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Thienylpyrroles

I. Synthesis *via* Copper Intermediates

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1-Methyl-2-pyrrolylcopper was prepared through metalation of 1-methylpyrrole with butyllithium in a mixture of ether and *N,N*-tetramethylethylenediamine (TMEDA), followed by reaction with cuprous bromide. Reaction of the copper reagent with 2- and 3-iodothiophene and iodobenzene produced preparatively useful yields of the unsymmetrical coupling products 1-methyl-2-(2-thienyl)-pyrrole (II), 1-methyl-2-(3-thienyl)pyrrole (IX), and 1-methyl-2-phenylpyrrole (XIII). Minor amounts of the symmetrical coupling products were also formed. In addition, terheterocyclic derivatives were formed in quite large amounts in the reaction with iodothiophenes. This seems to be due to the metalation of 2-iodothiophene in the 5-position, and 3-iodothiophene in the 2- (predominantly) and 5-position by the copper reagent.

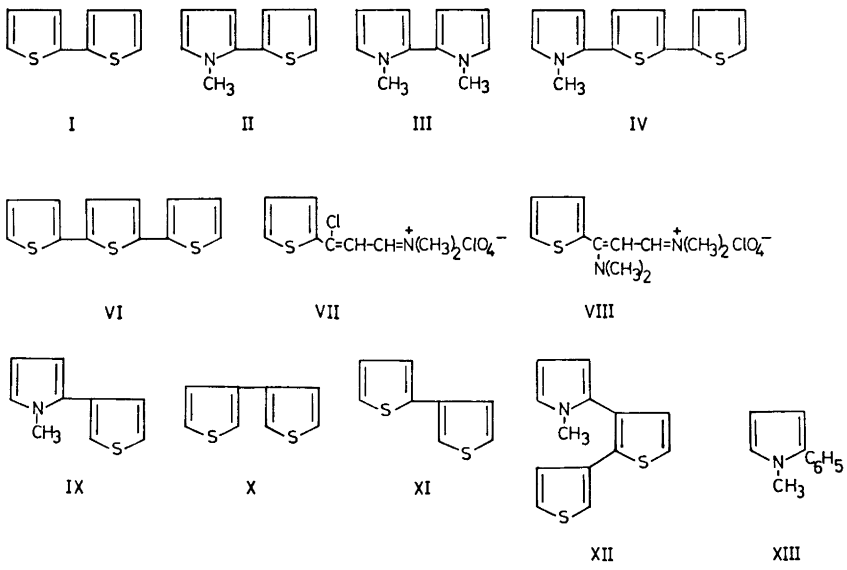
The complexing of organolithium derivatives with TMEDA has a specific rate-enhancing effect on the metalation reaction. Thus, while reaction between phenyllithium and 2-iodothiophene in ether exclusively gives halogen-metal exchange to yield 2-thienyllithium and iodobenzene, the presence of one equivalent of TMEDA gives metalation, leading to 5-iodo-2-thienyllithium and benzene.

In connection with our studies of substitution reactions of biheterocycles [1,2] we were interested in investigating the chemistry of the thienylpyrroles, an almost unknown class of compounds. During recent years, the usefulness of organocopper compounds for forming carbon – carbon σ-bonds has been demonstrated by Corey and Posner,[3] House *et al.*[4] and Nilsson *et al.*[5,6] Unsymmetrical biarenes have been obtained through the reaction of arylcopper reagents, prepared by the reaction of arylmagnesium bromides or aryllithium compounds with copper(I) iodides or copper(I) bromides, with iodobenzenes in pyridine or quinoline.[5,6] However, in the reaction of phenylcopper with iodobenzenes, biphenyl and symmetrically substituted biphenyls are also formed due to simultaneously occurring copper-iodine exchange.[7] The amount of symmetrically substituted biphenyls formed varies with the structure of the iodobenzene.[7] On the other hand, Nilsson and coworkers in the reaction

of 2-thienylcopper with iodobenzenes, besides the unsymmetrical coupling product, obtained 2,2′-bithiophene and the symmetrical coupling product from the iodobenzenes in only about 1 % yield.[5,8] Unsymmetrical biarenes have also been obtained in the reaction of lithium diphenylcuprate with 1-iodonaphthalene in ether solution in the presence of nitrobenzene.[4] In this case, however, halogen-metal exhange appears to precede the coupling reaction.

In order to prepare 1-methyl-2-(2-thienyl)pyrrole according to the above methods, either 2-thienylcopper could be reacted with 2-iodo-1-methylpyrrole or 1-methyl-2-pyrrolylcopper with 2-iodothiophene. Due to the known instability of simple halopyrroles (2-iodo-1-methylpyrrole is not described in the literature), we investigated the second alternative first.

In contrast to thiophene, 1-methylpyrrole is metalated slowly in ether with alkyllithium derivatives.[9] Even after 20 h of reflux, only a 42 % yield is obtained However, by complexing the alkyllithium reagent with *N*,*N*-tetramethylethylenediamine (TMEDA),[10,11] 1-methylpyrrole could be smoothly metalated in high yield.[12] After refluxing for 1 h, a 70 % yield of 1-methyl-2-



pyrrolylcarboxylic acid was obtained upon carbonation. Reaction of 1-methyl-2-pyrrolyllithium with copper(I) bromide yielded a brown precipitate, which was reacted with 2-iodothiophene in pyridine. In order to avoid the presence of 2-iodothiophene in the product, which made separation more difficult, excess of the copper reagent was used in this and in the following experiments. The progress of the reaction was followed by hydrolyzing aliquots and analyzing by VPC, the different components being identified by combined VPC-mass spectrometry. After 1 h reflux, both the starting 2-iodothiophene and 2-iodo-1-

methylpyrrole were present together with the coupled products 2,2′-bithiophene (I), 1-methyl-2-(2-thienyl)pyrrole (II), and 1,1′-dimethyl-2,2′-bipyrrole (III). After 3 h reflux, the iodo compounds had disappeared and the reaction mixture was worked up. An interesting observation was that the relative amount of I, compared to II + III, decreased with time. Besides the "dimeric" coupling products, "trimeric" derivatives were also formed, mostly 1-methyl-2-(5-(2,2′-bithienyl))-pyrrole (IV) and traces of terthiophene (VI) were detected. In addition, an unknown compound (V) with molecular weight 163, not identical with II or the 3-thienyl isomer, was observed. Integration of the peaks in the gas chromatogram indicated that the relating amounts I:II:III: IV:V:VI are approximately 7:53:24:14:2: < 1.

