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Synthesis of Aliphatic Dialkylamino Alcohols from Thiophene Derivatives

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In light of the data that we obtained in studying the reductive desulfurization of tertiary amines of the thiophene series (1), it is of interest to investigate the possibility of obtaining, by an analogous route, aminospirits, which, as is known, are an important fragment in the synthesis of physiologically active substances, in particular those of anesthetic, spasmolytic, or hypotensive character. In this connection it should be noted that, despite the very broad range of applications of amino alcohols, the methods for their preparation are limited in some cases by the composition of the initial natural substances, and in others by the very principles underlying the synthesis.

The method developed by us for preparing dialkylamino alcohols is illustrated by the following scheme:

$$\text{A} \quad \text{thiophene} \longrightarrow \text{thiophene}{-}\text{CHO} \xrightarrow[\text{HCOOH}]{\text{HNR}_2} \text{thiophene}{-}\text{CH}_2\text{NR}_2 \xrightarrow{\text{n-BuLi}} \text{Li}{-}\text{thiophene}{-}\text{CH}_2\text{NR}_2 \longrightarrow$$

$$\xrightarrow[\text{H}_2\text{O}]{\text{CH}_2{-}\text{CH}_2\text{O}} \text{HOCH}_2\text{CH}_2{-}\text{thiophene}{-}\text{CH}_2\text{NR}_2 \xrightarrow{\text{Re}{-}\text{Ni}} \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NR}_2$$

β-Oxyethylation of tertiary amines can be carried out by the action of ethylene oxide on the corresponding organolithium compounds (2). The number of methylene units separating the amino group from the hydroxy group, even when thiophene itself is used, reaches seven; and if dithienylmethane is taken as the starting product, it increases to twelve. In addition, possibilities are created for changing the degree of branching of the chain if one starts from dithienylmethanes substituted in the methylene group by various alkyl radicals.

The question of the structure of the organolithium compounds formed by the action of butyllithium on tertiary amines of the thiophene series, and consequently of the structure of the aminospirits obtained from them, could not be regarded in advance as unambiguously resolved, since, in accordance with Gilman’ s views (3), it is possible to imagine that coordination of the lithium alkyl may occur both at the sulfur atom and at the nitrogen atom. In this connection we carried out a counter-synthesis of one of the aminospirits obtained by us, 5-diethylaminomethyl-2-β-oxyethylthiophene (I), according to a scheme that can lead to the formation of an aminospirit only of structure I:

$$\text{B}\quad \text{thiophene} \xrightarrow{\text{n-BuLi}} \text{thiophene--Li} \xrightarrow[H_2O]{CH_2{-}CH_2O} \text{thiophene--}CH_2CH_2OH \longrightarrow \text{thiophene--}CH_2CH_2OCOCH_3 \text{ (I}$$

$$\longrightarrow OHC\text{--thiophene--}CH_2CH_2OCOCH_3 \text{ (III)} \xrightarrow[HCOOH]{HN(C_2H_5)_2} (C_2H_5)_2NCH_2\text{--thiophene--}CH_2CH_2OH \text{ (I)}$$

On comparison of the aminospirit I formed in this way with the aminospirit of the same composition obtained according to scheme A, it was found that they are identical.

Thus, it may be considered proven that the reaction of formation of organolithium compounds from tertiary amines of the thiophene series proceeds according to scheme A, and that the aminospirans formed from them do indeed have the structure indicated therein.

