LITHIATION OF SOME 3[2-(2'-BROMOPHENYL)ETHYL]THIOPHENES AND INTRAMOLECULAR TRANSMETALATION

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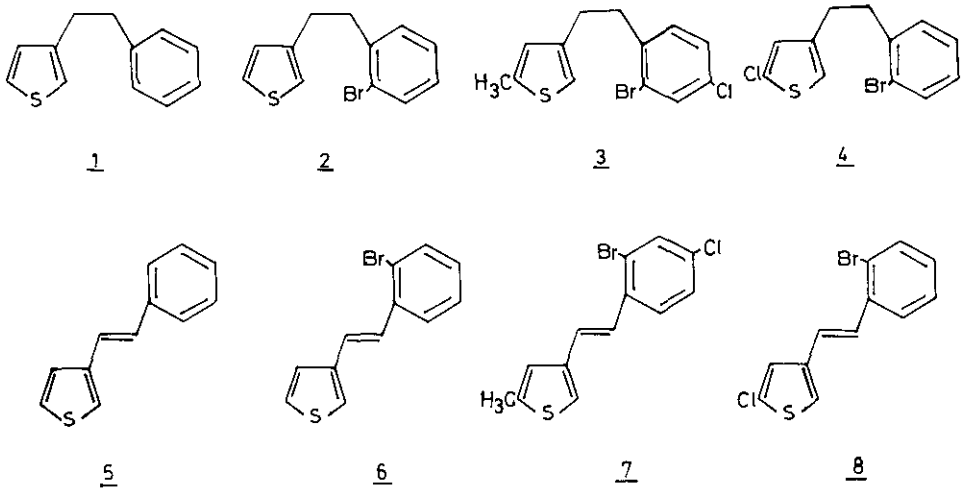
Abstract - The reaction of some halo-1-(thienyl)-2-phenylethanes such as 3-(2-phenylethyl)thiophene (1), 3-[2-(2'-bromophenyl)ethyl]thiophene (2), 4-[2-(2'-bromo-4'-chlorophenyl)ethyl]-2-methylthiophene (3) and 4-[2-(2'-bromophenyl)ethyl]-2-chlorothiophene (4) with butyllithium and lithium-diisopropylamide (LDA) under various conditions has been investigated. Competition between halogen-metal exchange in the benzene ring and metalation of the thiophene ring was observed and an intramolecular transmetalation reaction was found.

In connection with our work on potentially neuroleptic spirocyclic compounds,[1-3] we have investigated the reaction of 3-(2-phenylethyl)thiophene (1), 3-[2-(2'-bromophenyl)ethyl]thiophene (2), 4-[2-(2'-bromo-4'-chlorophenyl)ethyl]-2-methylthiophene (3) and 4-[2-(2'-bromophenyl)ethyl]-2-chlorothiophene (4) with organolithium compounds under various conditions. We wished to obtain information on the relative rate of metalation of thiophenic α-positions versus halogen-lithium exchange on bromophenyl moieties, as well as on the further inter- or intramolecular rearrangements of organolithium derivatives in which the lithium is not substituting the most acidic hydrogen in the molecule.

The compounds 1-4 were all prepared in similar ways, the key step being an 'olefin' synthesis via the Wadworth-Emmons-Horner modification of the Wittig reaction[4] followed by homogeneous catalytic hydrogenation over the Wilkinson catalyst chlorotris(triphenylphosphine)rhodium.[5] Thus, 1 was prepared starting from diethyl benzylphosphonate and 3-thiophenecarboxaldehyde followed by hydrogenation of the predominant (E)-3-(2-phenylethenyl)thiophene (5). Similarly, (E)-3-[2-(2'-bromophenyl)ethenyl]thiophene (6) was prepared from diethyl (2-bromophenyl)methylphosphonate and 3-thiophenecarboxaldehyde, which upon hydrogenation gave (2).



1 2 3 4

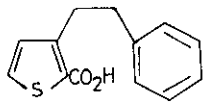
5 6 7 8

The components used for the synthesis of 3 were 5-methyl-3-thiophenecarboxaldehyde and diethyl [(2-bromo-4-chlorophenyl)methyl]phosphonate. The latter compound was prepared from 4-nitrotoluene. Its bromination was best achieved with dibromoisocyanuric acid in conc. sulfuric acid.[6] Reduction of 2-bromo-4-nitrotoluene with iron and conc. hydrochloric acid,[7] followed by diazotization of the resulting 4-amino-2-bromotoluene and Sandmeyer reaction gave 2-bromo-4-chlorotoluene,[8] which through bromination with N-bromosuccinimide in the presence of azobisisobutyronitrile was converted to 2-bromo-1-bromomethyl-4-chlorobenzene, which by the usual Arbusov reaction was converted to the desired diethyl [(2-bromo-4-chlorophenyl)methyl]phosphonate. The (E)-4-[2-(2'-bromo-4'-chlorophenyl)ethenyl]-2-methylthiophene (7) obtained in the Wadworth-Emmons-Horner reaction was hydrogenated to 3.

