

Ring-opening Reactions of Heterocyclic Metalorganics. V. On the Metalation of 2,5-Dimethylthiophenes and Related Compounds with Alkylolithium-*N,N,N',N'*- tetramethylethylenediamine Complexes

SALO GRONOWITZ* and TORBJÖRN FREJD

Division of Organic Chemistry 1, Chemical Center, University of Lund, Box 740, S-220 07 Lund 7, Sweden

The reaction of 2,5-dimethylthiophene with alkylolithium-*N,N,N',N'*-tetramethylethylenediamine complexes has been studied. After reaction with carbon dioxide, varying relative amounts of 3-carboxy-5-methyl-2-thienylacetic acid and 2,5-dimethyl-3-thiophenecarboxylic acid were formed, depending upon the solvent. A maximum yield of 16 % of the former acid was obtained when hexane was used as solvent. The low yield was shown to depend to some extent upon ring-opening of the intermediate lithium derivatives.

3-Carboxy-2-methyl-5-thienylacetic acid was synthesized and shown not to be formed in the above reaction.

In the reaction of 3,4-dichloro-2,5-dimethylthiophene with ethyllithium-TMEDA complex followed by carbon dioxide, 4-chloro-2,5-dimethyl-3-thiophenecarboxylic acid and 4-chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid are formed in the relative proportions 3:4, but in low total yield. Methods for the authentic synthesis of these two acids have been worked out.

The reaction of tetramethylthiophene with the metalating agent gave a low yield of 3,4,5-trimethyl-2-thienylacetic acid. A large number of highly unsaturated compounds was also formed, giving clear evidence for the ring-opening ability of 2-thenyllithium derivatives. A method for the synthesis of 2,4,5-trimethyl-3-thienylacetic acid has been worked out.

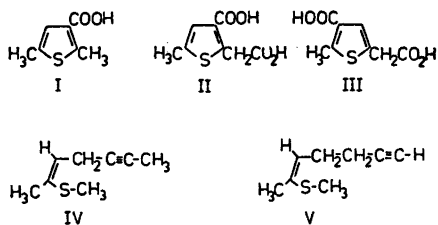
The only preparatively useful case of lateral metalation was that of 1,2,5-trimethylpyrrole, which gave 1,5-dimethyl-2-pyrrolylacetic acid in a 38 % yield.

It has been found that complexes between alkylolithium derivatives and certain diamines

* To whom correspondence should be addressed.

such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or 1,4-diazabicyclo[2,2,2]octane (DABCO) metalate faster than alkylolithium derivatives in hexane and ether¹⁻³ and also metalate substrates such as benzene¹ and toluene¹ (to yield benzylolithium) which are not attacked by ethereal alkylolithium derivatives.

We were therefore interested in studying the reaction of 2,5-dimethylfuran, 2,5-dimethylthiophene, and 1,2,5-trimethylpyrrole and some of their derivatives with these alkylolithium-amine complexes, in order to find out if metalation occurs, and if so, whether it occurs on the methyl group or in the 3-position. These compounds do not react with ethereal alkylolithium derivatives. A recent short communication by Meth-Cohn *et al.*⁴ has prompted us to publish our hitherto obtained results as they in part do not agree with those obtained by these authors. We found that treatment of 2,5-dimethylthiophene with ethereal ethyllithium-TMEDA followed by reaction with carbon dioxide gave in low yield a mixture of two acids in the proportions 1:3. By silylation and combined GLC-mass spectrometry the minor component was identified as 2,5-dimethyl-3-thiophenecarboxylic acid (I), which was confirmed by comparison with an authentic sample. The molecular weight of the silyl derivative of the major component (344), which had the longer retention time, indicated it to be a diacid and to have the composition C₈H₈O₄S. This compound could be obtained pure by recrystallization from meth-



anol-chloroform-hexane (2:20:10), m.p. 217–219°C. Its NMR spectrum indicated it to be 3-carboxy-5-methyl-2-thienylacetic acid (II). The main argument was the presence of the characteristic long-range coupling⁵ of 1 Hz between the thiophene hydrogen and the methyl group. The compound with m.p. 219°C has been claimed⁴ to be 3-carboxy-2-methyl-5-thienylacetic acid (III).

We could prove that this assignment is erroneous by the synthesis of authentic III (*cf.* below) and careful GLC analysis using its dimethylsilyl derivative, which clearly showed that this compound was not formed in the metalation of 2,5-dimethylthiophene.

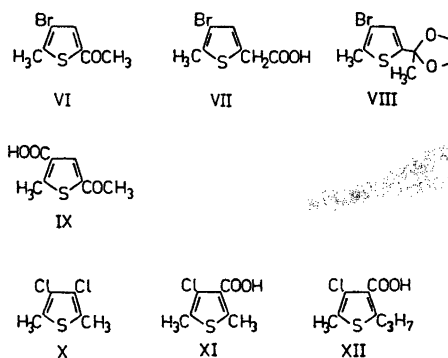
We could increase the yield of acidic products from about 8% to 16% by using butyllithium-TMEDA in hexane. The same yields were obtained by Meth-Cohn *et al.*⁴ GLC analyses of the silylated mixture showed three components in the proportions 2:8:92. The latter two were the trimethylsilyl derivatives of I and II, respectively, while the minor component with the shortest retention time was not identified. No traces of the trimethylsilyl derivative of III were found. Through recrystallization from the solvent system mentioned above, II was easily obtained pure. However, in spite of many attempts to use different reaction times and temperatures and also other amines such as DABCO, the yield of acidic products could not be increased. One of the reasons for this became apparent, when the reaction mixture from the treatment of 2,5-dimethylthiophene with ethereal ethyllithium-TMEDA was reacted with methyl iodide. GLC analysis of the neutral fraction showed the presence of at least ten components. The major component (80%) was 2,5-dimethylthiophene. The IR spectrum of the residue after evaporation of this compound showed absorptions at 3280 ($\equiv\text{C}-\text{H}$), 2210 ($\text{C}\equiv\text{C}$) and 2080 cm^{-1} ($\text{C}\equiv\text{C}$). The ^1H NMR spectrum (CCl_4) of the crude product showed absorptions at δ 3.1 ($\equiv\text{C}-\text{H}$, $\text{CH}_2-\text{C}\equiv\text{C}$) and

5.25–5.70 ($\text{C}=\text{CH}-$) and several lines in the methyl region. No absorptions were found in the aromatic region.

