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Stereochemistry of 3,3′-Bithienyls

III.* On a Difference Between Ethyllithium and Butyllithium in Reaction with Dibromo-3,3′-bithienyls. Preparation of 3,3′-Bithienylmonocarboxylic Acids

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Various dibromo-3,3′-bithienyls were reacted with *one* equivalent of ethyllithium or butyllithium at −70°, and the mixtures obtained were carbonated after 2 min. 2,2′-Dibromo-3,3′-bithienyls gave mainly monocarboxylic acids in reaction with butyllithium, but ethyllithium yielded mixtures consisting of about 60 % dicarboxylic acid and 40 % monocarboxylic acid. 4,4′-Dibromo-3,3′-bithienyl (IV) was metalated at one of the 5-positions, and when those were blocked by methyl groups, a mixture of a 4′-monocarboxylic acid and a 2,4′-dicarboxylic acid was obtained with both lithium reagents. The 2,4′-dicarboxylic acid was also the main product of the reaction of 4,4′-dibromo-5,5′-dimethyl-3,3′-bithienyl (VI) with excess ethyllithium or butyllithium.

The formation of dicarboxylic acids is suggested to be a consequence of the aggregated structure of organolithium compounds. The metalation of IV at the 5-position can be explained as a transmetalation by the bithienyllithium first formed, but dibromo compound VI must have been metalated at the 2-position by the alkyllithium. A possible explanation for this and the differences between ethyllithium and butyllithium in reaction with 2,2′-dibromo-3,3′-bithienyls is given.

When optically active 2,2′,4,4′-tetrabromo-3,3′-bithienyl (Ib)[1] was treated with 2 equiv. of ethereal ethyllithium for 2 min at −70°, followed by carbonation, it gave racemic 4,4′-dibromo-2,2′-dicarboxy-3,3′-bithienyl (IIb),[1] but traces of optically active 2,4,4′-tribromo-2′-carboxy-3,3′-bithienyl (IIIb) could be found in the product.[2] On attempting to prepare the racemic monoacid IIIb from racemic tetrabromo compound Ib in a similar way by using only one equivalent of alkyllithium, it was found that both ethyllithium and butyllithium gave a mixture of the same carboxylic acids but in quite different

* For Part II, see Ref. 22.

ratios. The two lithium reagents have been widely used in these laboratories for a long time in reactions with thiophene derivatives without any difference being noticed. For the preparation of racemic and optically active 3,3′-bithienylmonocarboxylic acids, and from a structural and mechanistic point of view it was of interest to obtain more detailed information about the behaviour of various dibromo-3,3′-bithienyls toward the two alkyllithium compounds.

There is good evidence from ^{7}Li and ^{1}H NMR spectra of ethereal solutions of methyllithium and ethyllithium at low temperatures[3] and from ^{13}C-^{7}Li spin-spin coupling in methyllithium,[4] that these compounds have a tetrameric structure in donor solvents. It is proposed that the lithium atoms are situated at the apexes of a tetrahedron, and the alkyl groups are each equally bonded to three lithium atoms, which gives a cubic structure for methyllithium.[4] This is in accordance with the crystal structure.[5]

The nature of the carbon-lithium bonds is expected to be the same in other alkyllithium reagents,[4] and there is evidence for a tetrameric structure in butyllithium as well. Thus colligative measurements show that butyllithium like other alkyllithium compounds is tetrameric in ether at 25°, while charge delocalized reagents like benzyllithium are monomeric, and sp^2-hybridized like phenyllithium, are dimeric.[6] It has also been suggested that butyllithium may be hexameric [7] or a solvated dimer.[8,9]

The mechanism of the reaction of alkyllithium compounds has been discussed by several authors.[10–14] A review of metalations by organolithium compounds covering the literature until 1966 has been given by Mallan and Bebb.[15] Metalation and halogen-metal exchange reactions involving thiophene derivatives have been surveyed by Gronowitz.[14]

RESULTS

For this investigation, 3,3′-bithienyls with bromine atoms at various positions were desirable, and some new such compounds had to be prepared. Of special interest were 2,2′-dibromo- and 4,4′-dibromo-3,3′-bithienyls, since they have quite similar geometry with regard to the relative spatial positions of the halogen atoms.

Compounds Ia, Ib, and IV (Schemes 1 and 2) have been described in the literature.[16,1,17] 2,2′-Dibromo-5,5′-dimethyl-3,3′-bithienyl (Ic), 2,2′-dibromo-4,4′,5,5′-tetramethyl-3,3′-bithienyl (Id), and 4,4′-dibromo-2,2′,5,5′-tetramethyl-3,3′-bithienyl (X, Scheme 4) were prepared in good yields from 5,5′-dimethyl-3,3′-bithienyl,[18] 4,4′,5,5′-tetramethyl-3,3′-bithienyl,[19] and 2,2′,5,5′-tetramethyl-3,3′-bithienyl,[20] respectively, by bromination with *N*-bromosuccinimide (NBS) in acetic acid-chloroform.[16]

It was found that the two 2,2′-dibromo compounds Ic and Id were unstable, especially the former, which became black with the evolution of hydrogen bromide after a few hours at room temperature. The great instability of Ia has been pointed out previously by Kellogg *et al.*[16] The decomposition tendency seems to be characteristic for 2,2′-dibromo-3,3′-bithienyls without deactivating substituents in at least one ring. Thus for example 4,4′-dibromo-3,3′-bithienyl (IV), 2,2′,4,4′-tetrabromo-3,3′-bithienyl (Ib), 2,2′,5,5′-tetrabromo-3,3′-bi-

thienyl,[21] and aldehyde and carboxy derivatives of 2,2′-dibromo-3,3′-bithienyl [22] are stable. The stability of 2-bromo-2′-carboxy-3,3′-bithienyl (IIIa) is notable, and also 2,2′-dibromo-4-carboxy-4′-hydroxymethyl-3,3′-bithienyl [22] can be stored at room temperature without change.