In order to obtain 4, we synthesized 2-chloro-4-thiophenecarboxaldehyde from 2,4-dibromothiophene via 4-bromo-2-chlorothiophene.[9] It was allowed to react with diethyl [(2-bromophenyl)methyl]-phosphonate to give (E)-4-[2-(2'-bromophenyl)ethenyl]-2-chlorothiophene (8), which was then hydrogenated.

Metalation of 1 with ethereal butyllithium at room temperature or with butyllithium in tetrahydrofuran at 0°C gave, after reaction with carbon dioxide, 3-(2-phenylethyl)-2-thiophenecarboxylic acid (9) and 4-(2-phenylethyl)-2-thiophenecarboxylic acid (10) in the proportions 20:80 and 25:75, and in total yields of 82 % and 71 %, respectively. The isomer distribution was thus not much different from that obtained in the metalation of 3-methylthiophene.[10] Pure 10 was obtained from the reaction mixture through fractional crystallization from toluene. Authentic 9 was prepared through halogen-metal exchange between butyllithium and 2-bromo-3-(2-phenylethyl)thiophene (11) at -70°C followed by reaction with carbon dioxide. Compound 11 was prepared from 1 through bromination with N-bromosuccinimide in acetic acid-carbon tetrachloride. When 1 was treated with LDA in ether-

hexane solution at room temperature, no large change in isomer distribution occurred and 9 and 10 were obtained in the proportion 17:83. However, the total yield was in this case much lower. The isomer distribution was determined by Glc analyses of the trimethylsilyl derivatives.



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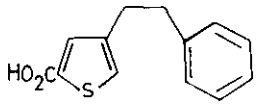

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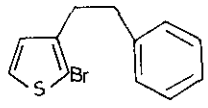

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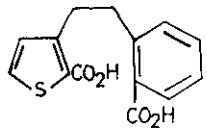

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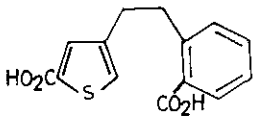

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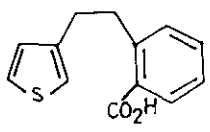

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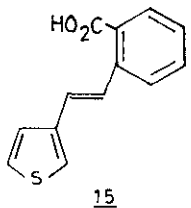

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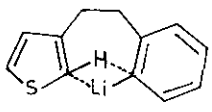

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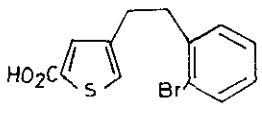

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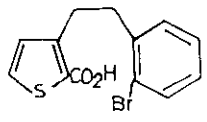

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Compound 2 reacted extremely slowly with ethereal butyllithium at -70°C. At room temperature, a mixture of 9 and 3-[2-(2'-carboxyphenyl)ethyl]-2-thiophenecarboxylic acid (12) was formed upon reaction with carbon dioxide. The product distribution was very difficult to reproduce, and 9 and 12 were obtained in ratios varying from 7:3 to 3:7, depending partly upon the amount of butyllithium used. If a deficient amount of butyllithium was used, 9 was obtained almost exclusively.

When 2 was reacted with butyllithium in tetrahydrofuran at -70°C, 9 and another dicarboxylic acid, 4-[2-(2'-carboxyphenyl)ethyl]-2-thiophenecarboxylic acid (13), were obtained in about equal amounts, besides traces of 10, after reaction with carbon dioxide. At 0°C, 9 and 10 were obtained in a 5:2 ratio. The structures were evident from ^{1}H nmr and mass spectra.

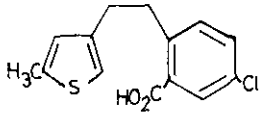
Under no conditions could the expected primary product 2-[2-(3'-thienyl)ethyl] benzoic acid (14) be found. Authentic 14 was prepared through hydrogenation of 2-[2-(3'-thienyl)ethenyl] benzoic acid (15), obtained by the phosphonate method from 2-formylbenzoic acid and diethyl (3-thienylmethyl)phosphonate. It thus seems probable that the initially formed 3-[2-(2'-lithiophenyl)ethyl]-thiophene is very unstable and rapidly intramolecularly rearranged to the 2-lithio derivative via the cyclic state 16 in the ethereal reaction.

The formation of 12 is more difficult to rationalize. It is possible that metalation of the

2-position followed by rapid halogen-metal exchange with butyllithium gives the appropriate dilithium derivative. The halogen-metal exchange must be rapid because no 3-[2-(2'-bromophenyl)-ethyl]-2-thiophenecarboxylic acid could be detected. It is also difficult to understand why no 13 was formed. Another possibility is therefore that the initial lithium derivative formed upon halogen-metal exchange is selectively metalated in the thiophenic 2-position. In tetrahydrofuran, on the other hand, in which metalation is faster than in ether, it is possible that at -70°C the first-formed lithium derivative is stable enough to be further metalated in the 5-position, and that the ortho-5-lithio derivative does not rearrange. At room temperature, rapid intra- and intermolecular rearrangements could explain the formation of the products.

The reaction with LDA is of course much simpler, since no halogen-metal displacement can occur, and upon reaction with carbon dioxide 4-[2-(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid (17) and 3-[2-(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid (18) were obtained in the proportion 83:17, thus the same as in the metalation of 1 with LDA. The total yield was, however, only 30 %.