By means of column chromatography on silica gel, followed by distillation or recrystallization, II (40 % yield), III and IV could be obtained pure. Their structure follows from the mode of synthesis, and was confirmed by NMR spectra and alternative synthesis in some cases.

The three pyrrolic ring-hydrogens of II gave rise to an ABX spectrum, and from the three characteristic coupling constants [13] it is evident that the pyrrole ring is 2-substituted. The three thiophenic ring-hydrogens give rise to an ABB′ spectrum with $J_{AB}+J_{AB'}=6.1$ c/s, which identifies the A hydrogen resonance as that of hydrogen 5 (Fig. 1).

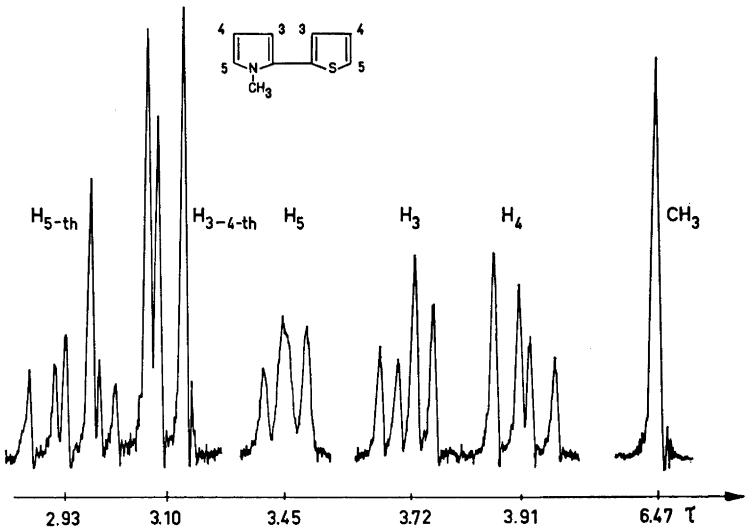


Fig. 1. NMR spectrum at 60 Mc/s of 1-methyl-2-(2-thienyl)pyrrole in $CDCl_3$ solution.

The NMR spectrum of III was also of the ABB′ type, showing a 1:2:1 triplet centered at $\tau=3.36$ ppm, and a doublet at $\tau=3.89$ ppm, with $J_{AB}+J_{AB'}=4.3$ c/s. From the known large chemical shift differences between α- and β-hydrogens in pyrroles,[14] and from the coupling constants ($J_{35}+J_{45}$), it is obvious that III is 1,1′-dimethyl-2,2′-bipyrrole.

The structure of IV follows from its NMR spectrum (Fig. 2), which shows three one-hydrogen bands as quartets with coupling constants 2.6, 3.7, and 1.9 Hz, identifying these bands as those of the hydrogens in a 2-substituted pyrrole ring. Two doublets at 2.91 and 2.74 ppm with splittings of 3.8 Hz indicate a 2,5-disubstituted thiophene ring, and further, the spectrum shows three quartets with coupling constants 1.3, 3.7, and 4.9 Hz, indicating a 2-substituted thiophene ring.

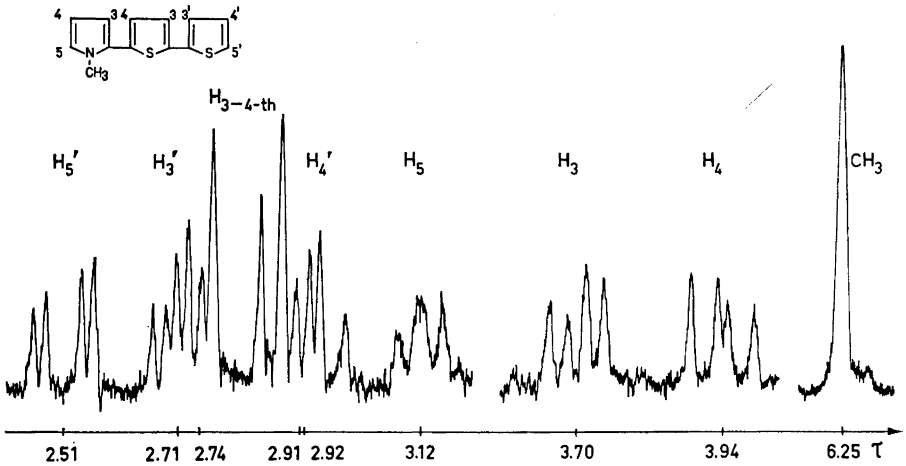


Fig. 2. NMR spectrum at 60 Mc/s of 1-methyl-2-(5-(2,2′-bithienyl))pyrrole in DMSO solution.

We also attempted to prepare II by a method analogous to that for 1-methyl-2-phenylpyrrole, described by Arnold and Holy.[15] 2-Acetylthiophene was reacted with dimethylformamide and phosphorus oxychloride, to give the perchlorate VII in 31 % yield, which through reaction with dimethylamine was transformed to the perchlorate VIII in 60 % yield. However, ring-closure of the latter compound with sodium hydride in *N*,*N*-dimethylformamide yielded a very low yield of II, which had the same IR spectrum as the product obtained in the unsymmetrical coupling. Another possible route to II would be methylation of 2-(2-thienyl)pyrrole, which might be prepared in analogy with the preparation of 2-phenylpyrrole, from 2-acetylthiophene and dimethylaminonitroethylene.[16] III could be prepared by the direct coupling of 1-methyl-2-pyrrolyllithium with cupric chloride, a reaction which has been extensively used in this laboratory for the preparation of symmetrical bithiophenes,[17] but in the present case the yield was low.

The reaction between 2-thienylcopper and 2-iodo-1-methylpyrrole was more difficult to study. The latter compound, prepared through the reaction of 1-methyl-2-pyrrolyllithium and iodine at −65°C, was very unstable, and thus the crude ethereal solution was used in the reaction. Combined VPC and mass-spectral analysis of the reaction products from the reaction with thienylcopper indicated that besides 2-iodo-1-methylpyrrole and 2-bromo-1-

methylpyrrole, I, II, and III were formed in the proportions 54:42:1. The small amount of III is not unexpected, since 2-thienyllithium did not give halogen-metal exchange with 2-iodo-1-methylpyrrole. Due to the instability of 2-iodo-1-methylpyrrole and the greater difficulties involved in separating II from the relatively large amounts of I which are formed, this route is less attractive for the synthesis of II.