For the synthesis of 4,4′-dibromo-5,5′-dimethyl-3,3′-bithienyl (VI, Scheme 3) 4,4′,5,5′-tetrabromo-3,3′-bithienyl, m.p. 156–158°, was prepared in 40 % yield from 4,4′-dibromo-3,3′-bithienyl (IV) and bromine in refluxing acetic acid. The PMR spectrum (CS_2) of the product exhibited only one peak at 2.70 τ. This value was very close to that found for 2,2′,4,4′-tetrabromo-3,3-bithienyl (Ib) ($\tau_{5,5'}$ = 2.73 ppm, m.p. 159–161° [1]), and also the melting points were quite similar. However, the IR spectrum was different from that of Ib, which indicated that bromination of IV had taken place at the 5,5′-positions. The IR spectrum of the new compound exhibited peaks at 875, 990, and 1270 cm^{-1}, and that of Ib at 855, 1005, and 1290 cm^{-1}.

Iodination of IV with iodine-iodic acid [23] gave a better yield (54 %) than bromination. Therefore the product obtained, 4,4′-dibromo-5,5′-diiodo-3,3′-bithienyl, was chosen as starting material instead of the tetrabromo compound for the preparation of VI. The intermediate 5,5′-dilithium derivative obtained from the iodine compound and ethyllithium at −70° was reacted with dimethyl sulphate, which gave VI in 73 % yield. Carbonation of the dilithium compound, obtained as above or in a similar way from 4,4′,5,5′-tetrabromo-3,3′-bithienyl, in both cases gave the same acid, 4,4′-dibromo-5,5′-dicarboxy-3,3′-bithienyl. Thus iodination of IV had taken place at the same positions as bromination.

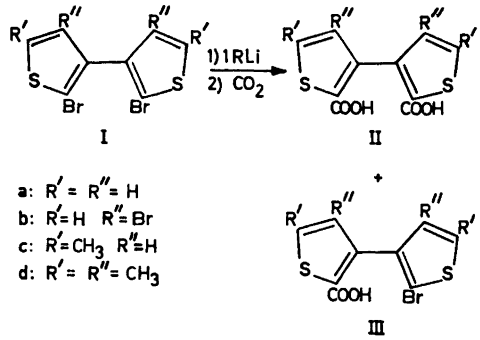
The OCH_3 resonance of 4,4′-dibromo-5,5′-dicarbomethoxy-3,3′-bithienyl, obtained from the corresponding acid with diazomethane, occurred at 6.17 τ. Since this value is characteristic for carbomethoxy groups at the 5,5′-positions in 3,3′-bithienyl,[24] it further confirms the assigned structures of the compounds mentioned.

Table 1. Reaction between dibromo-3,3′-bithienyls and one equivalent of alkyllithium.

No. of expt.	Halide	mmol of halide	ml of ether	Composition of product mixture RLi	Diacid (%)	Monoacid (%)	g of prod.
1	Ia	4.6	75	EtLi	IIa (55)	IIIa (45)	0.75
2	Ia	4.6	75	BuLi	IIa (10)	IIIa (90)	0.75
3	Ib	5.2	50	EtLi	IIb (60)[a]	IIIb (40)	1.1
4	Ib	5.2	50	BuLi	IIb (5)[a]	IIIb (95)	1.0
5	Ic	2.8	75	EtLi	IIc (60)[b]	IIIc (40)	0.5
6	Ic	5.0	150	BuLi	IIc (5)[b]	IIIc (95)	0.9
7	Id	2.1	175	EtLi	IId (100)[c]	–	0.2
8	Id	2.1	175	BuLi	IId (15)[c]	IIId (85)	0.45
9	IV	12	40 (THF)	EtLi	–	V	2.1
10	IV	6.2	30 (THF)	BuLi	–	V	0.8
11	VI	2.8	50	EtLi	IX (40)	VIII (60)	0.55
12	VI	5.7	100	BuLi	IX (50)	VIII (50)	1.0
13	X	6.5	50	EtLi	XII (10)[d]	IX (90)	0.5
14	X	6.5	50	BuLi	XII (10)[d]	IX (90)	0.5

[a] $\tau_{5,5'}$ = 2.10 ppm.
[b] $\tau_{4,4'}$ = 3.25 ppm, τ_{CH_3} = 7.56 ppm.
[c] τ_{CH_3} = 7.60 ppm and 8.28 ppm.[19]
[d] τ_{CH_3} = 7.42 ppm and 7.98 ppm.

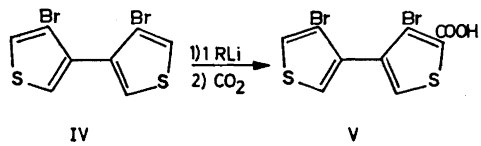
The results of the reactions between the dibromo compounds and 1 equiv. of alkyllithium are collected in Table 1. The composition of the various products obtained in experiments 1 – 7 was easily deduced from the corresponding PMR spectra by comparison with the spectra of the pure mono- and dicarboxylic acids. Diacids IIb, IIc, and IId have been prepared previously.[22,18,19]



Scheme 1.

Diacid IId (in low yield) was the only product obtained in experiment 7. This experiment, and the others in Table 1, was performed twice, with the same result using different preparations of ethyllithium and dibromo compound Id.

In the PMR spectrum (DMSO-d_6) of the product of experiment 8, the 5-CH_3 resonance of monoacid IIId at 7.60 τ was not resolvable from the 5,5′-CH_3 resonance of diacid IId. Neither were the 4,4′-CH_3 resonances of monoacid IIId at 8.22 τ resolvable. With some uncertainty the composition was determined to be 10 – 15 % diacid IId, and 90 – 85 % monoacid IIId. The acid mixture was esterified, and in the PMR spectrum (CS_2) of the product, all τ-values were the same as for the corresponding acids, except that for the 4,4′-CH_3 resonances of monoacid IIId, which was now split and occurred at 8.19 τ and 8.26 τ. Analysis of the composition using the OCH_3 resonances at 6.48 τ (ester of IId) and 6.43 τ (ester of IIId) gave 15 % IId and 85 % IIId in the product mixture of experiment 8, in agreement with the composition previously determined.