In order to obtain additional evidence for an intramolecular transmetalation, the reaction of 3 was investigated. In this compound the 5-position is blocked and the 4'-chloro group could be expected to increase the rate of halogen-metal exchange and stabilize the 2'-lithio derivative. At -70°C, ethereal butyllithium gave exclusively halogen-metal exchange, and after reaction with carbon dioxide a 59 % yield of 4-chloro-1-[2-(2'-methyl-4'-thienyl)ethyl]-2-benzoic acid (19) was obtained. If the temperature was allowed to rise to 0°C, rearrangement started to occur and after carbonation, 19 and 3-[2-(4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxylic acid (20)[1] were obtained in a ratio of 7:3.



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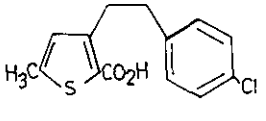

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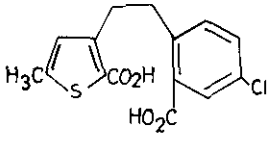

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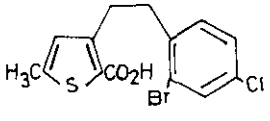

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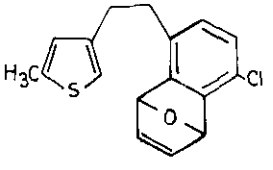

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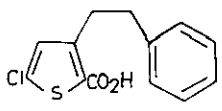
If the reaction was carried out directly at 0°C, a mixture of 19 and 20 and the dicarboxylic acid 3-[2-(2'-carboxy-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxylic acid (21) was obtained

in the proportions 7:1:2, respectively, according to glc analysis of the silyl esters.

In tetrahydrofuran, the results were even more clear-cut. At -70°C, only 19 was obtained after one hour, while reaction at 0°C only gave the rearranged product 20.

In none of these experiments could the acid obtained through direct thiophene metalation of 3 be found. Authentic 3-[2-(2'-bromo-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxylic acid (22) was prepared by Vilsmeyer formylation of 3, followed by silver oxide oxidation of the intermediate 3-[2-(2'-bromo-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxaldehyde. The compound 22 could not be obtained by metalation with LDA followed by reaction with carbon dioxide. No acids could be isolated, but in the neutral phase a large number of components was present. This is probably due to metalation at the 3'-position followed by benzyne formation.[10] If the metalation with LDA was carried out in the presence of furan, glc showed the formation of two major compounds, besides many minor one. The nmr spectrum of the crude product showed olefinic singlets at 5.66 δ and 5.83 δ, and one of the main components showed weak molecular ions at m/e 303, 301 and strong peaks at m/e 111 (100 %) and 191, 193, giving some indication that its structure might be 23. It is known that in the metalation of 1-bromo-3-chlorobenzene predominantly 3-chlorobenzyne is formed.[12]

The reaction of 4 with butyllithium in ether at -70°C was very slow, and even after several hours only 10-15 % of an acid mixture was obtained. At -60°C to -40°C, the main acids formed were 5-chloro-3-(2-phenylethyl)-2-thiophenecarboxylic acid (24) (13 %), 2-[2-(2'-chloro-4'-thienyl)-ethyl]benzoic acid (25) (44 %) and 5-chloro-3-[2-(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid. It is thus evident that even at this low temperature metalation of the thiophenic 2-position competes with halogen-metal exchange in the bromophenyl moiety, and some rearrangement has also occurred. At higher temperatures the amount of 24 increased at the expence of 25, and dimetalation also occurred, leading to the formation of 5-chloro-3-[2-(2'-carboxyphenyl)ethyl]-2-thiophene-carboxylic acid (27) upon reaction with carbon dioxide. In this case, reaction of 4 with LDA followed by reaction with carbon dioxide gave only 26, which was easily obtained pure. In tetrahydrofuran, more easily interpretable results were obtained. After 3 h at -70°C, a mixture of 24 and 26 in the proportion 7:3 was obtained, showing that at this temperature halogen-metal exchange and intramolecular rearrangement are faster than direct metalation of 4. It was even more pronounced at 0°C as then only 24 was obtained, as could be expected.



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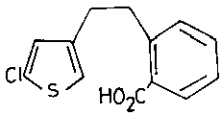

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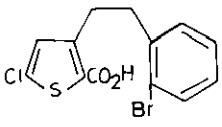

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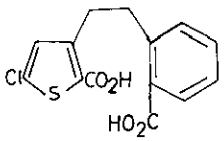

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EXPERIMENTAL

Gas chromatographic analyses were performed with a Perkin-Elmer 900 apparatus equipped with a flame-ionization detector. The following columns were used: OV 1 (3 %) on Chrom Q 80/100 mesh (2.5 m, 350°), OV 1 (3 %) on Chromosorb W 80/100 mesh (1.7 m, 350°) and OV 17 (3 %) on Varaport 30 100/120 mesh (2.5 m, 350°). Mass spectra were recorded on an LKB 9000 mass spectrometer at 70 eV. Nmr spectra were recorded on a Varian A-60 or a Jeol MH-100 spectrometer with tetramethylsilane (TMS) as internal standard.