The reaction of 1-methyl-2-pyrrolylcopper with 3-iodothiophene gives an even more complex reaction mixture than the reaction with 2-iodothiophene. In the gas chromatogram of the crude product, at least 16 components could be detected. Through combined VPC-mass spectrometry, structures or partial structures could be established for most of them. The coupled product consists of about 70 % of biheterocycles and 30 % of terheterocycles. The main component (72 %) of the biheterocyclic fraction was the desired unsymmetrical coupling product 1-methyl-2-(3-thienyl)pyrrole (IX). (NMR: *cf.* Fig. 3.)

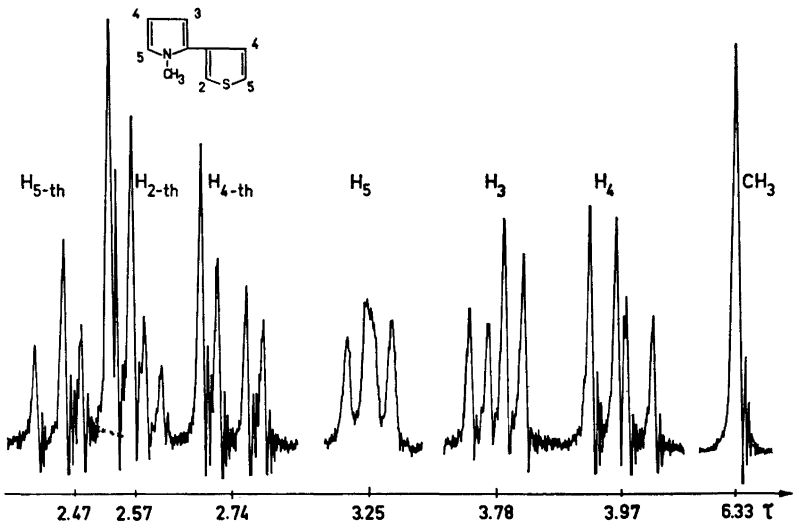


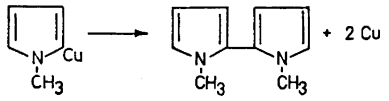
Fig. 3. NMR spectrum at 60 Mc/s of 1-methyl-2-(3-thienyl)pyrrole in DMSO solution.

Besides the expected III (17 %) and 3,3'-bithiophene (X) (3 %), this fraction also contained small amounts of II (6 %) and 2,3'-bithiophene (XI) (2 %). The formation of II and XI is surprising, since the 3-iodothiophene used contained less than 0.1 % of 2-isomer. Apparently some rearrangement has occurred.

Combined VPC-mass spectral analysis indicated that the terarene fractioned contained at least three different bithienylpyrroles and one thienylbipyrrole. The dominant component ($\approx$65 %) of the terarene fraction is most likely 1-methyl-2-(3-(2,3'-bithienyl))pyrrole (XII) (*cf.* below).

Due to the presence of the terarenes it was difficult to obtain pure IX by column chromatography followed by fractional distillation. However, in an experiment carried out in quinoline, an 8 % yield of pure IX was obtained.

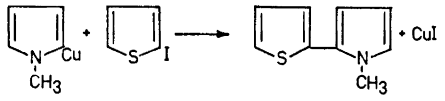
III is most probably formed according to reaction (1)



(1)

III

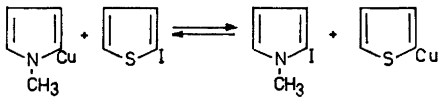
It is possible that some of this compound could have been formed by oxidative coupling, due to the unintentional presence of oxygen, as organic copper compounds are very sensitive to oxygen.[18,19] The unsymmetrical coupling product is certainly predominantly formed according to reaction path (2).



(2)

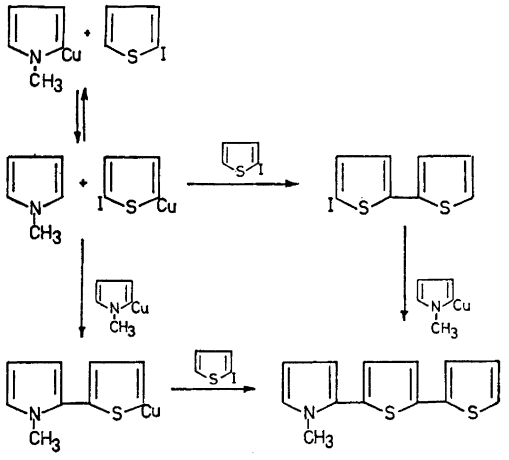
II

Halogen-metal exchange according to (3) followed by coupling is one of



(3)

the routes which could yield I as well as II and III. However, it is also possible that a certain amount of I is formed by an Ullmann-type coupling between 2-iodothiophene and the copper formed according to reaction (1). We found that when 2-iodothiophene was refluxed with copper powder for 3 h in pyridine, 2 % of I was formed. Certainly the copper *in statu nascendi* formed in reaction step (1) should be more reactive. However, it should be noted that the presence of 2-iodo-1-methylpyrrole at the start of the reaction does not necessarily



IV

indicate that halogen-metal exchange has taken place, as we found that reacting 1-methyl-2-pyrrolylcopper with cuprous iodide, which is formed according to reaction (2), yielded 2-iodo-1-methylpyrrole.