Combined GLC-MS gave the relative percentages, retention times, and molecular weights presented in the experimental part. The component with a molecular weight of 140 could have the structure IV or V.

The three components with the molecular weight 154 are most probably different *C*-methylated derivatives of IV and V, while the three components with the molecular weight 168 are dimethylated derivatives. It is also possible that some fully alkylated thiophenes such as tetramethylthiophene or trimethyl-ethylthiophene are present. No attempts were made to isolate any of the compounds and prove their structure. However, it is evident from these results that metalation is relatively slow and that the lithiated derivatives ring-open in a way similar to that recently demonstrated for 3-thienyllithium derivatives.^{6–8} The different products observed can be formed by methylation before or after the ring-opening (after prior lithiation). It is also obvious that the presence of I (obtained upon carbonation) can not be taken as binding evidence that metalation first occurs in the 3-position and then in the 2-methyl group, as it is known that thienylic metal organic reagents react with carbon dioxide under allylic rearrangement.⁹ Nor do these experiments give any definitive evidence for ring-opening of 2-thienyllithium derivatives (however, *cf.* below).

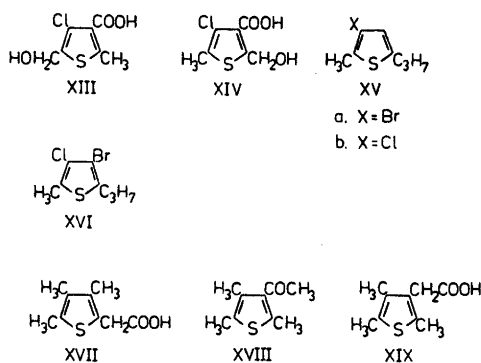
The synthesis of authentic III caused some trouble. Starting from the known 5-acetyl-3-bromo-2-methylthiophene (VI),¹⁰ we could prepare methyl 3-bromo-2-methyl-5-thienylacetate in 65% yield using acid-catalyzed reaction with



thallium(III) nitrate in methanol according to Taylor, Swann and McKillop.¹¹ Alkaline hydrolysis then gave 3-bromo-2-methyl-5-thienylacetic acid (VII). However, attempts to prepare III by halogen-metal exchange using two or three equivalents of butyllithium failed. A complex mixture of products was obtained upon reaction with carbon dioxide, in part due to metalation of the CH₃ group in 3-bromo-2-methyl-5-thienylacetic acid, as evidence for the presence of a thienylmalonic acid in the product was found. However, it was possible to prepare III by introducing the carboxyl functions in opposite order. The ketone VI was acetalized to give 2-(3-bromo-2-methyl-5-thienyl)-2-methyl-1,3-dioxolane (VIII), which upon halogen-metal exchange with butyllithium at -70 °C followed by reaction with carbon dioxide and hydrolysis gave 5-acetyl-2-methyl-3-thiophenecarboxylic acid (IX). Treatment of IX with thallium nitrate in methanol followed by alkaline hydrolysis of the methyl ester gave III. In order to obtain more information on the possibility of lateral metalation and the stability of 2-thienyllithium derivatives, we studied the reaction of 2,5-dimethyl-3,4-dichlorothiophene (X) with ethyllithium-TMEDA.

The synthesis of X caused also some trouble. As early as 1937, Steinkopf found that direct chlorination of 2,5-dimethylthiophene with chlorine in carbon tetrachloride led mainly to tar formation.¹² We also had no success with chlorination with *N*-chlorosuccinimide in acetic acid, which also led to tar formation. Starting from tetrachlorothiophene, prepared by the reaction of hexachlorobutadiene with sulfur,¹³ we obtained 3,4-dichloro-2,5-dilithiothiophene by treatment with butyllithium according to Gilman *et al.*,¹⁴ which upon reaction with dimethyl sulfate gave X in 72 % yield. However, the reaction of X with ethereal ethyllithium-TMEDA led first to halogen-metal exchange followed by side-chain lithiation of the intermediate 4-chloro-2,5-dimethyl-3-thienyllithium, as reaction with carbon dioxide gave 4-chloro-2,5-dimethyl-3-thiophenecarboxylic acid (XI) and 4-chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid (XII) in low yield, and in the approximate proportions 3:4. These acids were not separated. From the neutral phase, 60 % of starting material was recovered. The proportions and structures of the acids were deter-

mined by combined GLC-mass spectrometry of the trimethylsilylated derivatives and from the NMR spectrum of the crude product, which showed the presence of the propyl grouping, and by comparison with authentic samples. The acid XI was prepared by chlorination of 2,5-dimethyl-3-thiophenecarboxylic acid with *N*-chlorosuccinimide in acetic acid. Unexpectedly, this chlorination did not proceed cleanly, but also yielded a chloro-hydroxymethyl-methylthiophenecarboxylic acid, which could be either 4-chloro-5-hydroxymethyl-2-methyl-3-thiophenecarboxylic acid (XIII) or 4-chloro-2-hydroxymethyl-5-methyl-3-thiophenecarboxylic acid

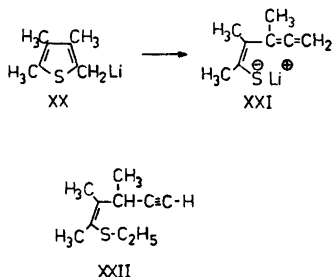


(XIV) according to NMR spectra and analyses. This compound was obtained in good yield when two equivalents of *N*-chlorosuccinimide were used. Obviously chlorination at one of the two possible thenylic positions takes place, after which the thenylchloride derivative is hydrolyzed during work up. Reaction of 3-bromo-2-methyl-5-propylthiophene¹⁵ (XVa) with butyllithium at -70 °C followed by hexachloroethane¹⁶ gave the corresponding chloro derivative (XVb), which was brominated with bromine in acetic acid to yield 3-bromo-4-chloro-5-methyl-2-propylthiophene (XVI). Halogen-metal exchange of the crude brominated product with butyllithium followed by reaction with carbon dioxide gave authentic XII.