2-Bromo-4-nitrotoluene. To 27.4 g (0.20 mol) of 4-nitrotoluene in 220 ml of conc. sulfuric acid, a solution of 28.7 g (0.10 mol) of N,N-dibromoisocyanuric acid in 280 ml of conc. sulfuric acid was added with stirring, and the mixture was stirred for 30 min. The mixture was poured onto crushed ice, the precipitate was filtered off and washed with 0.1 M sodium hydroxide solution and water, yielding 38.0 g (88 %) of the title compound, mp 77-78°C after recrystallization from ethanol. Literature value:[7] mp 76-77°C.

2-Bromo-4-chloro-benzyl bromide. This compound was prepared according to the detailed description given in Ref. 13. From 198.4 g (0.966 mol) of 2-bromo-4-chlorotoluene,[8] 171.9 g (0.966 mol) of N-bromosuccinimide, 1.7 g of azobisisobutyronitirle and 950 ml of carbon tetrachloride, 153.8 g (56 %) of the title compound, bp 138-142°C/12 mmHg, n_D^{20} = 1.6299, was obtained.

Diethyl benzylphosphonate. A mixture of 59.8 g (0.35 mol) of benzyl bromide and 75.6 g (0.46 mol) of triethyl phosphite was heated under nitrogen at about 120°C for one h and at 150°C for another 2 h. The product was distilled in vacuo, yielding 73.2 g (92 %) of the title compound, bp 91-97°C/0.05 mmHg. Nmr ($CDCl_3$): δ 7.30 (C_6H_5, s, 5H), 3.99 ($\underline{CH_2}CH_3$, m, 4H), 3.13 ($\underline{CH_2}$-P, d, 2H), 1.22 ($CH_2\underline{CH_3}$, t, 6H), J (CH_2CH_3) 7.4 Hz, J (CH_2-P) 22.0 Hz.

Diethyl (2-bromo-benzyl)phosphonate. This compound was prepared as described above. From 249.9 g (1.00 mol) of 2-bromobenzyl bromide and 216.0 g (1.30 mol) of triethylphosphite, 298.8 g (97 %) of the title compound, bp 112-122°C/0.02 mmHg, n_D^{22} = 1.5238, was obtained. Nmr ($CDCl_3$): δ 6.90-7.73 (C_6H_4, m, 4H), 4.05 ($\underline{CH_2}CH_3$, o, 4H), 3.40 (CH_2-P, d, 2H), 1.25 ($CH_2\underline{CH_3}$, t, 6H), J (CH_2CH_3) 7.6 Hz, J (CH_2-P) 22.0 Hz, J (P-OCH_2) 8.6 Hz. Found: C 42.92; H 5.24; Br 27.10. Calc. for $C_{11}H_{16}BrO_3P$ (307.1): C 43.02; H 5.25; Br 26.02.

Diethyl [(2-bromo-4-chlorophenyl)methyl]phosphonate. This compound was prepared as described above. From 213.3 g (0.75 mol) of 2-bromo-4-chlorobenzylbromide and 162.8 g (0.98 mol) of triethyl phosphite 166.6 g (65 %) of the title compound, bp 131-133°C/0.02 mmHg, was obtained. Nmr ($CDCl_3$): δ 7.62-7.18 (C_6H_3, m, 3H), 4.07 ($\underline{CH_2}CH_3$, o, 4H), 3.36 (CH_2-P, d, 2H), 1.28 ($CH_2\underline{CH_3}$, t, 6H), J (CH_2CH_3) 7.3 Hz, J (CH_2-P) 22.4 Hz, J (CH_2OP) 8.3 Hz. Found: C 38.40; H 4.38. Calc. for

$C_{11}H_{15}BrClO_3P$ (341.6): C 38.68; H 4.43.

General procedure for the preparation of trans diarylethenes by the phosphonate method. To a cooled suspension of 0.90 mol freshly prepared sodium methoxide in 200 ml of anhydrous N,N-dimethylformamide, a mixture of 0.60 mol of aldehyde and 0.60 mol of phosphonate was added dropwise with stirring. After the addition was complete, the mixture was stirred at 0°C for 15 min and at room temperature for 90 min, poured into ice-cold water and extracted with ether. The combined ether phases were washed with M sodium bisulfite solution and water, and dried over calcium chloride. After evaporation of the solvent, the product was analyzed by glc and recrystallized from hexane or ethanol.

(E)-3-(2-Phenylethenyl)thiophene (5). From 45.6 g (0.20 mol) of diethyl benzyl phosphonate and 22.4 g (0.20 mol) of 3-thiophenecarboxaldehyde, 42.9 g (100 %) of the title compound was obtained, mp 126-128°C after recrystallization from hexane. Nmr ($CDCl_3$): δ 7.49-7.20 (aromatic, m, 8H), 7.11 (=CH, d, 1H), 6.87 (=CH, d, 1H), J (CH=CH-t) 16.8 Hz. Found: C 77.20; H 5.32; S 17.00. Calc. for $C_{12}H_{10}S$ (186.3): C 77.38; H 5.41; S 17.21.