Continuing the work in the indicated direction, from amines of the thiophene series (V, IV, VI, VII), of which VI was obtained for the first time, we synthesized, by the method described above, the thiophene aminospirans: I, VIII, IX, X

(V) $R = H$ (IV) $R = H$ (VII) $R =$ thiophene ring bearing $C(CH_3)(C_2H_5)-$

(VIII) $R = -CH_2CH_2OH$ (VI) $R =$ thiophene ring bearing $-CH_2-$

(IX) $R = HOCH_2CH_2-$thiophene ring$-CH_2-$

(X) $R = HOCH_2CH_2-$thiophene ring$-C(CH_3)(C_2H_5)-$

As a result of reductive desulfurization they gave, respectively, aliphatic dialkylamino alcohols:

$$HO(CH_2)_7N(C_2H_5)_2 \qquad \text{(XI)}$$

piperidine ring bearing H and $N-(CH_2)_7OH$
(XII)

$$HO(CH_2)_{12}N(C_2H_5)_2 \qquad \text{(XIII)}$$

$$HO(CH_2)_6C(CH_3)(C_2H_5)(CH_2)_5N(C_2H_5)_2 \qquad \text{(XIV)}$$

Experimental Part

β-Oxyethylthiophene acetate (II). To a solution of 17.8 g (0.14 mole) of β-oxyethylthiophene and 22 g (0.28 mole) of dry pyridine in 50 ml of dry benzene, 13.2 g (0.17 mole) of acetyl chloride was added dropwise with stirring. The mixture was treated with 100 ml of ice water, and the benzene layer was separated; the aqueous layer was extracted with benzene. The benzene solution was washed with sodium bicarbonate solution. After distillation of the solvent and redistillation, 18.6 g (79% of theory) of acetate II was obtained, b.p. 115–117°/16 mm; n_D^{20} 1.5088; d_4^{20} 1.1303; found MR_D 44.96; calculated MR_D 44.81.

Found, %: C 56.59; 56.30; H 5.86; 5.88; S 18.74; 18.72
$C_8H_{10}SO_2$. Calculated, %: C 56.44; H 5.92; S 18.84

5-(β-Acetoxyethyl)-2-thiophenealdehyde (III). Acetate II was formylated by the method of Weston and Michaels (4). From 16.85 g (0.1 mole) of (II), 12.3 g (0.09 mole) of N-methylformanilide, and 13.9 g (0.09 mole) of phosphorus oxychloride, 10.7 g (54.5% of theory) of acetate III was obtained, b.p. 178–180°/15 mm; n_D^{20} 1.5511; d_4^{20} 1.2142.

Found, %: C 55.16; 54.95; H 5.28; 5.29; S 15.83; 16.17
$C_9H_{10}SO_3$. Calculated, %: C 54.52; H 5.08; S 16.17

The 2,4-dinitrophenylhydrazone melts at 200–201°.

Found, %: N 14.61; 14.94
$C_{15}H_{14}SN_4O_6$. Calculated, %: N 14.80

5-Diethylaminomethyl-2-β-oxyethylthiophene (I).
a) From 7 g (0.35 mole) of III, 4.25 g (0.106 mole) of 96% formic acid, and 5.17 g (0.07 mole) of diethylamine, by the method of Smith and Cavaillito (5), already used in our laboratory (1), 1.7 g of substance was obtained, b.p. 162–165°/15 mm; n_D^{20} 1.5292. Naphthylurethane I, m.p. 65° (from heptane).

Found, %: C 69.35; 69.51; H 6.93; 6.76; S 7.91
$C_{22}H_{26}SN_2O_2$. Calculated, %: C 69.08; H 6.85; S 8.38

b) Oxyethylation of 14.2 g (0.08 mole) of diethyl-2-thenylamine (IV) (1) was carried out under the conditions described (2). The mixture was hydrolyzed, the ether layer was separated, and the aqueous layer was extracted with ether. On distillation of the residue after removal of the solvent, 8.1 g of amino alcohol I was obtained, b.p. 148–150°/7 mm; n_D^{20} 1.5310; d_4^{20} 1.0543; found MR_D 62.61; calculated MR_D 62.59.

Found, %: C 61.85; 61.98; H 9.20; 9.11; S 14.87; 14.69
$C_{11}H_{19}SNO$. Calculated, %: C 61.92; H 8.98; S 15.03

Naphthylurethane, m.p. 63–64°. The mixed sample gave no depression of the m.p.