The trimethylsilyl derivatives of authentic XI and XII had the same retention times (GLC) and mass spectra as the trimethylsilyl derivatives of the acids formed in the metalation experiments. The acid XII was most probably formed by coupling of the thenyllithium derivative with ethyl chloride formed in the halogen-

metal exchange or ethylbromide from the ethyllithium preparation.

We also prepared tetramethylthiophene by dichloromethylation of 2,5-dimethylthiophene to give 3,4-dichloromethyl-2,5-dimethylthiophene followed by reduction with lithium aluminium hydride.¹⁷ Reaction of tetramethylthiophene with ethereal ethyllithium-TMEDA gave after reaction with carbon dioxide only 5% of 3,4,5-trimethyl-2-thienylacetic acid (XVII). The structure followed from the fact that this acid was not identical with 2,4,5-trimethyl-3-thienylacetic acid (XIX), prepared through acetylation of 2,3,5-trimethylthiophene followed by transformation of the 4-acetyl derivative (XVIII) by the thallium nitrate method.¹¹ If the lithiated mixture was reacted with excess ethyl bromide, a neutral phase was obtained which GLC analysis showed to consist of two major components besides at least 15 minor ones. One of the major components (60%) was starting material, while the second one, according to combined GLC-mass spectroscopy, had a molecular weight of 168. Due to its instability it was not possible to obtain this compound pure by distillation *in vacuo* or chromatographic methods. The IR spectrum of the crude product, however, had absorptions at 3300, 2080, and 2100 cm^{-1} , indicating the presence of acetylenic compound(s), including terminal triple bonds. It seems therefore quite clear that the 2-thienyl-



lithium derivative (XX) ring-opens primarily to the allene (XXI), which in the presence of ethyllithium can be isomerized to an acetylene. Under these conditions, alkylation by ethyl bromide can occur on sulfur to give the compound with the molecular weight of 168, which could have a structure such as (XXII). A similar ring-opening of 3-methyl-2-benzo[b]-thienylmagnesium chloride was reported by

Gaertner,¹⁸ and of some 2-lithiomethylthiazoles by Meyers *et al.*¹⁹

We also attempted the metalation of 2,5-dimethylfuran and 1,2,5-trimethylpyrrole with butyllithium-TMEDA. With the former compound no defined acidic products were obtained, while the metalation of 1,2,5-trimethylpyrrole with butyllithium-TMEDA in hexane gave a 32% yield of 1,5-dimethyl-2-pyrrolic acid. The acid was identified by its NMR spectrum and had the same melting point as a sample prepared in another way.²⁰ From the neutral phase most of the unreacted starting material could be recovered. In this case apparently no complications due to ring-opening occurred. However, prolonged reaction time did not increase the yield.

EXPERIMENTAL

3-Carboxy-5-methyl-2-thienylacetic acid (II).

(a) To 165 ml (0.10 mol) of 0.63 M ethereal ethyllithium, 11.6 g (0.100 mol) of TMEDA was added and 10 min later 11.2 g (0.100 mol) of 2,5-dimethylthiophene all at once (yellow precipitate). After 2 h reflux the reaction mixture was poured onto solid carbon dioxide in ether. The mixture was acidified with 5 N HCl and the aqueous phase was extracted with ether. The combined ether phases were then extracted with 2 N NaOH. Acidification of the basic water solution gave 1.55 g of an acid (~8%), a sample of which was dissolved in ether and silylated with BSA. Combined GLC-MS analysis showed the presence of two components with the relative percentages 25:75, and with *m/e* 228 and 344, respectively. The most abundant component was the least volatile one. By mixing the above sample with authentic silylated 2,5-dimethyl-3-thiophenecarboxylic acid (I) it was shown after GLC analysis (SE 30, 2.0 m, 150–200 °C, 4 °C/min) that the most volatile component was the trimethylsilylester of I. The most abundant component had a shorter retention time than that of the authentic silylated 3-carboxyl-2-methyl-5-thienylacetic acid (III), as shown by a "mixing" analysis (as above). (Retention times 9.5 and 10.6 min for the silylated II and III, respectively, on the above column).

The pure title acid (II), m.p. 217–219 °C was obtained through recrystallization from a mixture of methanol, chloroform, and hexane (2:20:10). IR: C=O 1700 and 1640 cm^{-1} . NMR (DMSO-*d*₆): δ 7.04 (4-H, q, 1 H); 2.38 (5-CH₃, d, 3 H); 4.06 (2-CH₃, s, 2H). $J_{4-H,5-CH_3}$ 1.1 Hz. [Found: C 47.8; H 4.18; S 15.9. Calc. for C₈H₈O₄S. (M.wt. 200.21): C 48.00; H 4.03; S 16.01].

(b) To 143 ml (0.200 mol) of 1.4 M butyllithium in hexane, 23.2 g (0.200 mol) of TMEDA was added. After 10 min, 11.2 g (0.100 mol) of 2,5-dimethylthiophene was added rapidly. A yellow precipitate was formed and the reaction mixture was allowed to stand at room temperature ($\sim 20^\circ\text{C}$) for 2 h, whereupon it was poured onto solid carbon dioxide in ether. The carbonated mixture was extracted with 1 M NaOH (3×100 ml) and the collected water portions were extracted with ether. After acidification of the water phase it was again extracted with ether (3×50 ml). A sample of this ether phase was silylated with BSA and analysed by GLC (SE 30, 2.0 m, 150–200 $^\circ\text{C}$, 4 $^\circ\text{C}/\text{min}$). Three components were found in the proportions (retention times in min) 2(2.6): 8(2.9): 90(9.5). The latter two were identical with those in experiment (a). The first one was not identified. No traces of compounds with longer retention times were found.