(E)-3-[2-(2'-Bromophenyl)ethenyl]thiophene (6). From 122.8 g (0.40 mol) of diethyl 2-bromobenzylphosphonate and 44.8 g (0.40 mol) of 3-thiophenecarboxaldehyde 106.9 g (98 %) of the title compound was obtained, mp 48.5-49.5° after recrystallization from hexane. Nmr ($CDCl_3$): complex multiplet between 7.62-6.91 δ. Found: C 64.50; H 3.20; S 11.90. Calc. for $C_{12}H_9BrS$ (263.2): C 54.35; H 3.42; S 12.09.

(E)-4-[2-(2'-Bromo-4'-chlorophenyl)ethenyl]-2-methylthiophene (7). From 205 g (0.60 mol) of diethyl [(2-bromo-4-chlorophenyl)methyl]phosphonate and 85.2 g (0.60 mol) of 2-methyl-4-thiophenecarboxaldehyde[14] 182 g (97 %) of the title compound was obtained, mp 82-84°C after recrystallization from hexane. Nmr ($CDCl_3$): δ 7.59-7.17 (benz., m, 3), 7.14 (=CH, d, 1), 7.05 (thioph., s, 2), 6.91 (=CH, d, 1), 2.49 (CH_3, d, 3), J (CH=CH-t) 16.1 Hz, J (CH_3-3) 1.1 Hz. Found: C 49.80; H 3.21; S 10.20. Calc. for $C_{13}H_{10}BrClS$ (313.65): C 49.78; H 3.21; S 10.22.

(E)-(4-[2-(2'-Bromophenyl)ethenyl]-2-chlorothiophene (8). From 184.2 g (0.60 mol) of diethyl 2-bromophenyl)methyl phosphonate and 87.9 g (0.60 mol) of 5-chloro-2-thiophenecarboxaldehyde,[15] 170.7 g (95 %) of the title compound, mp 68-69°C after recrystallization from hexane, was obtained. Nmr ($(CD_3)_2SO$): δ 8.00-6.80 (benz., thioph., CH=CH, m, 8). Found: C 48.15; H 2.67; S 10.67. Calc. for $C_{12}H_8BrClS$ (299.6): C 48.10; H 2.69; S 10.70.

General procedure for the preparation of 1,2-diarylethanes. Through a suspension of 0.1 mol of the (E)-1,2-diarylethene in 300 ml of absolute ethanol, nitrogen gas was bubbled for 15 min. Then 0.8 g of tristriphenylphosphine rhodium(I) chloride was added and the mixture hydrogenated in a Parr apparatus at 60-70°C and a hydrogen pressure of 60-30 psi. Hydrogenation was usually complete in 4-5 h. The alcohol was evaporated and the residue chromatographed on a short silica gel

column using chloroform as an eluent. The catalyst-free solution was evaporated and the residue distilled in vacuo.

3-(2-Phenylethyl)thiophene (1): yield 87 %, bp 70-80°C/0.03 mmHg. Nmr ($CDCl_3$): δ 7.26-7.13 (arom., m, 6), 6.92-6.86 (arom., m, 2H), 2.93 (CH_2, s, 4H). Found: C 76.40; H 6.35. Calc. for $C_{12}H_{12}S$ (188.3): C 76.55; H 6.42.

3-[2-(2'-Bromophenyl)ethyl]thiophene (2): yield 88 %, bp 120-126°C/0.1 mmHg. Nmr ($CDCO_3$): δ 7.55-7.47 (H-3', m, 1), 7.24-6.90 (arom., m, 6), 3.07-2.83 (CH_2, m, 4).

4-[2-(2'-Bromo-4'-chlorophenyl)ethyl]-2-methylthiophene (3): yield 77 %, bp 148-156°C/0.02 mmHg. Nmr ($CDCl_3$): δ 7.56-7.96 (benz., m, 3H), 6.66-6.56 (thioph., m, 2), 3.08-2.66 (CH_2, m, 4), 2.43 (CH_3, d, 3), J (CH_3-3) 1.1 Hz. Found: C 49.20; H 3.84; S 9.90. Calc. for $C_{13}H_{12}BrClS$ (315.7): C 49.47; H 3.83; S 10.16.

4-[2-(2'-Bromophenyl)ethyl]-2-chlorothiophene (4): yield 85 %, bp 117-124°C/0.001 mmHg, n_D^{22} = 1.6112. Nmr ($CDCl_3$): δ 7.64-7.42 and 7.24-6.94 (benz., 2m, 4H), 6.69 (H-4, d, 1), 6.52 (H-3, d, 1), 3.03 (CH_2, s, 4), J (3,4) 3.8 Hz. Found: C 47.74; H 3.40; S 10.50. Calc. for $C_{12}H_{10}BrClS$ (301.6): C 47.78; H 3.34; S 10.63.

2-Bromo-3-(2-phenylethyl)thiophene (11). To 4.0 g (0.021 mol) of 3-2-(phenylethyl)thiophene in 15 ml of chloroform and 15 ml of acetic acid, 4.0 g (0.022 mol) of N-bromosuccinimide was added and the mixture stirred at room temperature for 30 min. The reaction mixture was diluted with an equal volume of water, the chloroform layer was separated, washed once with potassium hydroxide solution, once with water, dried over magnesium sulfate and evaporated to yield 3.5 g of crude product. Nmr ($CDCl_3$): δ 7.26-7.15 (benz., m, 5), 7.11 (H-5, d, 1), 6.69 (H-4, d, 1), J (4,5) 5.6 Hz.