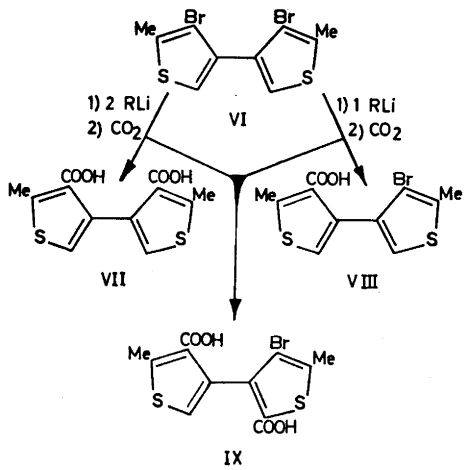
Scheme 2.

Reacting 4,4′-dibromo-3,3′-bithienyl (IV, Scheme 2) with butyllithium and ethyllithium as above, followed by carbonation, gave in both cases as the major product an acid which was shown to be 4,4′-dibromo-5-carboxy-

-3,3'-bithienyl (V). The PMR spectra exhibited an AB quartet and a singlet with relative intensities 2:1. The PMR spectrum of the methyl ester also contained the AB pattern and the singlet due to the aromatic hydrogens, and in addition a singlet from the OCH_3 group, with relative intensities 2:1:3 (see Experimental). The OCH_3 resonance occurred at 6.17 τ, which is a typical value for a carbomethoxy group situated at a 5-position in 3,3'-bithienyl (*cf.* above). For a carbomethoxy group at a 2- or 4-position, a value of 6.30–6.55 τ is expected.[24,25] The coupling constant of the AB quartet, 3.4 c/s, was the same as in the starting material IV.[17]

Thus 4,4'-dibromo-3,3'-bithienyl was metalated at the 5-position on reaction with both ethyllithium and butyllithium. On addition of a solution of IV to one equivalent of butyllithium, cooled to $-70°$, about half of the product mixture was monoacid V, the rest being mainly 4,4'-dicarboxy-3,3'-bithienyl. The latter compound can be prepared in good yield by adding IV to an excess of butyllithium at $-70°$.[17]

To avoid metalation at the 5,5'-positions, 4,4'-dibromo-5,5'-dimethyl-3,3'-bithienyl (VI) was chosen for studying the reaction between 4,4'-dibromo compounds and alkyllithium. The PMR spectra of the products of experiments 11 and 12 in both cases showed the same pattern with two series of bands. The relative intensities of the two series were different for ethyllithium and butyllithium, thus making the identification easier. In the first series, the aromatic hydrogen resonances occurred at 2.72 τ and 2.83 τ, while the methyl resonances were found at 7.37 τ and 7.63 τ. The relative intensities of the four bands were 1:1:3:3. Comparison with the PMR spectra of other 5,5'-dimethyl



Scheme 3.

compounds, for instance Ic, Id, VI, X, XI, and XII,[20] indicated that the peak at 7.63 τ originated from a methyl group situated adjacent to bromine or hydrogen, while the band at 7.37 τ could be ascribed to a 5-methyl group

adjacent to a 4-carboxy group. After esterification of the product mixture with diazomethane, it was found that one carbomethoxy group ($\tau = 6.52$ ppm, CS_2) was associated with the first series of bands. In the ester, the methyl resonances had essentially the same values ($\tau = 7.65$ ppm and 7.38 ppm) as in the acid, but the aromatic hydrogen resonances were shifted to 3.14 τ and 3.23 τ. On the basis of PMR, this series of bands was ascribed to 4-bromo-4′-carboxy-5,5′-dimethyl-3,3′-bithienyl (VIII, Scheme 3).

In the second series of bands, the aromatic hydrogen resonance occurred at 2.90 τ and the methyl resonances at 7.32 τ and 7.57 τ, with relative intensities 1:3:3. From the PMR spectrum of the esterification product it was found that two carbomethoxy groups ($\tau = 6.48$ ppm and 6.54 ppm) were associated with the second series of bands. Also in this ester, the methyl resonances were nearly unchanged at 7.35 τ and 7.60 τ, while the aromatic hydrogen resonance was shifted to 3.30 τ. As above, it was found that only one methyl group (at 7.32 τ) was situated adjacent to a 4-carboxy group, while the other at 7.57 τ was situated adjacent to a 4-bromine. Thus, the second carboxy group must be placed at an α-position, which is also consistent with the single aromatic hydrogen resonance. Two structures can be suggested, namely 4-bromo-2′,4′-dicarboxy-5,5′-dimethyl-3,3′-bithienyl and 4-bromo-2,4′-dicarboxy-5,5′-dimethyl-3,3′-bithienyl (IX, Scheme 3). In the former compound, the carboxy groups are situated on the same aromatic ring, which implies a preceding lithium intermediate with two lithium atoms at the same thiophene nucleus. Such compounds have been prepared from diiodothiophenes,[14] but their formation in the reaction above is very improbable. Therefore the second series of bands was ascribed to diacid IX.

From the relative intensities of the two series of bands it was found that the reaction between dibromo compound VI and butyllithium yielded after carbonation a 1:1 mixture of monoacid VIII and diacid IX, while ethyllithium in the same way gave a mixture consisting of 60 % VIII and 40 % IX. In both cases, traces of diacid VII could be detected by PMR at 2.98 τ (see below).

In order to confirm the structures of VIII and IX, the mixtures of esters obtained with diazomethane from the reaction product of VI and ethyllithium (expt. 22) was investigated on a combined gas chromatograph-mass spectrometer. The gas chromatogram showed two peaks with relative intensities 3:2, in agreement with the composition found by PMR. The mass spectrum associated with the first band exhibited a molecular ion peak at m/e 331, consistent with the molecular weight of the methyl ester of VIII (331.3). For the second substance, a molecular ion peak was found at m/e 389, which is consistent with the molecular weight of the dimethyl ester of IX (389.3). In both cases, the isotope distribution showed the presence of one bromine, and the base peaks at m/e 251 and m/e 309, respectively, could be explained by loss of bromine.