The largest difference between our coupling results with 2- and 3-iodothiophenes and those of Nilsson and co-workers lies in the relatively large amounts of terheterocyclics formed. We believe this to be due to the metalation of the acidic 5-position of 2-iodothiophene by 1-methyl-2-pyrrolylcopper to form 2-iodo-5-thienylcopper, which either couples with 2-iodothiophene and then with 1-methyl-2-pyrrolylcopper, or in the opposite order, to give IV (*cf.* scheme 4). Evidence for this hypothesis was found in the reaction of 1-methyl-2-pyrrolylcopper with iodobenzene, which has no hydrogens of comparative acidity. 1-Methyl-2-phenylpyrrole was obtained in 41 % yield and less than 1 % of "terarenes", with molecular weight of 233 (1 pyrrole and 2 phenyl rings) and 236 (2 pyrrole and 1 phenyl ring), were obtained. The major by-products were III (about 6 %) and about 1 % of an unknown compound with a molecular weight of 245. It is obvious that this method for the preparation of 1-methyl-2-phenylpyrrole is more convenient than the method previously described in the literature.[15]

Additional evidence was obtained from some metalation experiments. No reaction occurred between 2-thienyllithium and 2-iodo-1-methylpyrrole, 2-thiophenecarboxylic acid being the only product obtained upon carbonation (73 % yield). 1-Methyl-2-pyrrolyllithium in ether-TMEDA, on the other hand, gives both halogen-metal exchange and metalation of 2-iodothiophene at −20°C, as 2-thiophenecarboxylic acid and 5-iodo-2-thiophenecarboxylic acid in the proportions 7:3 are obtained in a total yield of 43 %. If the reaction is carried out at 0°C, the mixture of organolithium compounds appears to be rather unstable, as only an 8 % yield of 5-iodo-2-thiophenecarboxylic acid could be isolated. Metalation was even more pronounced with 3-iodothiophene. At −5 to −10°C, reaction with 1-methyl-2-pyrrolyllithium in ether-TMEDA yielded only 3-iodo-2-thiophenecarboxylic acid and 4-iodo-2-thiophenecarboxylic acid in the relative proportions 4:1, and in a total yield of 33 %. Based on this observation, the main terarene obtained in the reaction with 3-iodothiophene is assigned structure XII.

These results are quite unexpected. Although it has earlier been demonstrated that 3-bromothiophene is metalated in the 2-position,[20] the fact that 2-iodothiophene is metalated is quite astounding, since iodo-metal interchange is usually much more rapid than metalation.

We were interested in determining whether our results could be ascribed to some peculiar property of 1-methyl-2-pyrrolyllithium or to the solvent system. The following experiments indicated the latter to be the case. Reaction of 2-iodothiophene with phenyllithium in ether at room temperature gave exclusively halogen-metal exchange, since 2-thiophenecarboxylic acid was obtained in 55 % yield upon carbonation.[21] In the presence of TMEDA, however, 5-iodo-2-thiophenecarboxylic acid was obtained in 30 % yield.

The strong rate enhancing effect in metalation with organolithium compounds complexed with TMEDA has been well documented during recent years. However, we believe this to be the first observation that this complex-formation selectively enhances metalation over halogen-metal exchange.

We hope to investigate this effect more closely. If there is a parallel between the reaction patterns of organolithium and organocopper compounds, it is obvious that the formation of terarenes could be avoided either by carrying out the metalation of *N*-methylpyrrole in anhydrous ether [9] without TMEDA, accepting the longer reaction time and lower yield of 1-methyl-2-pyrrolyllithium, or by using menthyllithium as the metalating agent. The efficiency of menthyllithium in metalations has recently been demonstrated by Glaze and Freeman,[22] who found it to metalate toluene in ether solution. We metalated 1-methylpyrrole directly with butyllithium in ether according to Shirley *et al.*[9] After 21 h reflux, at least 60 % of 1-methyl-2-pyrrolyllithium had been formed, judging from the yield of 1-methyl-2-pyrrolylcarboxylic acid obtained upon carbonation.

Coupling in the same way as described above, however, did not reduce the amount of "terarenes" formed. The relative amounts of biheterocycles to terheterocycles was 4:1. At least 5 different terheterocycles were present. The composition of the biheterocycles did not differ very much from that obtained in the presence of TMEDA, as it consisted of 53 % of II, 44 % of III and 3 % of I. By means of column chromatography, a 13 % yield of II could be obtained. Due to the lower yield and technical difficulties in the synthesis, the coupling in ether-TMEDA is to be preferred. It thus appears that 2-iodothiophene is more easily metalated by organocopper than by organolithium derivatives. The formation of terthiophene, quaterthiophene and quinquethiophene in the reaction of 2-iodothiophene with copper bronze also provides evidence in this direction.[23] However, we also observed the formation of ter- and quaterthiophene (about 10 % of the coupling products) in the reaction of 2-thienyllithium with CuBr, which yielded I as the main product in 30 % yield.

We also attempted the direct coupling of equimolar amounts of 2-thienyllithium and 1-methyl-2-pyrrolyllithium with one or two equivalents of cuprous bromide or cuprous iodide. The compounds I, II and III were formed, and no terheterocycles were detected. However, the yield was so low (less than 10 %) that in spite of the fact that this method does not necessitate the prior synthesis of 2-iodothiophene, it cannot compete with the coupling with iodo compounds.

We also briefly investigated the House procedure, preparing the *ate* complex lithium di(2-thienyl)cuprate. However, as this in the reaction with iodonaphthalene yielded I and 2-(1-naphthyl)thiophene in the proportion of 7:1, this route was not further investigated.

EXPERIMENTAL

1-Methyl-2-pyrrolylcarboxylic acid. To a solution of 5.7 g (70 mmol) of 1-methylpyrrole and 10.0 g (86 mmol) of tetramethyl ethylenediamine (TMEDA) in 50 ml of anhydrous ether, 100 ml of 1.06 N ethyllithium was added dropwise with stirring under nitrogen. After refluxing for 1 h, the mixture was cooled to room temperature and poured onto powdered carbon dioxide, covered with ether. When the temperature had risen to 0°C, water and dilute hydrochloric acid were added, the ether phase separated and the aqueous phase extracted with ether. The combined ether phases were extracted with 2 N sodium hydroxide. The precipitate formed upon acidification with hydrochloric acid was filtered off, yielding 6.1 g (70 %) of 1-methyl-2-pyrrolylcarboxylic acid, m.p. 135–138°C after

recrystallization from aqueous ethanol; literature m.p. 135–136°C.[8] NMR ($CDCl_3$): $\tau_3 = 2.88$ ppm, $\tau_5 = 3.17$ ppm, $\tau_4 = 3.86$ ppm, $\tau_{CH_3} = 6.09$ ppm, $\tau_{COOH} = -2.1$ ppm, $J_{35} = 1.9$ c/s, $J_{45} = 2.5$ c/s, $J_{34} = 4.0$ c/s. When 85 ml of 1.05 N ethereal butyllithium and 5.7 g of 1-methylpyrrole in 50 ml of ether were refluxed for 21 h, and then reacted with carbon dioxide and worked up as described above, 5.0 g (57 %) of 1-methyl-2-pyrrolylcarboxylic acid was obtained. After 1 h reaction time, the yield was 21 %.