3-[2-(2'-Bromo-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxaldehyde. To a mixture of 5.0 g (0.016 mol) of 4-[2-(2'-bromo-4'-chlorophenyl)ethyl]-2-methylthiophene and 1.44 g (0.020 mol) of N,N-dimethylformamide cooled with ice, 3.04 g (0.020 mol) of phosphorous oxychloride was added dropwise with stirring. The mixture was stirred for an additional 30 min with cooling, and then heated to 75°C for 30 min, poured onto ice and allowed to stand over night. The pH of the mixture was then adjusted with 5 M sodium hydroxide solution to 6-7. The organic phase was taken up in ether, washed with dilute hydrochloric acid, water and sodium bicarbonate, dried over magnesium sulfate and evaporated, yielding 5.0 g (92 %) of the title compound, mp 70-73°C after recrystallization from hexane. Nmr ($CDCl_3$): δ 9.78 (CHO, s, 1), 7.55 (H-3', d, 1), 7.19 (H-5', q, 1), 7.02 (H-6', d, 1), 6.70 (H-4, q, 1), 3.27-2.90 (CH_2, m, 4), 2.50 (CH_3, d, 3), J (3,5') 2.1 Hz, J (5',6') 8.4 Hz, J (CH_3-4) 0.9 Hz. Found: C 48.90; H 3.53; S 9.28. Calc. for $C_{14}H_{12}BrClOS$ (343.65): C 48.93; H 3.52; S 9.33.

Reaction of compounds 1-4 with butyl lithium reagents. General procedure: To 1-3 g (3.2-11.2 mmol) of the diaryl ethane in anhydrous ether or anhydrous tetrahydrofuran, 1.3 equivalents of

butyllithium in hexane was added (when not otherwise stated) at the appropriate temperature and stirred at -70°C usually for 1-7.5 h and then at 0°C for 15 min or at room temperature for 30 min. The reaction mixture was then poured onto freshly crushed carbon dioxide covered with ether or tetrahydrofuran. After a few hours, water was added and the water phase separated. (Ether was added for the extraction if tetrahydrofuran had been used as solvent.) The alkaline water phase was acidified with 1 M hydrochloric acid. The precipitated organic acid was taken up in ether and the aqueous phase extracted with ether. The combined ether phases were washed with 0.5 N hydrochloric acid, dried over magnesium sulfate and evaporated. Nmr spectra were run on the crude products, which were silylated with BSA and analyzed by glc and combined glc-mass spectrometry. Then separation of pure compounds was attempted and in some cases also achieved.

Reaction with lithium diisopropylamide (LDA). General procedure: Lithium diisopropylamide was prepared by mixing 1.1 g (0.011 mol) of freshly distilled diisopropylamine in 10 ml of anhydrous ether with 7.6 ml (0.011 mol) of butyllithium in a dropping-funnel under nitrogen. When the evolution of butane had subsided and the mixture had reached room temperature, it was added dropwise to 2.7 g (0.010 mol) of compound 1, 2, 3 or 4 in 50 ml of anhydrous ether at room temperature. When the addition was complete, the mixture was refluxed for 3 min. (In one experiment with compound 2, the reaction mixture was refluxed for 1 h, but this gave only a 2 % better yield of acid, after reaction with carbon dioxide. The mixture was cooled to room temperature and then poured onto crushed carbon dioxide covered with ether and then worked up and analyzed as described above.)

Reaction of 3-(2-phenylethyl)thiophene (1).

a) Reaction with butyllithium in ether at room temperature for 30 min. From 2.0 g of (1), 2.02 g (82 %) of crude acid mixture was obtained, which according to glc analyses of silyl esters consisted of 80 % of 4-(2-phenylethyl)-2-thiophenecarboxylic acid (10) and 20 % of 3-(2-phenylethyl)-2-thiophenecarboxylic acid (9). Recrystallization from toluene, followed by trituration with boiling hexane (which dissolved residual 9), and recrystallization from toluene gave pure 4-(2-phenylethyl)-2-thiophenecarboxylic acid (10), mp 150-152°C. Nmr ($CDCl_3$): δ 7.25-7.17 (benz., m, 5), 7.59 (H-3, d, 1), 7.09 (H-5, d, 1), 2.89 (CH_2, s, 4H), J (3,5) 1.7 Hz. *Found*: C 67.60; H 5.32. Calc. for $C_{13}H_{12}O_2S$ (232.3): C 67.21; H 5.21.

b) Reaction with butyllithium in tetrahydrofuran at 0°C for 30 min. From 2.0 g of 1, 1.74 g of crude acid mixture was obtained, which according to glc analyses of silyl esters consisted of 75 % of 10 and 25 % of 9.

c) Reaction with LDA. The crude acid mixture obtained from 1 in 32 % total yield consisted of 10 and 9 in the proportion of 83:17.