After evaporation of the ether, 3.2 g of the crude acid mixture was collected; yield 16 %. (17 % was reported in Ref. 4, but no details were given).

Ring-opening experiment on 2,5-dimethylthiophene with ethyllithium-TMEDA. To 130 ml (0.100 mol) of 0.77 M ethereal ethyllithium, 11.6 g (0.100 mol) of TMEDA was added. To this mixture, 11.2 g (0.100 mol) of 2,5-dimethylthiophene was added in a rapid stream. The reaction mixture was refluxed for 2 h (a yellow precipitate was formed), whereupon 42.6 g (0.300 mol) of methyl iodide was added. Reflux was maintained for another hour, after which the mixture was hydrolyzed with water. The ether phase was washed with 2 N HCl and water to neutral reaction. GLC of the dried ether phase showed 10 components, of which the starting material amounted to about 80% (OV 17 3 %, 1.9 m, 80–190 $^\circ\text{C}$, 4 $^\circ\text{C}/\text{min}$). Evaporation left 3.0 g of crude product not containing 2,5-dimethylthiophene. IR: 3280, ($\equiv\text{C}-\text{H}$), 2210, ($\text{C}\equiv\text{C}$), and 2080 cm^{-1} ($\text{C}\equiv\text{C}$). NMR (CCl_4) of the crude product: δ 3.1 ($\equiv\text{C}-\text{H}$ and/or $-\text{CH}_2-\text{C}\equiv\text{C}$); 5.25–5.70 (m, $\text{C}=\text{CH}-$) and several lines in the methyl region. There were no absorptions in the aromatic region. A combined GLC-MS analysis of the crude mixture gave the following data: (BDS 10 %, 2.0 m, 125 $^\circ\text{C}$).

Peak No.	1	2	3	4	5	6	7	8	9
Rel. %	22	27	18	10	7	2	5	2	6
Ret. time (min)	7.4	8.2	9.0	9.5	11.5	12	13	14	15
m/e	140	154	154	154	168		168		168

Peaks No. 6 and 8 were too small to give reliable mass numbers. For possible structures, see discussion. No attempts were made to isolate any of the compounds.

5-Acetyl-3-bromo-2-methylthiophene (VI).

From 35.0 g (0.250 mol) of 2-acetyl-5-methylthiophene, 85 g (0.64 mol) of AlCl_3 and 43 g

(0.27 mol) of bromine, 38.2 g (70 %) of the title compound was obtained. B.p.₁₁ 142–148 $^\circ\text{C}$ [lit.¹⁰ 71 % b.p.₁₀ 140–144 $^\circ\text{C}$].

5-Acetyl-2-methyl-3-thiophenecarboxylic acid (IX). 5-Acetyl-3-bromo-2-methylthiophene (VI), 8.67 g (0.0396 mol), was acetalized with 20 ml of ethylene glycol and 0.25 g of *p*-toluenesulfonic acid in refluxing toluene (150 ml) with water separation (18 h). The reaction mixture was poured onto a saturated NaHCO_3 solution and washed with water. After drying and evaporation, the residue was distilled, giving the acetal (VII) contaminated with ~ 10 % of the starting material according to GLC analysis; b.p.₁ 95–105 $^\circ\text{C}$, 5.86 g (56 %). The acetal, 5.26 g (0.0200 mol), was dissolved in 50 ml of ether and cooled to -70°C , after which 16 ml (0.020 mol) of 1.25 M butyllithium in hexane was added dropwise. When the addition was complete, the reaction temperature was allowed to rise to -30°C (the warming-up took $\sim 1/2$ h), and the reaction mixture was poured onto solid carbon dioxide in ether. The organic layer was extracted with 3×50 ml of 2 M NaOH solution. The water phase was acidified with conc. HCl and heated to boiling. After filtration, the solution was left overnight at room temperature whereupon 1.3 g of white crystals was filtered off and the filtrate was evaporated to half of its volume, which gave another 1.5 g of the acid; yield 76 %. Recrystallization from water gave the pure acid, m.p. 167–168 $^\circ\text{C}$. NMR ($\text{DMSO}-d_6$): δ 8.03 (4-H, s, 1 H); 2.53 (2- CH_3 or COCH_3 , s, 3 H); 2.72 (COCH_3 or 2- CH_3 , s, 3 H). [Found: C 52.7; H 4.35; S 17.5. Calc. for $\text{C}_8\text{H}_8\text{O}_3\text{S}$ (M.wt. 184.21) C 52.16; H 4.38; S 17.41].

3-Carboxy-2-methyl-5-thienylacetic acid (III). A mixture of 500 mg (2.71 mmol) of 5-acetyl-2-methyl-3-thiophenecarboxylic acid (IX), 1.25 g (2.82 mmol) of thallium trinitrate trihydrate and 1.0 ml of perchloric acid (70 %) in 15 ml of methanol was stirred for 18 h at room temperature. The white precipitate (thallium mononitrate) was filtered off and the filtrate diluted with 100 ml of water. The water phase was extracted with 3×30 ml of chloroform and the collected organic portions were extracted with 3×30 ml 2 M NaOH. The basic water solution was left at room temperature for 1 h and was then acidified. Thus, 280 mg (52 %) of crude III was collected, m.p. $\sim 222^\circ\text{C}$. Recrystallization from methanol:water (8:2) gave the pure acid, m.p. 224–226 $^\circ\text{C}$. A silylated sample of the crude product showed only one peak with a retention time of 10.6 min. on the gas chromatogram (SE 30, 2.0 m, 150–200 $^\circ\text{C}$, 4 $^\circ\text{C}/\text{min}$). Combined GLC-MS gave the mass number 344 which corresponds to the bis-trimethylsilylester of the title compound (calc. for $\text{C}_{14}\text{H}_{24}\text{O}_4\text{SSi}_2$ 344). NMR ($\text{DMSO}-d_6$): δ 7.17 (4-H, broad s, 1 H); 2.67 (2- CH_3 , s, 3 H); 3.78 (5- CH_2 , broad s, 2 H). IR: $\text{C}=\text{O}$ 1700 and 1640 cm^{-1} . The IR spectrum was only slightly different from that of 3-carboxy-5-methyl-2-