1,1'-Dimethyl-2,2'-bipyrrole (III). A solution of 1-methyl-2-pyrrolyllithium, prepared as described above from 300 ml 1.0 N ethyllithium, 20 g (0.25 mol) of 1-methylpyrrole, 35 g of TMEDA, and 100 ml of ether was cooled to −50°C, and 34.0 g (0.25 mol) of anhydrous cupric chloride was added. When the temperature had risen to −10°C (after 1.5 h), 200 ml of 2 N hydrochloric acid was added dropwise. When the temperature of the mixture had increased to room temperature, the mixture was filtered, the ether phase separated, and the aqueous phase extracted with ether. The combined ether phases were washed with sodium bicarbonate solution and water, and dried over magnesium sulphate. Evaporation of the ether gave 5.5 g of a dark oil, which upon distillation yielded 1.6 g (8 %) of the title compound, b.p. 77–78°C/0.4 mmHg. NMR ($CDCl_3$): $\tau_{5,5'} = 3.36$ ppm, $\tau_{3,3',4,4'} = 3.89$ ppm, $J_{35} + J_{45} = 4.3$ c/s, $\tau_{CH_3} = 6.58$ ppm. (Found: M. wt. 160; C 75.0; H 7.76; N 17.6. Calc. for $C_{10}H_{12}N_2$ (160.1): C 74.97; H 7.55; N 17.48.)

1-Methyl-2-(2-thienyl)pyrrole (II). Reaction between 1-methyl-2-pyrrolylcopper and 2-iodothiophene in the presence of TMEDA. To a solution of 8.1 g (0.10 mol) of 1-methylpyrrole and 14.0 g (0.12 mol) of TMEDA in 100 ml of anhydrous ether, 100 ml of 1.06 N ethereal butyllithium was added dropwise with stirring, and under nitrogen. After refluxing the mixture for 1 h, it was cooled and pressed with nitrogen into a dropping-funnel, and added dropwise during 1 h to a stirred mixture of 19.0 g (0.13 mol) of cuprous bromide in 10 ml of anhydrous ether. After an additional hour, stirring was stopped, the brown precipitate allowed to settle, and the dark green ethereal solution was pressed off with nitrogen. More ether was added, and after stirring for a few minutes, the ethereal solution was pressed off. The combined ether phases were washed with water, dilute hydrochloric acid, sodium bicarbonate solution and again with water, and dried over magnesium sulphate. Evaporation of the ether gave 0.45 g of a residue which VPC showed to be a mixture of 1-methylpyrrole and 1,1'-dimethyl-2,2'-bipyrrole. To the brown precipitate, 10.5 g (0.050 mol) of 2-iodothiophene in 150 ml of anhydrous pyridine was added dropwise and the mixture refluxed. After 1 h, VPC analysis showed the presence of 2-iodothiophene and 2-iodo-1-methylpyrrole besides the three coupling products 2,2'-bithienyl, 1,1'-dimethyl-2,2'-bipyrrole, and 1-methyl-2-(2-thienyl)pyrrole. After 3 h reflux, when the iodo compounds had disappeared almost completely, the mixture was cooled, ether added, and the solid compounds were filtered off. The solution was then extracted several times with 1 N hydrochloric acid, in order to remove the pyridine, then with sodium bicarbonate solution and water, and dried over magnesium sulphate. After evaporation of the ether, 7.8 g of a green liquid, containing some pyridine, was obtained. VPC (5 % NPGS, 100–240°C programmed 8°C/min) and mass spectrometry showed that the following compounds had been formed (the figures in parenthesis indicate area percentages and retention times): III (24 %; 10.2 min); I (7 %; 11.3 min), II (53 %; 11.9 min), V unknown compound of molecular weight 163 (2 %; 15.6 min), IV 14 %; 27.4 min), VI (< 1 %; 26.7 min). Since it may be assumed that the sensitivity of the detector for the three biheterocycles is approximately the same, this would indicate that 1-methyl-2-(2-thienyl)pyrrole (II), 1,1'-dimethyl-2,2'-bipyrrole (III), and 2,2'-bithienyl (I) are present in the proportions 6:3:1. The crude reaction product was chromatographed on a silica gel (100–200 mesh) column, using first hexane and then a 1:1 mixture of hexane and benzene as eluent. From the first fractions, 0.52 g of I with the same physical properties as an authentic sample was obtained. An intermediate fraction contained 0.09 g of a mixture of about 90 % of II and 10 % of I. From the next fractions, 3.30 g (40 % yield) of II, containing about 5 % of terheterocyclic compounds, was obtained. Distillation *in vacuo* yielded analytically pure 1-methyl-2-(2-thienyl)pyrrole, b.p. 63°C/0.05 mmHg. NMR ($CDCl_3$): $\tau_{CH_3} = 6.47$ ppm. Pyrrolic resonances: $\tau_5 = 3.45$ ppm, $\tau_3 = 3.72$ ppm, $\tau_4 = 3.91$ ppm, $J_{34} = 3.7$ Hz, $J_{35} = 1.8$ Hz, $J_{45} = 2.6$ Hz. Thiophenic resonances: $\tau_5 = 2.93$ ppm, $\tau_{3,4} = 3.10$ ppm; $|J_{35} + J_{45}| = 6.1$ Hz. (Found: M. wt. 163; C 66.4; H 5.54; N 8.41; S 19.7. Calc. for C_9H_9NS (163.2): C 66.22; H 5.56; N 8.58; S 19.64.)

Continued elution with hexane:benzene (1:1) yielded first 0.09 g of 1-methyl-2-(5-(2,2'-bithienyl))pyrrole, m.p. 47–49°C after recrystallization from petroleum ether (b.p.