3-(2-Phenylethyl)-2-thiophenecarboxylic acid (9). From 2.0 g (0.0076 mol) of 2-bromo-3-(2-phenylethyl)thiophene and 6.5 ml (0.0099 mol) of butyllithium in hexane, 0.70 g (39 %) of the title compound was obtained at -70°C following the general procedure given above, mp 156-161°C after recrystallization from toluene. Nmr ($CDCl_3$): δ 7.23 (benz., s, 5), 7.46 (H-5, d, 1), 6.89 (H-4, d, 1), 2.86-3.43 (CH_2, m, 4), J (4,5) 5.1 Hz. Found: C 67.10; H 5.24; S 13.70. Calc. for $C_{13}H_{12}O_2S$ (232.3): C 67.21; H 5.21; S 13.80.

Reactions of 3-[2-(2'-bromophenyl)ethyl]thiophene (2).

a) Reaction with butyllithium in ether at room temperature for 30 min. From 2.0 g of 2, 1.60 g of crude acid mixture was obtained. The corresponding silyl esters were determined by combined glc-mass spectrometry, which indicated the presence of one monocarboxylic acid (30 %) and one dicarboxylic acid (70 %). The mixture was then boiled with toluene and the insoluble product recrystallized from aqueous ethanol, yielding not completely pure 3-[2-(2'-carboxyphenyl)ethyl]-2-thiophenecarboxylic acid, mp above 160°C. Nmr (DMSO): δ 7.65 (h-5, d, 1), 7.47-7.24 (benz., m, 3), 7.01 (H-4, d, 1), 3.24 (CH_2, s, 4), J (4,5) 5.1 Hz. Nmr of the crude product showed that the monocarboxylic acid present in the mixture was 3-(2-phenylethyl)-2-thiophenecarboxylic acid (9).

b) Reaction with butyllithium in THF at 0°C for 30 min. From 1.0 g of 2, 0.42 g of crude acid mixture was obtained. Combined glc-mass spectrometry of the silylation product showed the presence of two isomeric silyl esters of monocarboxylic acids. Nmr spectrum of the crude acid product showed that it consisted of 3-(2-phenylethyl)-2-thiophenecarboxylic acid (9) and 4-(2-phenylethyl)-2-thiophenecarboxylic acid in the proportions 5:2.

c) Reaction of 2 with butyllithium in THF at -70°C. From 2.0 g of 2, 1.2 g of acid mixture was obtained. From combined glc-mass spectrometry of the silyl esters, we found that trace amounts of 4-(2-phenylethyl)-2-thiophenecarboxylic acid (10) had been formed. The main components were 3-(2-phenylethyl)-2-thiophenecarboxylic acid (9) and 4-[2-(2'-(carboxyphenyl)ethyl]-2-thiophenecarboxylic acid (13) in about equal amounts. The dicarboxylic acid was obtained almost pure by recrystallization from toluene, mp 173-179°C. Nmr (DMSO): δ 7.93-7.84 (H-3, m, 1), 7.65 (H-3, d, 1), 7.41 (H-5, d, 1), 7.47-7.23 (benz., m, 3), 3.53-2.79 (CH_2, m, 4), J (3,5) 1.7 Hz.

d) Reaction with LDA. The crude acid mixture obtained in 30 % yield was shown by glc-mass spectrometry of the silylated derivatives to consist of 83 % of 4-[2-(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid (17) and 17 % of 3-[2-(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid (18). Recrystallization from toluene gave pure 17, mp 124°C. Nmr (DMSO): δ 7.64-7.51 (H-3, H-3', m, 3), 3.11-2.76 (CH_2, m, 4). Found: C 50.05; H 3.60; S 10.55; Br 25.50. Calc. for $C_{13}H_{11}BrO_2S$ (311.2): C 50.17; H 3.56; S 10.30; Br 25.68. 18 was not obtained pure but was characterized by the mass spectrum of its silyl derivative and by its nmr spectrum. Ms (silyl ester): m/e 384 (8 %), 382 (8 %), 369 (12 %), 367 (12 %), 259 (28 %), 213 (76 %), 185 (28 %), 73 (100 %). Nmr (DMSO): δ

7.64 (H-5, d, 1), 6.98 (H-4, d, 1), J (4,5) 5.1 Hz.

Reactions of 4-[2-(2'-bromo-4'-chlorophenyl)ethyl]-2-methylthiophene (3).

a) Reaction with butyllithium at -70°C for 1 h. Only 4-chloro-1-[2-(2'-methyl-4-thienyl)ethyl]-2-benzoic acid (19) was obtained in 59 % yield, mp 99-102°C, after recrystallization from toluene. Nmr (DMSO): δ 7.81 (H-3', d, 1), 7.43 (H-5', q, 1), 7.23 (H-6', d, 1), 6.75 (H-3, q, 1), 6.66 (H-5, t, 1), 3.26-2.66 (CH_2, m, 4), 2.40 (CH_3, d, 3), J (3',5') 2.4 Hz, J (3',4') 8.6 Hz, J (3,5) 1.1 Hz, J (CH_2-5) 1.1 Hz, J (CH_3-4) 1.0 Hz. Found: C 60.00; H 4.67; S 11.40. Calc. for $C_{14}H_{13}ClOS$ (280.8): C 59.89; H 4.67; S 11.42. Similar results were obtained in THF at -70°C.

