracts were dried and evaporated *in vacuo* to afford a syrup which showed in tlc two spots, corresponding to the two possible monotosyl derivatives. The crude product was dissolved in 3.4 ml of dimethylsulfoxide and 1.68 ml of a 20% aqueous solution of sodium hydroxide were added. The reaction mixture was stirred at room temperature for 1 hour and then water was added. The resulting solution was extracted with ethyl acetate and the organic extracts were dried and evaporated to dryness. The residue was chromatographed in a silica-gel column using ethyl acetate as eluent yielding, as main fraction, compound **15** (71%), mp 137-138° (benzene); ir (nujol): $\nu$ 3330 (-NH); 1615 (-C=O); nmr (deuteriochloroform): $\delta$ 2.97 (d, 3H, $CH_3$), 2.63-3.02 (m, 2H, -$CH_2$- epoxy), 3.18-3.59 (m, 1H, CH-epoxy), 3.83-4.57 (m, 2H, -O-$CH_2$), 5.85-6.50 (m, 1H, NH), 6.31 (d, 1H, J = 4.0 Hz, thiophene proton), 7.28 (d, 1H, J = 4.0 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{11}NO_3S$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.56; H, 5.16; N, 6.60.

(5-Acetyl-2-thienyl)glycerol (**16**).

Hydrolysis of compound **8** in the same conditions as described before for the hydrolysis of compound **14**, using a double amount of acetic acid, yielded compound **16** as a colourless solid (94%), mp 72-73° (cyclohexane-ethyl acetate); ir (nujol): $\nu$ 3360-3320 (-OH), 1620 (-C=O); nmr (dimethylsulfoxide-$d_6$): $\delta$ 2.47 (s, 3H, $CH_3$), 3.35-3.63 (m, 2H, -C$H_2$-OH), 3.68-4.32 (m, 3H, -O-$CH_2$-CH-), 4.80 (t, 1H, J = 5.6 Hz, -$CH_2$-O*H*), 5.17 (d, 1H, J = 5.6 Hz, -CH-O*H*), 6.56 (d, 1H, J = 4.6 Hz, thiophene proton), 7.83 (d, 1H, J = 4.6 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{12}O_4S$: C, 49.99; H, 5.59; S, 14.80. Found: C, 49.77; H, 5.67; S, 15.07.

1-(5-Acetyl-2-thienyloxy)-2,3-epoxypropane (**17**).

This compound was obtained from compound **16** in the same manner as mentioned before for compound **15**, yield 74%, mp 67-68° (*n*-hexane); ir (nujol): $\nu$ 1640 (C=O); nmr (deuteriochloroform): $\delta$ 2.50 (s, 3H, $CH_3$), 2.69-3.08 (m, 2H, -$CH_2$ epoxy), 3.24-3.58 (m, 1H, CH epoxy), 3.92 (m, 2H, -O-$CH_2$), 6.40 (d, 1H, J = 4.3 Hz, thiophene proton), 7.54 (d, 1H, J = 4.3 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{10}O_3S$: C, 54.54; H, 5.05; S, 16.16. Found: C, 54.28; H, 4.97; S, 16.34.

Oximation Reaction of Compound **17**.

This reaction was carried out in the same conditions as those described for compound **9** yielding the two isomers.

*E*-Isomer **18**.

This isomer was obtained in a yield of 36%, Rf (ethyl acetate) 0.25, mp 111-112° (*n*-heptane); ir (nujol): $\nu$ 3500-3100 (-OH); nmr (dimethylsulfoxide-$d_6$): $\delta$ 2.14 (s, 3H, $CH_3$), 3.56-4.30 (m, 5H, -$CH_2$-CH-$CH_2$-), 5.63-5.79 (s, 1H, OH), 6.39 (d, 1H, J = 4.0 Hz, thiophene proton), 7.11 (d, 1H, J = 4.0 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16; N, 6.57. Found: C, 50.66; H, 5.02; N, 6.65.

*Z*-Isomer **19**.

This isomer was obtained in a yield of 33%, Rf (ethyl acetate) 0.78, mp 147-148° (*n*-heptane); ir (nujol): $\nu$ 3500-3200 (-OH); nmr (dimethylsufloxide-$d_6$): $\delta$ 2.24 (s, 3H, $CH_3$), 3.67-4.29 (m, OH, -$CH_2$-CH-$CH_2$), 5.62-5.84 (s, 1H, OH), 6.54 (d, 1H, J = 4.0 Hz, thiophene proton), 7.32 (d, 1H, J = 4.0 Hz, thiophene proton).

*Anal.* Calcd. for $C_9H_{11}NO_3S$: C, 50.70; H, 5.16; N, 6.57. Found: C, 50.88; H, 5.11; N, 6.75.

1-(5-Methylcarbamoyl-2-thienyloxy)-2,3-epoxypropane (**15**) (From Compound **19**).

This reaction was carried out as described for the Beckmann rearrangement of compound **13**, yield 71%. This compound was identical in all respects with that obtained from compound **14**.

3-Isopropylamino-1-(5-methylcarbamoyl-2-thienyloxy)-2-propanol (**4**).

Isopropylamine (10 ml) and water (1 ml) was added to compound **15**. The reaction mixture was left for 4 days at room temperature and then evaporated to dryness. The residue was extracted with an aqueous 2*N* hydrogen chloride solution and this acidic layer was washed with diethyl ether, basified with a 10% aqueous solution of sodium hydroxide and extracted with diethyl ether. The evaporation of the solvent yielded a white solid which was recrystallized from tetrahydrofuran, yield 66%, mp 143-144°; ir (nujol): $\nu$ 3320 (-NH-), 3200-2680 (-NH and -OH), 1610 (C=O); nmr (dimethylsulfoxide-$d_6$): $\delta$ 0.92 (s, 3H, $CH_3$-C), 1.02 (s, 3H, $CH_3$-C), 2.24-2.47 (m, 1H, -C*H*-NH), 2.77 (d, 3H, $CH_3$N-), 2.82-3.26 (m, 2H, -C$H_2$-NH), 3.57-4.21 (m, 3H, -O-$CH_2$-CH-), 6.41 (d, 1H, J = 4.0 Hz, thiophene proton), 7.51 (d, 1H, J = 4.0 Hz, thiophene proton), 8.03-8.40 (m, 1H, -N*H*-CO).

*Anal.* Calcd. for $C_{12}H_{20}N_2O_3S$: C, 52.94; H, 7.35; N, 10.29; S, 11.76. Found: C, 52.80; H, 7.63; N, 10.48; S, 11.83.

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