40 – 60°C). NMR (DMSO). Pyrrolic resonances: $\tau_5 = 3.12$ ppm, $\tau_3 = 3.70$ ppm, $\tau_4 = 3.94$ ppm, $J_{35} = 1.9$ Hz, $J_{45} = 2.6$ Hz, $J_{34} = 3.7$ Hz. Thiophenic resonances: τ_3 or $\tau_4 = 2.74$ ppm, τ_4 or $\tau_3 = 2.91$ ppm, $J_{34} = 3.8$ Hz, $\tau_5' = 2.51$ ppm, $\tau_3' = 2.71$ ppm, $\tau_4' = 2.92$ ppm, $J_{3'5'} = 1.3$ Hz, $J_{4'5'} = 4.9$ Hz, $J_{3'4'} = 3.7$ Hz; $\tau_{CH_3} = 6.25$ ppm. (Found: M. wt. 245; C 64.18; H 4.71; N 6.05. Calc. for $C_{13}H_{11}NS_2$ (245.4): C 63.63; H 4.52; N 5.71.) From the last fraction, 1.34 g of a green liquid was obtained, which according to VPC consisted of about 85 % of III and 15 % of IV. Distillation *in vacuo* yielded pure III, b.p. 66°C/0.1 mmHg, with the same spectroscopic data as the sample described above.

Reaction between 1-methyl-2-pyrrolylcopper and 2-iodothiophene in the absence of TMEDA. A solution of 1-methyl-2-pyrrolyllithium was prepared as described above from 480 ml of 1.05 N ethereal butyllithium and 32.4 g (0.40 mol) of 1-methylpyrrole in 200 ml of ether by refluxing for 21 h. The mixture was transferred under nitrogen to a dropping-funnel, and during 1 h added dropwise with stirring to 35.8 g (0.25 mol) of cuprous bromide in 50 ml of anhydrous ether at room temperature. After stirring for an additional 90 min, 21 g (0.10 mol) of 2-iodothiophene dissolved in 200 ml of pyridine was added dropwise during 15 min. The ether was distilled off during 4 h, since the consistency of the reaction mixture did not allow decantation, and during this period the temperature of the mixture rose to 80°C. After refluxing for 1 h, the mixture was allowed to stand over night. Work-up as described above yielded 13.2 g of a dark product. Combined VPC-mass spectrometry (5 % NPGS and 3 % OV17) showed it to consist of approximately 80 % biarenes and 20 % terarenes. The composition of the biheterocyclic fraction was 53 % of II, 44 % of III, and 3 % of I. At least five different terarenes were detected. One had a molecular weight of 239, containing three pyrrole rings, two had a m. wt. of 242, containing two pyrrole rings and one thiophene ring, and two had a m. wt. of 245, containing one pyrrole and two thiophene rings. Chromatography of the crude reaction product on a silica gel column yielded 2.1 g (13 %) of II, containing about 2 % of terarenes.

2-Iodo-1-methylpyrrole. To a mixture of 32.4 g (0.40 mol) of 1-methylpyrrole, 58.0 g (0.50 mol) of TMEDA and 100 ml of anhydrous ether, 550 ml 0.90 N ethereal butyllithium was added dropwise with stirring under nitrogen, and the mixture was then refluxed for 1 h. After cooling to −70°C, the solution was poured under nitrogen into a suspension of 101.6 g (0.40 mol) of iodine in 150 ml of anhydrous ether cooled to −70°C. The reaction mixture was stirred at this temperature for 1 h. After the temperature had risen to about 0°C, 350 ml of water was added dropwise. The work-up was also carried out under nitrogen. The ether phase was separated, washed with water, sodium bisulphite solution, sodium bicarbonate solution and again with water, and then dried over magnesium sulphate. 650 ml of an ethereal solution, which according to VPC analysis contained 67 mg/ml of 2-iodo-1-methylpyrrole, was obtained and was used directly in the coupling reactions, due to the high instability of the compound. Fractionation of 495 ml of the ethereal solution yielded 19.4 g (30 %) of 2-iodo-1-methylpyrrole, b.p. 73.5 – 75°C/13 mmHg, as a pale yellow liquid, which became completely black after a few days at room temperature, but could be kept for an extended period at −15°C under nitrogen. NMR ($CDCl_3$): $\tau_{CH_3} = 6.43$ ppm, $\tau_5 = 3.22$ ppm, $\tau_3 = 3.68$ ppm, $\tau_4 = 3.90$ ppm, $J_{35} = 1.9$ Hz, $J_{34} = 3.7$ Hz, $J_{45} = 2.9$ Hz. (Found: M. wt. 207; C 29.3; H 3.08; I 59.0; N 6.82. Calc. for C_5H_6IN (207.0): C 29.02; H 2.90; I 61.31; N 6.77.)

Reaction between 2-thienylcopper and 2-iodo-1-methylpyrrole. To 8.4 g (0.10 mol) of thiophene in 50 ml of anhydrous ether, 110 ml of 0.9 N ethereal butyllithium was added under nitrogen with stirring, and the mixture was refluxed for 15 min. After cooling, this solution was added dropwise with stirring to 19.0 g (0.13 mol) of cuprous bromide in 10 ml of anhydrous ether at room temperature and then stirred for 1 h. A mixture of 155 ml of an ethereal solution containing 0.050 mol of 2-iodo-1-methylpyrrole and 120 ml of pyridine was added during 20 min. The ether was distilled off during 3 h, and the reaction mixture refluxed for 3.5 h. Work-up as described in the reaction between 1-methyl-2-pyrrolylcopper and 2-iodothiophene yielded 5.9 g of a dark-coloured liquid. VPC (5 % NPGS, 100 – 240°C, 8°C/min) showed the following area percentages: II (42 %), I (54 %), III (1 %) and a terarene, most probably IV (3 %). In addition, peaks were observed in the VPC, which combined VPC-mass spectrometry indicated to be due to 2-bromo-1-methylpyrrole, 2-iodo-1-methylpyrrole and monobromo derivatives of II and III.