b) Reaction with butyllithium in THF at 0°C for 15 min. Only 3- 2-(4'-chlorophenyl)ethyl -5-methyl-2-thiophenecarboxylic acid (20), mp 172-178°C after recrystallization from toluene was obtained. It had the same nmr spectrum as an authentic sample, mp 178.5-179.5, prepared previously.[1]

c) Reaction with butyllithium in ether at 0°C for 30 min. From 1.0 g of 3, 0.70 g of crude acid product was obtained. Silylation and combined glc-mass spectrometry in the usual way indicated the formation of the acids 19, 20 and of 3-[2-(2'-carboxy-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxylic acid (21) in the proportions 7:1:2. Treatment of the acid mixture with boiling toluene left the insoluble diacid 21, which was then recrystallized from ethanol, yielding almost pure 21, mp 248-257°C. Nmr (DMSO): δ 7.82 (H-3', d, 1), 7.46 (H-5', q, 1), 7.25 (H-6', d, 1), 6.71 (H-4, q, 1), 3.18 (CH_2, s, 4), 2.42 (CH_3, d, 3), J (5',6') 8.3 Hz, J (3',5') 2.4 Hz, J (CH_3-4) 1.0 Hz.

3-[2-(2'-Bromo-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxylic acid (22). To a suspension of silver oxide prepared from 0.52 g (3.1 mmol) of silver nitrate and 0.24 g (6.0 mmol) of sodium hydroxide in 5 ml of water 0.5 g (1.5 mmol) of 3-[2-(2'-bromo-4'-chlorophenyl)ethyl]-5-methyl-2-thiophenecarboxaldehyde was added and the mixture heated to boiling with stirring. After cooling, the reaction mixture was filtered and the precipitate washed with hot water. The filtrate was acidified with 0.5 M hydrochloric acid and extracted with ether. The combined ether phases were dried over magnesium sulfate, evaporated and recrystallized from toluene, yielding 0.36 g (67 %) of the title compound, mp 161-166°C. Nmr (DMSO): δ 7.66 (H-3', d, 1), 7.39 (H-5', q, 1), 7.27 (H-6', d, 1), 6.77 (H-4, q, 1), 3.28-2.80 (CH_2, m, 4), 2.42 (CH_3, d, 3), J (5',6') 8.5 Hz, J (3',5') 2.0 Hz, J (CH_3-4) 0.9 Hz. Found: C 47.80; H 3.51. Calc. for $C_{14}H_{12}BrClO_2S$ (359.65): C 46.75; H 3.36.

Reactions of 4-[2-(2'-bromophenyl)ethyl]-2-chlorothiophene (4).

a) Reaction with butyllithium in ether at -60°C for 1 h. From 2.0 g of 4, 0.17 g of crude acid mixture was obtained, which according to the usual glc-mass spectral analysis of the trimethylsilyl esters consisted of 13 % of 5-chloro-3-(2-phenylethyl)-2-thiophenecarboxylic acid (24),

44 % of 2-[2-(2'-chloro-4'-thienyl)ethyl]benzoic acid (25) and 43 % of 5-chloro-3-[2 -(2'-bromophenyl)ethyl]-2-thiophenecarboxylic acid (26). The mono acids 24 and 25 could be identified by their characteristic fragments in the mass spectrum at m/e 338, 340 and at m/e 207, respectively, and also by comparison with authentic 24 (cf. below). The structure of 26 was also proven by comparison with an authentic sample. Separation of the acids was not achieved.

b) Reaction with butyllithium in ether at -40°C for 1 h. From 2.0 g of 4, 0.15 g of crude acid mixture was obtained. Glc-mass spectral analysis of the trimethylsilyl esters indicated the acid mixture to consist of 10 % of 24, 51 % of 25 and 39 % of 26.

c) Reaction with butyllithium in ether at -20°C. From 2.0 g of 4, 0.79 g of crude acid mixture was obtained. Glc-mass spectral analysis indicated the presence of 35 % of 24, traces of 25, 42 % of 26 and 23 % of a dicarboxylic acid, which from the fragmentation of its trimethylsilyl ester was identified as 5-chloro-3-[2-(2'-carboxyphenyl)ethyl]-2-thiophenecarboxylic acid (27).

d) Reaction of 4 with butyllithium in THF at 0°C for 30 min. From 1.0 g of 4, 0.44 g (50 %) of 24 was obtained which according to glc-mass spectral analysis of the trimethylsilyl ester was the only acid present. Recrystallization from toluene gave pale yellow crystals, mp 95.5-99°. Nmr ($CDCl_3$): δ 7.31-7.13 (benz., m, 5), 6.72 (H-4, s, 1), 3.34-2.80 (CH_2, m, 4). Found: C 58.00; H 4.17. Calc. for $C_{13}H_{11}ClO_2S$ (266.7): C 58.53; H 4.16.

e) Reaction with LDA. The crude acid 26 obtained in 27 % yield was recrystallized from toluene, mp 158-160°C. Nmr (DMSO): δ 7.55 (H-3', 2t, 1), 7.32-7.10 (H-4', H-5', H-6', m, 3), 6.93 (H-4, s, 1), 3.40-2.88 (CH_2, m, 4). Found: C 45.25; H 2.93; S 9.27; Br 22.50. Calc. for $C_{13}H_{10}BrClO_2S$ (345.65): C 45.17; H 2.92; S 9.28; Br 23.12.

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