thienylacetic acid (II). [Found: C 48.4; H 4.12; S 16.0. Calc. for $C_9H_5O_4S$ (M.wt. 200.21): C 48.00; H 4.03; S 16.01].

3-Bromo-2-methyl-5-thienylacetic acid (VII). A mixture of 12.3 g (0.0562 mol) of 5-acetyl-3-bromo-2-methylthiophene (VI), 27.1 g (0.0610 mol) of thallium trinitrate trihydrate and 28 ml of perchloric acid (70 %) in 140 ml of methanol was stirred at room temperature for 12 h, whereupon the precipitate was filtered off and the filtrate diluted with 300 ml of water. The water phase was extracted with 3×100 ml of chloroform and the collected organic portions were washed with water and dried. Evaporation gave 12.1 g of crude methyl ester which was dissolved in benzene and chromatographed on an alumina column. Evaporation of the benzene yielded 9.1 g of a yellow liquid (65 %), which was stirred with 150 ml of 2 N NaOH solution at room temperature for 2 h. The reaction mixture was filtered and acidified with ice-cooled conc. HCl. The crystals were filtered off and washed with 10 ml of ice-water. Thus, 5.2 g acid was obtained. Another 0.8 g was obtained from the acidic filtrate through extraction with ether and evaporation: yield 6.0 g, m.p. $\sim 95^\circ\text{C}$ (45 % based on VI).

The pure acid was obtained through recrystallization from hexane, m.p. $98-100^\circ\text{C}$. NMR ($\text{DMSO}-d_6$): δ 6.78 (4-H, broad s, 1 H), 3.73 (5- CH_3 , broad s, 2 H), 2.30 (2- CH_3 , s, 3 H). [Found: C 35.5; H 3.02; S 13.8. Calc. for $C_9H_7BrO_2S$ (M.wt. 235.10): C 35.76; H 3.00; S 13.64].

An attempt to prepare 3-carboxy-2-methyl-5-thienylacetic acid (III) from 3-bromo-2-methyl-5-thienylacetic acid (VII). In 100 ml of THF, 2.1 g (8.9 mmol) of 3-bromo-2-methyl-5-thienylacetic acid (VII) was dissolved. The solution was cooled to -70°C and 13.6 ml (19.0 mmol) of 1.40 M butyllithium in hexane was added. The reaction mixture was left for 1 h at -70°C with stirring, and was then poured onto solid carbon dioxide in ether. The ethereal phase was extracted several times with 2 N NaOH. The combined aqueous phases were acidified with conc. HCl (ice-cooling) and the acidic crude product was taken up in ether, which was evaporated, leaving 2.0 g of a brown oil. Upon treatment with CCl_4 the oil crystallized. The crystals melted between 100 and 120°C with gas evolution. A sample of the crystals was dissolved in $\text{DMSO}-d_6$ and a NMR spectrum recorded, which showed the presence of aromatic protons around δ 6.67, methine protons at δ 4.83, methylene protons at δ 3.68, and methyl protons at δ 2.37 and 2.25. When the sample was heated slightly ($\sim 45^\circ\text{C}$), the signal at δ 4.38 had disappeared and that at δ 3.68 had increased in height. The methyl signal at δ 2.25 had also disappeared. These results indicated that a thienyl malonic acid was present, among other compounds.

When the experiment was repeated with 3 equiv. of butyllithium, it did not give the desired

thienylacetic acid. Instead a great deal of decomposition took place, which did not lead to significant amounts of acidic products.

Tetrachlorothiophene.¹³ Hexachlorobutadiene (587 g, 2.25 mol) was heated with 192 g (6.0 mol) of sulfur. The sulfur dichloride was distilled off at $135-136^\circ\text{C}/760$ mmHg, and the tetrachlorothiophene at $90-95^\circ\text{C}/12$ mmHg. The crude product was recrystallized from methanol in the cold (-25°C), giving 180 g of the title compound (36 %), m.p. $29-30^\circ\text{C}$. [Lit.¹³ m.p. $29.5-29.7^\circ\text{C}$, 90 %].

3,4-Dichloro-2,5-dimethylthiophene (X). Tetrachlorothiophene (22.2 g, 0.100 mol) was dissolved in 200 ml of ether. To this solution 186 ml (0.210 mol) of 1.13 M butyllithium in hexane was added at $5-10^\circ\text{C}$. After completion of the addition, the reaction mixture was allowed to reach room temperature. A white precipitate was formed. The suspension was stirred for another 1/2 h and 26.5 g (0.210 mol) of dimethylsulfate in 100 ml of ether was added dropwise (ice-cooling). After this addition (2.5 h) the reaction mixture was hydrolyzed with 20 ml of conc. ammonia solution and worked up by washing the ethereal layer with water to neutral reaction. After drying and evaporation of the solvent, the residue was distilled giving 13.1 g (72 %) of the title compound, b.p. $91-93^\circ\text{C}$. NMR (CCl_4): δ 2.33 (CH_3 , s). [Found: C 40.0; H 3.43. Calc. for $C_6H_4Cl_2S$ (M.wt. 181.08): C 39.80; H 3.34].