Reaction between 1-methyl-2-pyrrolylcopper and 3-iodothiophene. 1-Methyl-2-pyrrolylcopper was prepared from 8.1 g (0.10 mol) of 1-methylpyrrole, 14.0 g of TMEDA, 100 ml

of 1.09 N butyllithium, and 19.0 g of cuprous bromide, as described above. 10.5 g (0.050 mol) of 3-iodothiophene (containing less than 0.1 % of 2-iodothiophene, according to VPC analysis) in 150 ml of anhydrous pyridine was added, and the mixture stirred for 5 h at 75°C. Work-up as described above yielded 4.4 g of a liquid. VPC (5 % NPGS, 100 – 240°C, 8°C/min) combined with mass spectrometry showed the presence of 5 biheterocyclic and 4 terheterocyclic compounds. The relative areas for the "dimers" compared with the "trimers" were 7:3. The following compounds were formed (the figures in parenthesis indicating area percentages and retention times): III (12 %; 9.2 min), II (4 %; 11.0 min), XI (2 %; 11.1 min), IX (50 %; 11.7 min), X (2 %; 12.2 min), terarene M = 242 (1 %; 17.8 min), terarene XII (19 %; 18.4 min), terarene M = 245 (5 %; 18.9 min), terarene M = 245 (5 %; 29.6 min). Column chromatography on silica gel, using hexane and hexane:benzene (9:1) as eluents, followed by distillation, yielded 370 mg (4 %) of 1-methyl-2-(3-thienyl)pyrrole (IX), containing 10 % of terheterocycles, b.p. 115 – 120°C/0.6 mmHg.

1-Methyl-2-(3-thienyl)pyrrole (IX). The 1-methyl-2-pyrrolylcopper reagent was prepared as described above from 2.8 g (35 mmol) of *N*-methylpyrrole and 4.9 g of TMEDA in 100 ml of anhydrous ether, 45 ml 0.94 N ethereal ethyllithium, and 6.7 g (35 mmol) of cuprous iodide in 25 ml of ether. 7.4 g (35 mmol) of 3-iodothiophene in 18 g of quinoline was added, the ether distilled off, and the mixture heated for half an hour at 100 – 110°C. The usual work-up yielded 3.0 g of a dark oil. Chromatography on silica gel, using hexane as eluent, yielded 460 mg (8 %) of 1-methyl-2-(3-thienyl)pyrrole, m.p. 19 – 20.5°C, containing only traces of terheterocycles. NMR (DMSO): $\tau_{CH_3} = 6.33$ ppm. Pyrrolic resonances: $\tau_5 = 3.25$ ppm, $\tau_3 = 3.78$ ppm, $\tau_4 = 3.97$ ppm, $J_{35} = 1.9$ Hz, $J_{34} = 3.7$ Hz, $J_{45} = 2.6$ Hz. Thiophenic resonances: $\tau_5 = 2.47$ ppm, $\tau_2 = 2.57$ ppm, $\tau_4 = 2.74$ ppm, $J_{34} = 1.5$ Hz, $J_{25} = 3.0$ Hz, $J_{45} = 4.9$ Hz. (Found: M. wt. 163; C 65.4; H 5.42; N 8.43; S 19.6. Calc. for C_9H_9NS (163.2): C 66.22; H 5.56; N 8.58; S 19.64.)

1-Methyl-2-phenylpyrrole (XIII). This compound was prepared by a method analogous to that described for II from 24.3 g (0.30 mol) of 1-methylpyrrole, 42.0 g TMEDA, 320 ml 0.98 N butyllithium, 43.0 g (0.30 mol) of CuBr, and 30.6 g (0.15 mol) of iodobenzene in 250 ml of pyridine. The mixture was slowly heated to 100°C for 5 h, stirred at this temperature for 3 h, and then allowed to stand over night before work-up. 19.9 g of product was obtained after evaporation of the solvent. Combined VPC-mass spectrometry (5 % NPGS, 140 – 240°C; not programmed) showed it to consist of 93 % of XIII (retention time 10.8 min) and 6 % of III (7.6 min), about 1 % of a compound with m. wt. 245 (23.8 min), and less than 1 % of two terarenes with m. wt. 233 (one pyrrole ring; two phenyl rings) (26.5 min) and 236 (two pyrrole rings; one phenyl ring) (24.9 min). Fractional distillation gave 10.5 g of crystalline product, b.p. 91 – 98°C/1 mmHg, containing 94 % of XIII and 6 % III. Column chromatography on silica gel, using hexane as eluent, yielded 9.7 g (41 %) of 1-methyl-2-phenylpyrrole. Recrystallization from hexane gave white crystals, m.p. 51°C. Literature value:[15] 43 – 44°C. NMR (DMSO): $\tau_5 = 3.19$ ppm, $\tau_3 = 3.82$ ppm, $\tau_4 = 3.92$ ppm, $J_{34} = 3.6$ Hz, $J_{45} = 3.0$ Hz, $J_{35} = 1.8$ Hz, $\tau_{C_6H_5} = 2.66$ ppm, $\tau_{CH_3} = 6.46$ ppm.

Coupling experiments without iodoarenes. To 4.1 g (50 mmol) of 1-methylpyrrole and 7.0 g (60 mmol) TMEDA in 50 ml of anhydrous ether, 75 ml of 0.63 N butyllithium was added dropwise and the mixture refluxed for 1 h. At the same time, 75 ml of 0.63 N butyllithium was added to 4.2 g (50 mmol) of thiophene in 50 ml of anhydrous ether, and the mixture was stirred for 10 min. The two solutions were mixed and stirred for 20 min, and then, with stirring, added dropwise to 9.5 g (50 mmol) of cuprous iodide in 25 ml of anhydrous ether with ice-cooling. All operations were carried out under a nitrogen atmosphere. After stirring for 1 h at 0°C, 100 ml of 2 N hydrochloric acid was added dropwise during 30 min, and the mixture was stirred for an additional 30 min. The black viscous precipitate which had formed was filtered off, the ether phase washed with 1 N hydrochloric acid until no more precipitation occurred, then with sodium bicarbonate solution and water, and dried over magnesium sulphate. Evaporation of the ether yielded 2.5 g of a dark product, and analytical VPC (5 % NPGS, 140°C) showed the three different biarenes to be present in about the following proportions: 45 % of II, 40 % of III, and 15 % of I. Column chromatography on silica gel, using hexane as eluent, yielded first 280 mg of I, and then 870 mg (11 %) of II, which contained minor amounts (about 5 %) of 2-butyl-1-methylpyrrole, judging from its mass spectrum. Finally, continued elution with hexane:benzene (1:1) yielded 650 mg of II. In an experiment in which 1-methyl-2-

pyrrolyllithium (obtained from 8.1 g (0.10 mol) of 1-methylpyrrole, 14.0 g (0.12 mol) of TMEDA, 50 ml of ether, and 130 ml of 0.92 N ethyllithium), 2-thienyllithium (from 8.4 g (0.10 mol) of thiophene, 50 ml of ether and 130 ml (0.92 N) ethyllithium) and 14.3 g (0.10 mol) of cuprous bromide were used in the coupling, 1.92 g (12 %) of crude product was obtained which was shown by VPC to contain the biarenes in the proportions 43 % of II, 37 % of I, and 20 % of III. No terarenes could be detected.