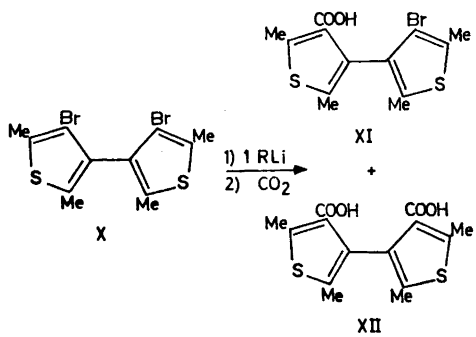
For the preparation of 4,4′-dicarboxy-5,5′-dimethyl-3,3′-bithienyl (VII), dibromo compound VI was added to a large excess of ethyllithium at $-70°$, and the mixture was carbonated with gaseous carbon dioxide. The PMR spectrum of the product exhibited two series of bands, one of which was identical with that found for diacid IX above. The second series of bands occurred at 2.98 τ and 7.37 τ, with the relative intensities 1:3, and was ascribed

to diacid VII. The latter τ-value is the same as that found for one of the methyl resonances of monoacid VIII, but the aromatic hydrogen resonances are different. After esterification of the product mixture, the PMR spectrum exhibited three carbomethoxy bands, two of which were identical with those for the diester of IX. The third occurred at 6.56 τ. According to these data, the mixture of acids consisted of 70 % of diacid IX and only 30 % of the expected diacid VII, the total yield being about 85 %.

Investigation of the mixture of esters on the combined gas chromatograph-mass spectrometer as above showed the presence of two substances in the ratio of about 3:7. The mass spectrum associated with the second peak in the chromatogram was identical with that assigned to the dimethyl ester of IX. The mass spectrum associated with the first substance exhibited a molecular ion peak at *m/e* 310, which is the molecular weight of the diester of VII (310.4). The base peak was found at *m/e* 278, which is the loss of 32 mass units. In the spectra of the methyl esters of VIII and IX, peaks were found at *m/e* M − 31, and this indicates loss of OCH_3, which is the normal fragmentation mode for such compounds. In methyl esters of *o*-methyl benzoic acids, however, elimination of methanol (M = 32, OCH_3 + H from the *o*-methyl group) has been observed,[26] which explains the fragmentation of the ester of VII. This *ortho* effect should also appear in the esters of VIII and IX, and in fact, peaks at *m/e* 219 and at *m/e* 277, respectively, in the mass spectra of these compounds may be explained by the loss of bromine plus methanol.

When the reaction between VI and excess alkyllithium was performed with butyllithium instead of ethyllithium, the product mixture after carbonation was found to consist of only 15 % of the desired diacid VII, and 85 % of diacid IX. The total yield was 75 − 80 %.

In 4,4′-dibromo-2,2′,5,5′-tetramethyl-3,3′-bithienyl (X, Scheme 4), all α-positions are blocked. When this compound was reacted with 1 equiv. of alkyllithium, followed by carbonation, it was found from the PMR spectra of the mixtures of acids and their esterification products, that both ethyllithium and butyllithium yielded about 90 % monoacid XI, and 10 % diacid XII.[20] The yield, however, was rather low (20 − 25 %), as in the reaction between the isomeric dibromo compound Id and ethyllithium.



Scheme 4.

In summary, 2,2′-dibromo-3,3′-bithienyls with 1 equiv. of butyllithium at −70° and subsequent carbonation gave mainly monocarboxylic acids, while ethyllithium yielded a mixture of mono- and dicarboxylic acids with the latter constituting at least 55 – 60 % of the product. 4,4′-Dibromo-3,3′-bithienyl was metalated at one of the 5-positions, and when those were blocked by methyl groups, the 2-position was attacked by both alkyllithium compounds.

DISCUSSION

Several interesting problems are connected with the above results. Alkyllithium compounds seem to have a tendency to give dilithium-3,3′-bithienyls (which are the precursors of the dicarboxylic acids) in reaction with dibromo-3,3′-bithienyls, despite the fact that the latter are in excess. In the reactions with 2,2′-dibromo-3,3′-bithienyls, an evident difference in this respect between ethyllithium and butyllithium is indicated, but such a difference is less pronounced in the reaction with 4,4′-dibromo-3,3′-bithienyls. Furthermore, the latter compounds are easily metalated at unblocked α-positions, although, at −70°, halogen-metal exhange reactions usually take place very much faster.

The metalation reactions may be most easily explained regarding 4,4′-dibromo-3,3′-bithienyl itself, as the behaviour toward alkyllithium is reminiscent of the reaction between 3-bromothiophene and butyllithium at room temperature.[13] Moses and Gronowitz [27] carefully investigated this reaction, and they showed that thienyllithium compounds were stable for several hours at −70°, but on warming to room temperature, transmetalations often took place. Gronowitz had previously found that phenyllithium and 3-bromothiophene at room temperature gave 3-bromo-2-thiophenecarboxylic acid in 71 % yield after carbonation.[13]

Recently Wiersema and Gronowitz [19] found that 4-bromo-2,3-dimethylthiophene with butyllithium underwent transmetalation even at −70°. After carbonation, a mixture was obtained consisting of 70 % 2,3-dimethyl-4-thiophenecarboxylic acid and 30 % 3-bromo-4,5-dimethyl-2-thiophene-carboxylic acid.

For a similar phenomenon in the benzo[b]thiophene series, Dickinson and Iddon [28] suggested an alternative route, involving ring-opening and ring-closure of the thiophene ring. They reacted 3-bromobenzo[b]thiophene with butyllithium at room temperature, and after carbonation, benzo[b]thiophene-2-carboxylic acid and 3-bromobenzo[b]thiophene-2-carboxylic acid were obtained as the major products, together with a trace of benzo[b]thiophene-3-carboxylic acid. By trapping the intermediate lithium compounds with dimethyl sulphate to give the methyl derivatives it was shown that the first formed 3-benzo[b]thienyllithium ring-opened at temperatures much over −70° to give the lithium mercaptide of *o*-mercaptophenylacetylene, which was further metalated by 3-benzo[b]thienyllithium to give the corresponding acetylide and benzo[b]thiophene. The acetylide on carbonation followed by acidification gave *o*-mercaptophenylpropiolic acid, which cyclised to the benzo[b]thiophene-2-carboxylic acid.