Metalation of 3,4-dichloro-2,5-dimethylthiophene with TMEDA-ethylithium (1:1). The 1:1 complex between TMEDA and ethyllithium was prepared from 3.24g (0.028 mol) of TMEDA and 56 ml (0.028 mol) of 0.50 M ethereal ethyllithium. To this mixture was added 5.00 g (0.0276 mol) of 3,4-dichloro-2,5-dimethylthiophene together with 50 ml of ether. The solution became yellow and turned brown at reflux for 1/2 h. The reaction mixture was then poured onto solid carbon dioxide in ether. The ethereal phase was extracted with 2 N NaOH solution and the basic portions were acidified. Thus, 1.0 g of an acid mixture was isolated (m.p. $117-150^\circ\text{C}$). A silylated sample (BSA) was analyzed by combined GLC-MS (OV 17, 2.0 m, $150-240^\circ\text{C}$, $15^\circ\text{C}/\text{min}$). Two components appeared in the proportions 3:4 (retention times 8 and 9 min, respectively). The mass numbers were 262 and 290, respectively. The ion distribution of the molecular fragments indicated that only one chlorine atom was present in each component. It was shown that the components were the trimethylsilyl esters of 4-chloro-2,5-dimethyl-3-thiophenecarboxylic acid (XI) and 4-chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid (XII) after comparison with the retention times of the authentic silylated acids (BSA). NMR (CDCl_3) of the acid mixture ($-\text{CH}_2-\overset{\text{a}}{\text{C}}(\text{H})-\overset{\text{b}}{\text{C}}(\text{H})-\overset{\text{c}}{\text{C}}(\text{H})_2$):

δ 3.23 (a, t, 2 H); 1.3-1.9 (b, 5 lines, 2 H); 1.02 (c, t, 3 H) and two singlets at δ 2.70 and 2.38 which were assigned to methyl protons. From

the neutral ether phase 3.25 g of the starting material (65 %) was recovered.

4-Chloro-2,5-dimethyl-3-thiophenecarboxylic acid (XI). 2,5-Dimethyl-3-thiophenecarboxylic acid (1.0 g, 6.4 mmol) was dissolved in 25 ml of acetic acid, and 0.86 g (6.4 mmol) of *N*-chlorosuccinimide was added. The mixture was stirred overnight and then refluxed for 1 h. Most of the acetic acid was then evaporated and 20 ml of water was added to the residue. This mixture was extracted with ether and the collected ether portions were extracted with 3 × 10 ml of 2 N NaOH. Acidification of the basic water phase gave 0.65 g of an acid mixture. A silylated (BSA) sample of this mixture was analyzed by GLC (OV 17, 100–220 °C, 12 °C/min) and found to contain 12 % of the starting material, 71 % of the title compound and 17 % of 4-chloro-5-hydroxymethyl-2-methyl-3-thiophenecarboxylic acid or 4-chloro-2-hydroxymethyl-5-methyl-3-thiophenecarboxylic acid. The title acid was obtained pure after three recrystallizations from methanol: water, m.p. 192–194 °C. NMR (DMSO-*d*₆): δ 2.53 (CH₃, s, 3 H) and 2.30 (CH₃, s, 3 H). [Found: C 44.1; H 3.76. Calc. for C₈H₈ClO₂S (M.wt. 190.65): C 44.10; H 3.70].

4-Chloro-2-hydroxymethyl-5-methyl-3-thiophenecarboxylic acid (XIV) or 4-chloro-5-hydroxymethyl-2-methyl-3-thiophenecarboxylic acid (XIII). To 1.56 g (0.0100 mol) of 2,5-dimethyl-3-thiophenecarboxylic acid in 50 ml of acetic acid, 3.18 g (0.0238 mol) of *N*-chlorosuccinimide was added. The reaction mixture was stirred at room temperature for 4 h and refluxed for 1 h. The acetic acid was evaporated and the residue treated as in the experiment above. Thus, 1.5 g (73 %) of the acid was obtained (m.p. ~170 °C). Recrystallization from methanol:water gave the pure acid (m.p. 177–179 °C). NMR (DMSO-*d*₆): δ 2.35 (CH₃, s, 3 H), 4.85 (–CH₂–, s, 2 H). Found *m/e* 206 (1 Cl), calc. for C₇H₇³⁶ClO₂S = 206. [Found: C 40.80; H 3.50; S 15.38. Calc. for C₇H₇ClO₂S (M.wt. 206.64): C 40.69; H 3.41; S 15.52].

3-Chloro-2-methyl-5-propylthiophene (XVb). 3-Bromo-2-methyl-5-propylthiophene (XVa) (9.1 g, 0.042 mol) was dissolved in 50 ml of dry ether and the solution was cooled to –70 °C, whereupon 75 ml (0.045 mol) of 0.6 M ethereal ethyllithium was added dropwise. After 15 min, 12 g (0.051 mol) of hexachloroethane in 150 ml of ether was added in 10 min. The reaction mixture was kept at –70 °C for another 4 h. The cooling bath was removed, the mixture was allowed to reach room temperature, and was then poured into water. The organic layer was separated and the water phase extracted with ether. After drying and evaporation of the solvent, the residue was distilled. Thus, 1.5 g (21 %) of the pure title compound was obtained, b.p.₁₃ 97–99 °C. Also a forerun, 4 g, b.p.₁₃ 93–97 °C, containing some hexachloroethane, was collected. NMR (CCl₄): δ 6.45 (4-H, broad

s, 1 H), 2.32 (2-CH₃, s, 3 H); (CH₂CH₂CH₃) δ 2.65 (a, t, 2 H); ~1.63 (b, 6 lines, ^a 2 H, ^b 2 H, ^c 2 H) (c, t, 3 H). *J*_{ab} 7.4 Hz; *J*_{bc} 7.0 Hz. [Found: C 53.9; H 6.24. Calc. for C₈H₁₁ClS (M.wt. 174.69): C 55.00; H 6.35].