Found, %:	N 7.09
$C_{22}H_{26}SN_2O_2$. Calculated, %:	N 7.32

Amines V and VI were obtained by the method described by us earlier (1,5).

N-(2-Thenyl)piperidine (V). From 22.4 g (0.2 mole) of thiophene aldehyde, 24 g (0.5 mole) of 96% formic acid, and 34 g (0.4 mole) of piperidine, 23.3 g (64.5% of the theoretical amount) of V was obtained; b.p. 102-104°/7 mm; n_D^{20} 1.5390; d_4^{20} 1.0443; found MR_D 54.38; calculated MR_D 54.25. Campbell and Keding (6) give b.p. 139.5°/29 mm; n_D^{25} 1.5373.

Found, %:	C 66.55; 66.36;	H 8.27; 8.34
$C_{10}H_{15}SN$. Calculated, %:	C 66.25;	H 8.34

Methiodide, m.p. 160° (from absolute alcohol). Campbell and Keding (6) give for the methiodide of V m.p. 59°. This figure is undoubtedly erroneous, as is evident from the fact that the methiodide obtained from V, which we synthesized by the Campbell and Keding method from chloromethylthiophene, also melted at 160° and gave no depression with the above methiodide.

Found, %:	N 4.47; 4.26
$C_{11}H_{18}SNJ$. Calculated, %:	N 4.33

5-Diethylaminomethyl-di-2-thenylmethane (VI). From 35 g (0.17 mole) of 5-(2-thenyl)thiophene-2-aldehyde (7), 20.7 g (0.49 mole) of 96% formic acid, and 25.2 g (0.35 mole) of diethylamine, 30.35 g (68% of theory) of the amine was obtained with b.p. 176-177.5°/7 mm; n_D^{20} 1.5641; d_4^{20} 1.0887; found MR_D 79.30; calculated MR_D 79.05.

Found, %:	C 63.23; 63.19;	H 7.17; 7.24;	S 24.23; 24.43
$C_{14}H_{19}S_2N$. Calculated, %:	C 63.34;	H 7.21;	S 24.16

Methiodide, m.p. 151.5-152.5° (from absolute alcohol).

Found, %:	N 3.20; 3.28
$C_{15}H_{22}S_2NJ$. Calculated, %:	N 3.44

5-(1-Piperidinomethyl)-2-β-oxyethylthiophene (VIII) was obtained analogously to I. From 14 g (0.08 mole) of V, 5.2 g (0.08 mole) of butyllithium, and 5.3 g (0.12 mole) of ethylene oxide, 5.8 g of amino alcohol was obtained with b.p. 173-177°/8 mm; n_D^{20} 1.5520; d_4^{20} 1.1040; found MR_D 65.22; calculated MR_D 65.01.

Found, %: C 63.64; 63.93; H 8.64; 8.43; S 14.05; 14.19
$C_{12}H_{19}SNO$. Calculated, %: C 63.95; H 8.50; S 14.23

Methiodide, m.p. 92-93° (from absolute alcohol)

Found, %: N 3.99; 4.11
$C_{13}H_{22}SNOJ$. Calculated, %: N 3.97

5′-Diethylaminomethyl-5-β-oxyethyl-2,2′-dithenylmethane (IX) was obtained analogously to I. From 39.5 g (0.15 mole) of VI, 9.6 g (0.15 mole) of butyllithium, and 10 g (0.22 mole) of ethylene oxide, 16.7 g (36.5% of theory) of IX was obtained; b.p. 198-204°/4 mm; m.p. 48-49° (from petroleum ether).

Found, %: C 62.17; 62.26; H 7.52; 7.54; S 20.58; 20.95
$C_{16}H_{23}S_2NO$. Calculated, %: C 62.09; H 7.49; S 20.72

Hydrochloride of the *p*-nitrobenzoate of IX—obtained by saturating an ethereal solution of the *p*-nitrobenzoate of IX with dry hydrogen chloride (8); m.p. 163.5-164° (from absolute alcohol).