An analogous ring-opening reaction had previously been observed by Gronowitz and Frejd, who found that 3-iodo-2,5-dimethylselenophene [29] as well as 3-iodo-2,5-dimethylthiophene [30] yield alkynes with alkyllithium.

However, the route suggested by Dickinson and Iddon involving opening of the thiophene ring does not explain the formation of 3-bromobenzo[b]thiophene-2-carboxylic acid in the reaction between 3-bromobenzo[b]thiophene and butyllithium. Neither can a similar reaction path be formulated to account for the fact that dibromo compounds IV and VI are metalated at the α-positions without loss of the β-halogens. The metalation of dibromo compound IV, producing V after carbonation, is best regarded as a transmetalation. The yield was not above 50 %, and according to IR, the recovered starting material was mixed with 3,3′-bithienyl or a monobromo derivative. In the IR spectrum of the acidic product, minor amounts of by-products could be observed which were not further investigated, and the occurrence of 4-bromo-4′-carboxy-3,3′-bithienyl and other possible carboxylic acids cannot be excluded. The best support for the above suggestion is the fact that 4,4′-dicarboxy-3,3′-bithienyl was obtained in good yield, when dibromo compound IV was added to a large excess of butyllithium which rapidly transformed all bithienyl into a 4,4′-dilithium derivative,[17] but when it was added to an insufficient amount of alkyllithium there was unreacted dibromo compound which could be attacked by the aryllithium formed.

It is improbable, however, that diacid IX (Scheme 3) is formed in a reaction involving metalation of dibromo compound VI by the lithium precursor of monoacid VIII, 4-bromo-4′-lithium-5,5′-dimethyl-3,3′-bithienyl, or in a metalation reaction between two molecules of the latter, since IX could be obtained in 60 – 65 % yield, and the entire yield of diacids VII and IX amounted to 75 – 85 % in a reaction in which dibromo compound VI was added to an excess of alkyllithium. Thus VI or 4-bromo-4′-lithium-5,5′-dimethyl-3,3′-bithienyl must have been metalated by alkyllithium. If VI were attacked first at a 2-position, some 4,4′-dibromo-2-carboxy-3,3′-bithienyl would have been observed in the PMR spectra of the carbonation products, at least when VI was reacted with one equivalent of alkyllithium. However, the only products found were monoacid VIII, diacid IX, and traces of diacid VII, which indicates that the bromo compound VI first gave a 4-monolithium derivative, which was then further attacked preferentially at the 2′-position.

The unusual behaviour of compound VI and the ability of 2,2′-dibromo-3,3′-bithienyls to give dilithium compounds with one equivalent of alkyllithium is best understood if it is assumed that the first formed monolithium derivative of 3,3′-bithienyl is aggregated with alkyllithium. It is reasonable to assume that before the initial reaction, an aggregated alkyllithium compound is in the immediate vicinity of the dibromobithienyl. Whatever the detailed reaction mechanism or the appearance of the attacking reagent, there is alkyllithium near the reaction centre which can aggregate with the aryllithium formed. This is very plausible on the basis of our present knowledge of the structure of organolithium reagents. By such aggregation, a second attack of alkyllithium could be directed to a suitable position of the same molecule, determined by the geometry of the complex.

In compound VI, the second reaction might take place much more easily at the less hindered 2-position occupied by the small hydrogen atom, giving diacid IX after carbonation, than at the 4-position with the bulky bromine atom. Accordingly, in compound X, where the α-hydrogens are replaced by methyl groups, a monolithium compound should be preferentially formed with one equivalent of alkyllithium, and this is also found to be the case (Table 1).

In 2-bromo-2′-lithium-3,3′-bithienyls, a second attack at a 4-hydrogen does not take place, since the β-positions of thiophenes usually are not reactive in metalation reactions.[14] Neither is the 4-position of tetrabromo compound Ib attacked. However, it is conceivable that the geometry of 3,3′-bithienyls would permit a second attack at a 2-position occupied by bromine if ethyllithium is used, but hardly with the more bulky butyllithium. Therefore, in the latter case, mainly monolithium derivatives are formed, while ethyllithium easily yields dilithium compounds.

Without exact knowledge of structure and bonding in mixed alkyl- and aryllithium compounds and of the preferred conformations of the bithienyls and the eventually existing aggregates it is difficult to fully understand the present results. Thus, for example, the geometries of the dibromo compounds IV and VI as well as of their monolithium derivatives should be very similar. Nevertheless their behaviour toward alkyllithium is quite different. If a methylene group is situated between the aromatic rings of IV, as in 4,4′-dibromo-3,3′-bithienylmethane, however, mainly 4-bromo-2,4′-dilithium-3,3′-bithienylmethane was formed in reaction with excess butyllithium at −70°.[31] This is quite analogous to the reaction of dibromo compound VI, and the two cases can probably be related to the same phenomenon. In both compounds, a second metalation reaction takes place at an "inner" 2-position, and this cannot be explained in terms of electronic effects from the halogen-metal exchange in one ring, since no such effects can be transmitted *via* the methylene group to the other ring in the bithienylmethane compound. It might be possible, however, that there is a conformation of an aggregated 4-monolithium derivative of the latter, which is sterically more suitable for an attack at the 2-position of the unmetalated ring than is the case in the 4-monolithium derivative of the more rigid IV. Therefore, in the latter, transmetalation at the open 5-position goes faster. If this possibility does not exist, as in compound VI, the 2-position is attacked, yielding diacid IX after carbonation. The influence of the different solvent used in experiments with compound IV has not yet been investigated.