1-Methyl-2-pyrrolyllithium and 2-iodothiophene. 14.7 g (70 mmol) of 2-iodothiophene was added dropwise with stirring to a solution of 1-methyl-2-pyrrolyllithium, prepared as described above from 5.7 g (70 mmol) of 1-methylpyrrole, 10.0 g (86 mmol) of TMEDA in 50 ml of ether, and 70 ml of 1.06 N butyllithium, cooled to −20°C. After stirring at this temperature for 15 min, the reaction mixture was poured onto solid carbon dioxide and worked up in the usual manner. 4.5 g (43 %) of an acid mixture, consisting of 70 % of 2-thiophenecarboxylic acid and 30 % of 5-iodo-2-thiophenecarboxylic acid, was obtained. The analysis was carried out by NMR (in DMSO), using the 4-hydrogen resonances of 2-thiophenecarboxylic acid at $\tau = 2.78$ ppm, and the singlet at $\tau = 2.55$ ppm from the 3- and 4-hydrogens of 5-iodo-2-thiophenecarboxylic acid. In an experiment carried out at 0°C, only 5-iodo-2-thiophenecarboxylic acid was isolated in low yield (8 %), m.p. 134 – 136°C after recrystallization from aqueous ethanol. Literature value:[24] m.p. 133 – 134°C. NMR ($CDCl_3$): $\tau_{COOH} = -1.23$ ppm, $\tau_3 = 2.50$ ppm, $\tau_4 = 2.72$ ppm, $J_{34} = 4.2$ Hz. VPC analysis of the neutral fraction indicated the presence of 2-iodothiophene and 2-iodo-1-methylpyrrole in the proportions 3:1.

2-Thienyllithium and 2-iodo-1-methylpyrrole. Ethereal butyllithium (40 ml, 0.70 N) was added dropwise with stirring to 2.5 g (30 mmol) of thiophene in 50 ml of anhydrous ether under nitrogen, and the solution stirred for 15 min. 6.2 g (30 mmol) of 2-iodo-1-methylpyrrole in 50 ml of anhydrous ether was added dropwise during 10 min, and the mixture was stirred for 10 min more, poured onto carbon dioxide, covered with ether, and worked up in the usual manner, yielding 2.8 g (73 %) of 2-thiophenecarboxylic acid with the same IR spectrum as an authentic sample. The mass spectrum of the acid product at 10 eV showed peaks at m/e 125, 210, and 254, the intensities of which were 2 %, 1 %, and 2 %, respectively, of the peak at $m/e = 128$ (2-thiophenecarboxylic acid). These peaks are ascribed to 1-methyl-2-pyrrolylcarboxylic acid, 2,2′-bithienyl-5-carboxylic acid, and 5-iodo-2-thiophenecarboxylic acid, respectively.

Phenyllithium and 2-iodothiophene. Ethereal phenyllithium was prepared in the usual manner from 15.7 g (0.10 mol) of bromobenzene, 1.4 g (0.20 mol) of lithium, and 100 ml of ether. 21.0 g (0.10 mol) of 2-iodothiophene in 50 ml of anhydrous ether was added to this solution during 10 min, and the mixture was stirred for an additional 10 min. Carbonation and the usual work-up yielded 7.1 g (55 %) of 2-thiophenecarboxylic acid with the same physical properties as an authentic sample. A mass spectrum at 10 eV, showed a peak at $m/e = 254$, ascribed to 5-iodo-2-thiophenecarboxylic acid, the intensity of which was 0.3 % of that of the peak at $m/e = 128$, ascribed to 2-thiophenecarboxylic acid.

Reaction between phenyllithium and 2-iodothiophene in the presence of TMEDA. To 110 ml of 0.8 N ethereal phenyllithium, 10.5 g (0.090 mol) of TMEDA in 25 ml of anhydrous ether was added dropwise at room temperature, and the mixture was stirred for 15 min. 14.7 g (0.070 mol) of 2-iodothiophene was added with stirring during 15 min, and then stirred for additional 10 min. The mixture was poured onto powdered carbon dioxide, covered with ether. When the temperature had risen to 0°C, water was added. The ether phase was extracted with water, and the combined aqueous phases acidified with 5 N hydrochloric acid, yielding 5.3 g (30 %) of 5-iodo-2-thiophenecarboxylic acid with the same physical properties as an authentic sample.

Reaction between 1-methyl-2-pyrrolyllithium and 3-iodothiophene in the presence of TMEDA. To a solution of 1-methyl-2-pyrrolyllithium prepared as above from 75 ml of 0.98 N butyllithium, 5.7 g (70 mmol) of 1-methylpyrrole, 10.0 g (86 mmol) of TMEDA, and 50 ml of ether, 14.7 g (70 mmol) of 3-iodothiophene in 50 ml of anhydrous ether was added dropwise during 15 min at −5 to −10°C. After additional 15 min, the reaction mixture was reacted with carbon dioxide and worked up in the usual manner, yielding 5.9 g of a mixture, consisting of 80 % 3-iodo-2-thiophenecarboxylic acid ($\tau_5 = 2.27$ ppm, $\tau_4 = 2.70$ ppm, $J_{45} = 5.1$ Hz in acetone) and 20 % 4-iodo-2-thiophenecarboxylic acid (τ_3 or $\tau_5 = 2.70$ ppm, τ_5 or $\tau_3 = 2.26$ ppm; $J_{35} = 1.4$ Hz in acetone). The shifts were compared with those of authentic samples.[25,26] The analyses were carried out by integration of appropriate NMR bands. VPC analyses were carried out on a Perkin-Elmer 900 gas

chromatograph or in connection with an LKB A-9000 mass spectrometer, using the following columns: 2 m × 1/8″, 5 % NPGS on chromosorb W, and 2.5 m × 1/8″, 3 % OV 17 on chromosorb Q. NMR spectra were recorded with a Varian A 60 NMR spectrometer. The elementary analyses were carried out at the Analytical Department of the Chemical Institute, University of Lund, and by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach.

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