Found, %: C 55.37; 55.59; H 5.37; 5.65
$C_{23}H_{27}S_2N_2O_4Cl$. Calculated, %: C 55.80; H 5.50

2-(5′-Diethylaminomethyl-2′-thienyl)-2-(5-β-oxyethyl-2-thienyl)butane (X) was obtained analogously to I. From 33.75 g (0.11 mole) of VII (1), 7.1 g (0.11 mole) of butyllithium, and 7.1 g (0.16 mole) of ethylene oxide, 26.1 g of X was obtained with b.p. 233-236°/7 mm; 213-216°/4 mm; n_D^{20} 1.5639; d_4^{20} 1.1045; found MR_D 103.52; calculated MR_D 103.66.

Found, %: C 64.77; 64.70; H 8.16; 8.29; S 18.13; 18.17
$C_{19}H_{29}S_2NO$. Calculated, %: C 65.09; H 8.34; S 18.29

Reductive desulfurization of amino alcohols of the thiophene series was carried out by the method previously described by us (1), using a skeletal Ni catalyst prepared by the method of Adkins (9).

1-Diethylaminoheptanol-7 (XI). From 35.4 g of I, after 30 minutes' heating with Raney Ni, 13.8 g (44.5% of theory) of a substance was obtained with b.p. 130-132°/9 mm. On redistillation, 12.6 g (XI) was obtained with b.p. 129.5-130°/9 mm; n_D^{19} 1.4569. Literature data: b.p. 132°/9.5 mm; n_D^{19} 1.4561 (10); b.p. 139-141°/25 mm (11).

Found, %: C 70.21; 70.15; H 13.32; 13.16
$C_{11}H_{25}NO$. Calculated, %: C 70.50; H 13.47

The hydrochloride of **(7-chloroheptyl)diethylamine (XV)** melted at 85° (cf. ([11])).

Found, %: N 5.66; 5.86
$C_{11}H_{25}NCl_2$. Calculated, %: N 5.78

1-Piperidinoheptanol-7 (XII). From 9 g of VIII, after 30 minutes' heating with Raney Ni, 4 g (50% of theory) of amino alcohol was obtained with b.p. 147-150°/7 mm. On redistillation, 2.4 g of XII was obtained with b.p. 144-147°/7 mm; n_D^{20} 1.4771; d_4^{20} 0.9253; found MR_D 60.88; calculated MR_D 60.88. The hydrochloride of **N-(7-chloroheptyl)piperidine** had m.p. 148-148.5° (re-precipitated from alcohol with ether).

Found, %: C 56.15; 56.45; H 10.07; 10.00; Cl 27.43
$C_{12}H_{25}NCl_2$. Calculated, %: C 56.68; H 9.91; Cl 27.89.

1-Diethylaminododecanol-12 (XIII). From 10 g of amino alcohol IX, after 30 minutes' heating with Raney Ni, 4 g (46% of theory) of a substance was obtained with b.p. 140-178°/7 mm. On redistillation, 2 g of XIII was obtained with b.p. 175-178°/7 mm; n_D^{20} 1.4611; d_4^{20} 0.8691; found MR_D 81.30; calculated MR_D 81.55.

Found, %: C 74.64; 74.56; H 13.63; 13.61
$C_{16}H_{35}NO$. Calculated, %: C 74.64; H 13.70.

1-Diethylamino-6-methyl-6-ethyldodecanol-12 (XIV). From 6.5 g of X, after 45 minutes' heating with Raney Ni, 2 g of substance was obtained with b.p. 170-193°/7 mm. On redistillation, 1.2 g of XIV was obtained with b.p. 190-192°/7 mm; n_D^{20} 1.4650; d_4^{20} 0.8662; found MR_D 95.59; calculated MR_D 95.41.

Found, %: C 75.97; 76.28; H 13.69; 13.71
$C_{19}H_{41}NO$. Calculated, %: C 76.18; H 13.80.

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Note: Figure translations are in progress. See original paper for figures.