In the literature, there are other reactions which seem to be analogous to the examples given above. Thus, for example, 3-(*o*-bromophenyl)thiophene was reacted with butyllithium under various conditions, and the mixture carbonated with gaseous carbon dioxide yielding almost pure 2-carboxy-3-(*o*-carboxyphenyl)thiophene.[32] The metalation at the 2-position of the thiophene ring may be explained in the same way as the metalation at the α-position of VI, discussed above. 3-(*p*-Bromophenyl)thiophene gave only a mixture of monocarboxylic acids in the same reaction.

Aggregation to a formed bithienyllithium compound might also explain the slow formation of a 5,5′-dilithium derivative on reaction between excess butyllithium and hexabromo-3,3′-bithienyl[1] or 4,4′,5,5′-tetraiodo-2,2′-di-

methyl-3,3'-bithienyl [33] at −70°. A 5-monolithium derivative was easily formed, but to obtain acceptable yields of a 5,5'-dilithium derivative, reaction times of more than 30 min were necessary. The halogen-metal reaction should be equally fast in both rings, unless the alkyllithium was bound by aggregation.

Östman found that 3-bromothiophene with a great excess of butyllithium gave 2,3-dilithiumthiophene by further metalation of the first formed 3-thienyllithium.[34] This reaction might also support the suggestion of aggregation of the first formed aryllithium with butyllithium which in this case should make the 2-position suitable for a renewed attack. In view of the electronic effects of a lithium atom at the 3-position of thiophene, further reaction is expected to occur at the 5-position.

EXPERIMENTAL

2,2'-Dibromo-5,5'-dimethyl-3,3'-bithienyl (*Ic*). 2.5 g (0.013 mol) of 5,5'-dimethyl-3,3'-bithienyl [18] was dissolved in 80 ml of acetic acid-chloroform (1:1), and the solution was cooled in ice water. 2 mg of hydroquinone was added, and in portions 4.6 g (0.026 mol) of *N*-bromosuccinimide (NBS). The reaction was completed within a few minutes, and the solution was diluted with water. The organic layer was washed with water, with sodium carbonate solution, and again with water. After drying over calcium chloride, the solvent was evaporated *in vacuo* at room temperature to yield 4.4 g (97 %) of Ic. Recrystallization from hot ligroin (b.p. 65−75°), cooled to −15°, gave 3.4 g, m.p. 90−91°, with the same IR spectrum as the first crystallized product. The substance decomposed after a few hours at room temperature, even under ligroin, if not stored at low temperature. PMR (CS_2): $\tau_{4,4'} = 3.37$ ppm, $\tau_{5,5'-CH_3} = 7.60$ ppm, $J_{CH_3-4} = 1.1$ c/s. [Found: C 34.0; H 2.27; S 18.2. Calc. for $C_{10}H_8Br_2S_2$ (352.1); C 34.11; H 2.29; S 18.21.]

2,2'-Dibromo-4,4',5,5'-tetramethyl-3,3'-bithienyl (*Id*), 1.7 g (90 %), m.p. 160−161°, was prepared as above from 1.1 g (0.0050 mol) of 4,4',5,5'-tetramethyl-3,3'-bithienyl [19] and 1.8 g (0.010 mol) of NBS. The substance should be stored at low temperature to prevent decomposition. PMR (CS_2): $\tau_{4,4'-CH_3} = 8.18$ ppm, $\tau_{5,5'-CH_3} = 7.70$ ppm, $J_{CH_3-CH_3} = 0.7$ c/s. [Found: C 37.9; H 3.16; S 17.0. Calc. for $C_{12}H_{12}Br_2S_2$ (380.2): C 37.91; H 3.18; S 16.86.]

4,4'-Dibromo-2,2',5,5'-tetramethyl-3,3'-bithienyl (*X*), 17.0 g (90 %), m.p. 89−91°, was prepared as above from 11.1 g (0.0500 mol) of 2,2',5,5'-tetramethyl-3,3'-bithienyl [20] and 17.8 g (0.100 mol) of NBS. PMR (CS_2): $\tau_{2,2'-CH_3} = 7.83$ ppm, $\tau_{5,5'-CH_3} = 7.65$ ppm, $J_{CH_3-CH_3} = 0.6$ c/s. [Found: C 38.35; H 3.92; S 16.56. Calc. for $C_{12}H_{12}Br_2S_2$(380.2): C 37.91; H 3.18; S 16.86.]

4,4',5,5'-Tetrabromo-3,3'-bithienyl. 3.0 g (0.019 mol) of bromine in 10 ml of acetic acid was added during 10 min to 3.0 g (0.0093 mol) of 4,4'-dibromo-3,3'-bithienyl (IV)[17] in 20 ml of refluxing acetic acid. After a further 5 min, the bromine vapours above the dark solution had disappeared, and the reaction mixture was allowed to attain room temperature. 1.8 g (40 %) of a solid crystallized in small needles. Evaporation of the solvent left a dark syrup, which was not further investigated. If the hot solution instead was poured onto ice, a sticky mass was obtained, which on treating with acetic acid or ligroin gave a 35−37 % yield of product. The analytical sample, m.p. 156−158°, was recrystallized from ligroin. PMR (CS_2): $\tau_{2,2'} = 2.70$ ppm. [Found: C 19.93; H 0.55; S 13.20. Calc. for $C_8H_2Br_4S_2$ (481.9): C 19.94; H 0.42; S 13.31.]

4,4'Dibromo-5,5'-diiodo-3,3'-bithienyl. A mixture of 16.2 g (0.0500 mol) of 4,4'-dibromo-3,3'-bithienyl (IV),[17] 60 ml of acetic acid, 20 ml of water, 30 ml of carbon tetrachloride, 3.5 g of iodic acid, and 10.2 g of iodine was stirred vigorously. 1 ml of conc. sulphuric acid in 10 ml of water was added, and the mixture was heated at 70° for 4 h. Addition of a further 0.5 g of iodic acid then caused rapid decolourization. The reaction mixture was poured onto ice, and the crude product filtered and recrystallized from acetic acid to yield 15.2 g (53 %) of 4,4'-dibromo-5,5'-diiodo-3,3'-bithienyl in fine needles. After one further recrystallization from acetic acid, 14.2 g remained. The analytical sample, m.p. 165−167°, was recrystallized from ligroin (b.p. 80−110°). PMR (CS_2): $\tau_{2,2'} = 2.57$

ppm. [Found: C 16.94; H 0.70; S 11.19. Calc. for $C_8H_2Br_2I_2S_2$ (575.9); C 16.69; H 0.35; S 11.14.]