4-Chloro-5-methyl-2-propyl-3-thiophenecarboxylic acid (XII). To 1.0 g (5.7 mmol) of 3-chloro-2-methyl-5-propylthiophene in 25 ml of acetic acid, 1.0 g (6.3 mmol) of bromine dissolved in 10 ml of acetic acid was added. After 4 h at room temperature, the reaction mixture was heated to reflux, cooled and poured into water. After extraction with ether, drying and evaporation the residue was distilled, giving 0.8 g (55 %) of almost pure 3-bromo-4-chloro-5-methyl-2-propylthiophene (XVI), b.p._{0.1} 77–80 °C. NMR (CCl₄): δ 2.38 (5-CH₃, s, 3 H); (CH₂CH₂CH₃) δ 2.70 (a, t, 2 H), 1.63 (b, 6 lines, ^a 2 H, ^b 2 H, ^c 2 H) (c, t, 3 H). This compound (0.61 g, 2.4 mmol) was dissolved in 10 ml of dry ether in a septum bottle and cooled to –70 °C, whereupon 1.8 ml (2.7 mmol) of 1.48 M butyllithium in hexane was injected with a syringe. After 15 min, the reaction mixture was poured onto solid carbon dioxide in ether. The usual work up yielded 0.35 g (67 %) of the title compound, m.p. 130–133 °C. Recrystallization from methanol:water gave the pure acid, m.p. 135–136 °C. NMR (DMSO-*d*₆): δ 2.32 (5-CH₃, s, 3 H); (CH₂CH₂CH₃) δ 2.93 (a, t, 2 H), 1.58 (b, 5 lines, ^a 2 H, ^b 0.90 (c, t, 3 H). *J*_{ab} = *J*_{bc} = 7.5 Hz. [Found: C 49.39; H 5.04; S 14.56. Calc. for C₉H₁₁ClO₂S (M.wt. 218.70): C 49.42; H 5.07; S 14.66].

Tetramethylthiophene.¹⁷ From 30.0 g (0.268 mol) of 2,5-dimethylthiophene, 72.4 g (0.804 mol) of 1,3,5-trioxane and HCl gas, 40.2 g (72 %) of 3,4-bis(chloromethyl)-2,5-dimethylthiophene was obtained, m.p. 68–69 °C (lit.¹⁷ m.p. 73 °C). The bis(chloromethyl) compound, 40.0 g (0.191 mol), was subsequently reduced with 16.8 g (0.442 mol) of lithium aluminium hydride in ether to give the title compound; yield 17.3 g (65 %), b.p.₁₃ 76–77 °C (lit.¹⁷ 67 %, b.p.₁₃ 74–79 °C).

3,4,5-Trimethyl-2-thienylacetic acid (XVII). A solution of 5.8 g (0.050 mol) of TMEDA in 25 ml of ether was added to 62.5 ml (0.050 mol) of 0.80 M ethyllithium in ether. After 10 min, 7.0 g (0.050 mol) of tetramethylthiophene¹⁷ in 50 ml of ether was added all at once. Additional ether was added to a total volume of 150 ml, and the mixture was refluxed for 2 h (ether was added to maintain 150 ml). At this point 50 ml of the mixture was withdrawn with a pipette and poured onto solid carbon dioxide in ether. To the rest 11 g (0.10 mol) of ethyl bromide was added and reflux was continued for another hour. The ether phase was washed with water, dil. HCl and water to neutral reaction and dried. Evaporation left 4.1 g of an oil. IR: 3300, (≡C–H) 2100 (C≡C) and 2080 cm^{–1} C≡C. GLC analysis showed about 15 components, of

which the most abundant was the starting material (60%). A component with $m/e=168$ amounted to 20% and could have the structure XXII suggested in the discussion. NMR (CCl_4) showed mainly the starting material; δ 2.20 and 1.90. Other signals were present in the aliphatic region, but could not be assigned to any specific structure. Attempted distillation of the crude product at reduced pressure was unsuccessful due to tar formation, and preparative TLC (silica gel, hexane:ether 9:1) gave no significant separation.

The carbonated ethereal portion was extracted with dil. NaOH solution and the collected basic water portions were acidified, giving 0.15 g of the title compound; yield 5%, m.p. $\sim 110^\circ\text{C}$. Recrystallization from hexane gave the pure acid, m.p. 116–118 $^\circ\text{C}$. IR: $\text{C}=\text{O}$ 1710 cm^{-1} . NMR (CDCl_3): δ 3.67 (2- CH_2 -, s, 2 H); 2.30 (CH_3 , s, 3 H), 2.00 (CH_3 , m, 6 H), 11.0 (CO_2H , s, 1 H). [Found: C 58.6; H 6.42; S 17.4. Calc. for $\text{C}_9\text{H}_{12}\text{O}_2\text{S}$ (M.wt. 184.26): C 58.67; H 6.56; S 17.40].

3-Acetyl-2,4,5-trimethylthiophene (XVIII).

To a mixture of 1.00 g (7.94 mmol) of 2,3,5-trimethylthiophene and 1.30 g (12.7 mmol) of acetic anhydride, 1 drop of 70% perchloric acid was added. Heat was evolved and the reaction mixture was stirred at room temperature overnight. It was then poured into water, extracted with ether and the ether phases washed with water to neutral reaction. After drying and evaporation of the solvent, 1.1 g of crude product remained, which was distilled, b.p._{0.5} 74–75 $^\circ\text{C}$, 0.75 g (56%). NMR (CCl_4): δ 2.45, 2.22, and 2.10 (aromatic CH_3 , 4 broad s with fine structure); 2.32 (COCH_3 , s). [Found: C 64.0; H 7.19; S 19.0. Calc. for $\text{C}_9\text{H}_{12}\text{OS}$ (M.wt. 168.26): C 64.25; H 7.19; S 19.06].

2,4,5-Trimethyl-3-thienylacetic acid (XIX).