4,4'-Dibromo-5,5'-dimethyl-3,3'-bithienyl (VI). 11.9 g (0.0207 mol) of 4,4'-dibromo-5,5'-diiodo-3,3'-bithienyl in 700 ml of anhydrous ether in a nitrogen-swept apparatus was added with stirring during 10 min to 75 ml of 0.7 M ethyllithium, cooled to −70°. After 30 min at −70°, 10.0 g (0.0800 mol) of dimethyl sulphate in 25 ml of anhydrous ether was added, and after 10 min more, the cooling bath was removed and the reaction mixture allowed to attain room temperature. Aqueous ammonium hydroxide was added to destroy the excess of dimethyl sulphate, and the stirring was continued for 2 h. The layers were separated, and the organic phase was washed with water, dilute hydrochloric acid, and again with water. After drying over calcium chloride, the solvent was removed *in vacuo*, leaving 6.8 g of a solid which was dissolved in carbon disulphide and chromatographed on aluminium oxide (neutral, activity 1). Elution with carbon disulphide:petroleum ether (b.p. 35−45°) 1:4 gave 5.3 g (73 %) of analytically pure VI, m.p. 74−75°. The IR spectrum of pure VI between 750 and 875 cm^{-1} exhibited a single peak at 795 cm^{-1}, peaks at 780 or 805 cm^{-1} being absent. PMR (CS_2): $\tau_{2,2'} = 2.96$ ppm, $\tau_{5,5'-CH_3} = 7.59$ ppm. [Found: C 34.4; H 2.37; S 18.2. Calc. for $C_{10}H_8Br_2S_2$ (352.1): C 34.11; H 2.29; S 18.21.]

Reaction between dibromo-3,3'-bithienyls and one equivalent of alkyllithium. General procedure. 2−5 mmol of the dibromo compound was dissolved in 50−175 ml of anhydrous ether (IV in tetrahydrofuran), depending on the solubility at −70°. At −70°, under nitrogen and with stirring, about 10 % less than an equimolar amount of ethereal alkyllithium was added dropwise with a pipette. After 2 min, gaseous carbon dioxide,* dried by passage through conc. sulphuric acid, was bubbled into the reaction mixture, which was then immediately warmed to room temperature on a water bath. After hydrolysis, the organic phase was separated and extracted with sodium carbonate solution. The aqueous phases were combined and acidified with dilute hydrochloric acid. The product was filtered, and dimethyl sulphoxide (DMSO) or deuterated DMSO (DMSO-d_6) solutions were analyzed by PMR.

By recrystallization from ethanol-water, pure monoacids could be obtained from some of the experiments with butyllithium.

For the PMR analyses, pure dicarboxylic acids were prepared by adding ether solutions of the corresponding dibromo compounds to excess alkyllithium at −70° and carbonating the mixture by gaseous carbon dioxide after 2−3 min. The products obtained after work-up were recrystallized from ethanol-water.

4,4'-Dibromo-5,5'-dicarboxy-3,3'-bithienyl. From 1.0 g (2.1 mmol) of 4,4',5,5'-tetrabromo-3,3'-bithienyl in 100 ml of anhydrous ether and 7.5 ml of 0.8 M ethyllithium in 15 ml of anhydrous ether. Yield 0.75 g (91 %), m.p. 305° (dec.). PMR (DMSO): $\tau_{2,2'} = 1.98$ ppm. [Found: C 28.95; H 0.93; S 15.38. Calc. for $C_{10}H_4Br_2O_4S_2$ (412.1): C 29.15; H 0.98; S 15.56.] *Dimethyl ester; m.p.* 222−223°.

4,4',5-Tribromo-5'-carboxy-3,3'-bithienyl. From 1.0 g (2.1 mmol) of 4,4',5,5'-tetrabromo-3,3'-bithenyl in 100 ml of anhydrous ether and 2.3 ml of 0.8 M butyllithium. Yield 0.18 g (22 %), m.p. 242−245°. PMR (DMSO): $\tau_2 = 2.16$ ppm, $\tau_{2'} = 2.00$ ppm. [Found: C 24.4; H 0.75; S 14.3. Calc. for $C_9H_3Br_3O_2S_2$ (447.0): C 24.18; H 0.68; S 14.35.] *Methyl ester;* m.p. 130−132°.

2,2'-Dicarboxy-3,3'-bithienyl (IIa). From 4.0 g (0.012 mol) of 2,2'-dibromo-3,3'-bithienyl (Ia)[16] in 60 ml of anhydrous ether and 30 ml of 1.1 M butyllithium. Yield 2.7 g (88 %), m.p. 295° (dec.). PMR (DMSO): $\tau_{aromatic} = 2.25$ ppm and 2.90 ppm. $J_{4-5} = 5.1$ c/s. [Found: C 46.59; H 2.59; S 25.03. Calc. for $C_{10}H_6O_4S_2$ (254.3): C 47.23; H 2.38; S 25.22.] *Dimethyl ester;* m.p. 198−199°.

2-Bromo-2'-carboxy-3,3'-bithienyl (IIIa) (Table 1, expt. 2). M.p. 177−179°. PMR (DMSO): $\tau_{4,5} = 2.98$ ppm and 2.45 ppm, $\tau_{4',5'} = 2.86$ ppm and 2.15 ppm. $J_{4-5} = 5.7$ c/s, $J_{4'-5'} = 5.1$ c/s. [Found: C 37.86; H 1.63; S 22.50. Calc. for $C_9H_5BrO_2S_2$ (289.2): C 37.38; H 1.74; S 22.18.] *Methyl ester;* m.p. 76−78°.

2,4,4'-Tribromo-2'-carboxy-3,3'-bithienyl (IIIb) (Expt. 4). M.p. 246−248°. PMR (acetone): $\tau_5 = 2.32$ ppm, $\tau_{5'} = 2.00$ ppm. [Found: C 24.61; H 0.77; S 14.19. Calc. for $C_9H_3Br_3O_2S_2$ (447.0): C 24.18; H 0.68; S 14.35.] *Methyl ester;* m.p. 90−91°.

2-Bromo-2'-carboxy-5,5'-dimethyl-3,3'-bithienyl (IIIc) (Expt. 6). M.p. 175° (dec.). PMR (DMSO-d_6): $\tau_4 = 3.31$ ppm, $\tau_{4'} = 3.18$ ppm, $\tau_{5-CH_3} = 7.62$ ppm, $\tau_{5'-CH_3} = 7.53$ ppm.

* It was found that carbonation with crushed dry ice easily gave hydrolysis.

J_{CH_3-4} = 1.1 c/s. [Found: C 42.0; H 2.99; S 20.0. Calc. for $C_{11}H_9BrO_2S_2$ (317.2): C 41.65; H 2.86; S 20.21.] *Methyl ester;* m.p. 54 – 56°.

2-Bromo-2'-carboxy-4,4',5,5'-tetramethyl-3,3'-bithienyl (*IIId*) (Expt. 8). M.p. 230° (dec.). PMR (DMSO-d_6): $\tau_{4,4'-CH_3}$ = 8.22 ppm, τ_{5-CH_3} = 7.69 ppm, $\tau_{5'-CH_3}$ = 7.60 ppm. [Found: C 46.0; H 3.86; S 18.5. Calc. for $C_{13}H_{13}BrO_2S_2$ (345.3): C 45.22; H 3.79; S 18.57.]

4,4'-Dibromo-5-carboxy-3,3'-bithienyl (*V*) (Expt. 9). Yield 1.5 g, m.p. 224 – 226°. PMR (DMSO): τ_2 = 2.00 ppm, $\tau_{2',5'}$ = 2.20 ppm and 2.25 ppm. $J_{2'-5'}$ = 3.4 c/s. [Found: C 29.7; H 1.16; S 17.4. Calc. for $C_9H_4Br_2O_2S_2$ (368.1); C 29.37; H 1.09; S 17.42.]

4,4'-Dibromo-5-carbomethoxy-3,3'-bithienyl. M.p. 109 – 111°. PMR (CS_2): τ_2 = 2.52 ppm, $\tau_{2',5'}$ = 2.69 ppm and 2.73 ppm. $J_{2'-5'}$ = 3.5 c/s. τ_{OCH_3} = 6.17 ppm. [Found: C 31.8; H 1.81; S 16.8. Calc. for $C_{10}H_6Br_2O_2S_2$ (382.1): C 31.43; H 1.58; S 16.78.]

Reaction between 4,4'-dibromo-5,5'-dimethyl-3,3'-bithienyl (*VI*) *and alkyllithium.*

A: 1 equiv. of alkyllithium. See Table 1, expts. 11 and 12, and the text.

B: 2 equiv. of alkyllithium. To 20 ml of 0.75 M ethyllithium, cooled to −70°, 2.1 g (6.0 mmol) of VI in 25 ml of anhydrous ether was added. Carbonation and work-up gave 1.8 g of a mixture which by PMR was shown to consist of about 30 % of the expected 4,4'-dicarboxy-5,5'-dimethyl-3,3'-bithienyl (VII) and 70 % of diacid IX, corresponding to *ca.* 25 % total yield of VII and 60 % total yield of IX.

In the same way, 1.3 g (3.7 mmol) of VI, in 15 ml of ether, added to 10 ml of 1.0 M butyllithium, cooled to −70°, gave 1.0 g of a mixture, consisting of about 15 % of VII, and 85 % of IX, corresponding to *ca.* 12 % total yield of VII, and 65 % total yield of IX.

The carboxylic acids VII, VIII, and IX were not separated. PMR data for the acids and the corresponding methyl esters are given in the text. The PMR and mass spectrometric data confirm the identity of the carboxylic acids VII, VIII, and IX, and their methyl esters.

4-Bromo-4'-carboxy-2,2',5,5'-tetramethyl-3,3'-bithienyl (XI) (Expts. 13 and 14). Yield: 0.3 g, m.p. 203 – 205°. PMR (DMSO-d_6): $\tau_{2,2'-CH_3}$ = 7.88 ppm and 7.95 ppm, τ_{5-CH_3} = 7.66 ppm, $\tau_{5'-CH_3}$ = 7.40 ppm. [Found: C 45.5; H 3.88; S 18.5. Calc. for $C_{13}H_{13}BrO_2S_2$ (345.3): C 45.22; H 3.79; S 18.57.]

Carboxylic methyl esters were prepared from the pure mono- and dicarboxylic acids with diazomethane. The methyl esters of compounds IIId, XI, and XII did not crystallize. The melting points of the dimethyl esters of IIb,[22] IIc, and IId were 161 – 162°, 134 – 136°, and 92 – 93°, respectively. The τ_{OCH_3}-values are given elsewhere, together with a discussion of their role in connection with structure determinations of 3,3'-bithienyls.[25]

All melting points are uncorrected, and were taken on a hot-stage microscope. The PMR spectra were obtained on a Varian A-60 spectrometer. Mass spectra were obtained with an LKB A 9000 combined gas chromatograph-mass spectrometer. Separation of the esters was carried out with an OV-1 5 % column. The temperature of the column was 200° and that of the ionisation chamber 290°. The energy of the ion beam was 70 eV. IR spectra were recorded on a Perkin-Elmer 257 infrared spectrophotometer. The micro analyses were carried out by Miss Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, West Germany, and by the Analytical Laboratory at the Chemical Center, Lund.

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