A mixture of 0.50 g (3.0 mmol) of 3-acetyl-2,4,5-trimethylthiophene, 1.6 g (3.6 mmol) of thallium trinitrate trihydrate and 1.0 ml of 70% perchloric acid in 5 ml of methanol was stirred at room temperature for 18 h. The precipitated thallium mononitrate was filtered off, and 50 ml of water was added to the filtrate. After extraction with CHCl_3 , drying and evaporation of the solvent, 0.55 g of a brown oil remained. This oil (the methyl ester of the title compound according to NMR) was refluxed in a mixture of 2 g of potassium hydroxide, 10 ml of water and 10 ml of ethanol for 4 h. The ethanol was evaporated and the residual solution acidified with dilute HCl. Thus, 0.35 g (63%) of the title compound was isolated, m.p. 100–102 $^\circ\text{C}$. Recrystallization from hexane in the cold (-25°C) gave the pure acid, m.p. 104–106 $^\circ\text{C}$. NMR ($\text{DMSO}-d_6$): δ 1.95 (CH_3 , s, 3 H), 2.23 (CH_3 , broad s, 6 H); 3.37 (3- CH_2 -, s, 2 H). IR: $\text{C}=\text{O}$ 1705 cm^{-1} . [Found: C 58.4; H 6.63; S 17.1. Calc. for $\text{C}_9\text{H}_{12}\text{O}_2\text{S}$ (M.wt. 184.26): C 58.67; H 6.56; S 17.40].

1,5-Dimethyl-2-pyrrolylacetic acid. A solution of 5.8 g (0.050 mol) of TMEDA in 40 ml of hexane

was added to 20 ml (0.050 mol) of 2.5 M butyllithium in hexane. During 40 min, 5.45 g (0.0500 mol) of trimethylpyrrole in 30 ml of hexane was added. The reaction mixture was stirred for 1 h at room temperature and then refluxed for 1/2 h. A brown precipitate was formed. The mixture was poured onto solid carbon dioxide and ether. The acid was extracted with aqueous sodium hydroxide solution. Acidification gave 2.42 g (32%) of the title compound. M.p. $\sim 114^\circ\text{C}$. Recrystallization from ligroin yielded the pure acid, m.p. 119–120 $^\circ\text{C}$ (lit.²⁰ m.p. 119.5 $^\circ\text{C}$). IR: $\text{C}=\text{O}$ 1700 cm^{-1} . NMR ($\text{DMSO}-d_6$): δ 3.33 (1- CH_3 , s, 3 H); 2.14 (5- CH_3 , broad s, 3 H); 3.52 (2- CH_2 -, s, 2 H); 5.73 (3-H, d, q); 5.65 (4-H, d). $J_{3,4}$ 4.9 Hz; $J_{4-H,5-\text{CH}_3}$ 0.8 Hz.

GLC analyses were performed on a Varian 1400 Gas chromatograph. IR spectra were recorded on a Perkin Elmer 257 Grating Infrared Spectrophotometer, NMR spectra on a Varian A 60 spectrometer and mass spectra on an LKB 9000 mass spectrometer. Commercial BSA (*N,O*-bis(trimethylsilyl) acetamide, Pierce Chemical Company) was used as silylating agent. GLC analyses for identification were performed by mixing the sample to be analyzed with authentic samples of known substances ("mixing analyses"). MgSO_4 was used as drying agent. All reactions with metal organics were performed in a dry oxygen-free nitrogen atmosphere.

Acknowledgements. The authors are grateful to Mr. Rolf Carlsson for some preliminary experiments. Grants from the Swedish Natural Science Research Council to S. G. and from the Royal Physiographic Society in Lund to T. F. are gratefully acknowledged.

REFERENCES

- Eberhardt, G. G. and Butte, W. A. *J. Org. Chem.* 29 (1964) 2928.
- Screttas, C. G. and Eastman, J. F. *J. Amer. Chem. Soc.* 87 (1965) 3276.
- Petersson, D. *J. Org. Chem.* 32 (1967) 1717.
- Clarke, A. J., McNamara, S. and Meth-Cohn, O. *Tetrahedron Lett.* (1974) 2373.
- Hoffman, R. A. and Gronowitz, S. *Ark. Kemi* 16 (1960) 563.
- Gronowitz, S. and Frejd, T. *Acta Chem. Scand.* 24 (1970) 2556.
- Gronowitz, S. and Frejd, T. *Int. J. Sulfur. Chem. A* 2 (1972) 165.
- Gronowitz, S. and Frejd, T. *Acta Chem. Scand.* 27 (1973) 2242.
- Gaertner, R. *J. Amer. Chem. Soc.* 73 (1951) 3934.
- Lantz, R. and Hörnfeldt, A.-B. *Chem. Scr.* 2 (1972) 9.
- McKillop, A., Swann, B. P. and Taylor, E. C. *J. Amer. Chem. Soc.* 93 (1971) 4920.
- Steinkopf, W. and Köhler, W. *Justus Liebigs Ann. Chem.* 532 (1937) 250.

13. Geering, E. J. *J. Org. Chem.* 24 (1959) 1128.
14. Gilman, H. and Smith, M. R. *J. Organometal. Chem.* 42 (1972) 1.
15. Kindly provided by Mr. R. Lantz. Preparation as indicated in Ref. 10.
16. Gronowitz, S., Hörnfeldt, A.-B. and Petersson, K. *Synth. Commun.* 3 (1973) 213.
17. Gaertner, R. and Tonkyn, R. G. *J. Amer. Chem. Soc.* 73 (1951) 5872.
18. Gaertner, R. *J. Amer. Chem. Soc.* 74 (1952) 2991.
19. Meyers, A. I. and Knaus, G. N. *J. Amer. Chem. Soc.* 95 (1973) 3408.
20. Lukes, R. and Preucil, J. *Collect. Czech. Chem. Commun.* 7 (1935) 482.

Received February 26, 1975.