was used (THF, 1:1 $LiAlH_4$) with a reaction time of 3.5 h. The alkaline extracts gave a yellow oil (35%), which recrystallized from ether to furnish compound **4** as colorless crystals, mp 224-225 °C. The acid extracts (pH ~2) produced a pale yellow solid (55%), which after recrystallization from ether yielded compound **3**, mp 134-138 °C, as white crystals.

**Reaction of 2 with $LiAlH_4$.** The sodium salt of **2** (167 mg) was added in small amounts to a stirred suspension of lithium aluminum hydride (57 mg) in dry ether (30 mL). The mixture was then refluxed for 2 h and worked up as described for the preparation of **5**. The isolated product (130 mg) was identified as *trans*-2-hydroxymethyl-1,2,3-triphenylaziridine (**5**).

**Acknowledgment.** This work was supported by Consiglio Nazionale delle Ricerche (Rome), Grant CT78.01193.03 (to N.U.) and Grant CT78.0100003 (to G.C.), for which we are grateful. The calculations were carried out using the IBM 370/145 computer at the C.C.U.C. of the University of Calabria.

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# Electrophilic Heteroaromatic Substitutions. 2.[1] Mechanism of the Side-Chain Halogenation of Polysubstituted α-Methylpyrroles with Molecular Chlorine

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*Received May 11, 1979*

**Abstract:** The mechanism of the α-side-chain chlorination with molecular chlorine in dichloromethane or chloroform solution at low temperatures and in the dark of polysubstituted α-methylpyrroles **1–4** has been investigated with regard to the nature of the reagent and to the fate of the attacking as well as the substituent halogen in the reaction products. Careful product analysis was carried out by radiochemical measurements (chlorine exchange), NMR spectra, standard halide ion titration, and preparative layer chromatography (PLC) techniques. The results suggest that the overall process consists of two main steps, i.e., the electrophilic nuclear attack and the subsequent rearrangement of the halogen to the side chain. Halogen migration from nucleus to side chain may occur from either the adjacent β or the vinylogous α′ position. The present data provide a considerable extension of the concept of nonconventional electrophilic halogenation of aromatic molecules into the field of pyrroles.

## Introduction

Side-chain halogenations of polysubstituted α-methylpyrroles have been known for a long time[3-5] and have been recognized as intermediate steps in the preparation of a number of pyrrole oligomers such as dipyrrylmethanes, dipyrrylmethines, and porphyrins.[1,5-7] However, very little attention has been paid to the mechanism of these reactions. In one instance, the side-chain chlorination with sulfuryl chloride was assumed to occur by a free-radical mechanism.[8]

In view of the relevance of these reactions for a deeper understanding of the chemistry of pyrroles we have undertaken a systematic investigation related to their course and mechanism. Some striking analogies[9] with the nonconventional electrophilic substitutions of highly activated methyl-substituted benzenes,[10] naphthalenes,[11] benzothiophenes, and benzofurans[12] have led us to the hypothesis that similar reaction mechanisms also apply to appropriately substituted pyrroles under suitable conditions.

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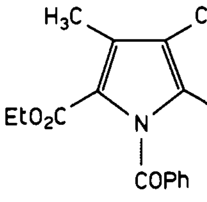
**Table I.** Effects of Light and Radical Scavengers on the Chlorination of Pyrrole **1** in Dichloromethane Solution at −28.0 ± 0.5 °C[a]

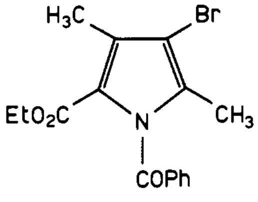
| conditions | time, s | mL $Na_2S_2O_3$[b] | % reaction |
|---|---|---|---|
| dark | 2.5 | 0.740 | 83.30 |
| | 3.1 | 0.690 | 84.42 |
| | 3.8 | 0.650 | 85.33 |
| | 4.0 | 0.620 | 86.00 |
| dark[c] | 2.2 | 0.790 | 82.17 |
| | 2.7 | 0.730 | 83.52 |
| | 3.0 | 0.700 | 84.20 |
| | 4.0 | 0.600 | 86.46 |
| daylight | 1.9 | 0.830 | 81.26 |
| | 2.2 | 0.790 | 82.17 |
| | 3.2 | 0.680 | 84.65 |
| daylight[c] | 2.1 | 0.800 | 81.94 |
| | 2.5 | 0.760 | 82.84 |
| | 3.7 | 0.580 | 86.91 |

[a] Initial concentrations: $[Cl_2] = 1.157 \times 10^{-4}$ M; $[\mathbf{1}] = 2.317 \times 10^{-4}$ M. [b] A $1.047 \times 10^{-3}$ M solution was used. [c] In the presence of $1.157 \times 10^{-}$ M galvinoxyl.

In this paper we wish to report on the dark chlorination of compounds **1–4** with molecular chlorine in aprotic solvents (such as $CH_2Cl_2$). The results not only support the view that the reactions proceed by a mechanism involving electrophilic attack of the reagent on the ring and subsequent rearrangement to the side chain but also reveal new interesting features for the pyrrole ring.



**1**



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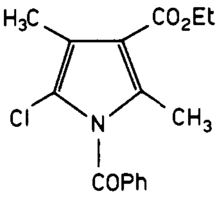
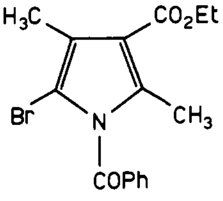


**2**



**4**

## Results and Discussion

It should be noted at once that the substrates used in this investigation (**1–4**) have been planned with a number of structural features which appeared to be suitable for the interpretation of the results: (1) the absence of any unsubstituted ring position prevents competition with nuclear substitution; (2) the *N*-benzoyl group rules out any intermediacy of the conjugate base at the pyrrole nitrogen; (3) there is only one side chain (methyl) for each of the $\alpha$- and $\beta$-type positions; (4) the nuclear halogen has leaving-group properties.

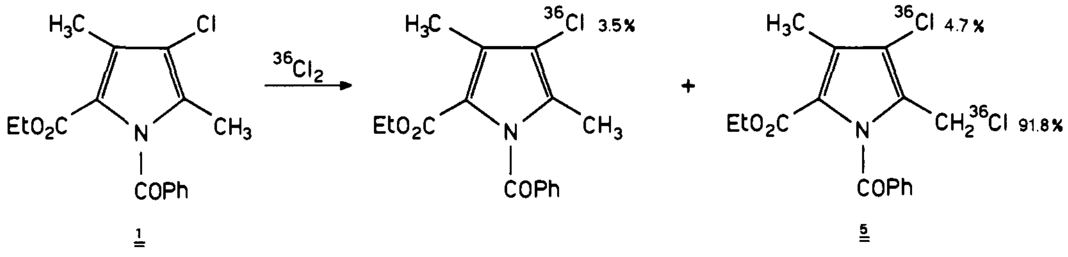
**Nature of the Reaction.** All substrates have been found to react with molecular chlorine (solvent: $CH_2Cl_2$ or $CHCl_3$) very rapidly, at temperatures as low as −28 °C in complete exclusion of light. They undergo side-chain substitution exclusively at the $\alpha$ position to extents ranging between 90 and 99%. Chlorine was usually kept short relative to substrate (molar ratio about 1:3) in order to minimize the formation of polychloromethyl derivatives.

Under the stated reaction conditions there is little chance for the reaction to involve a radical mechanism since very rapid electrophilic halogenations effectively compete with radical paths in the dark.[10b] This is further supported by the finding that times at a given reaction percent (Table I) are unaffected by sunlight and by such a strong radical scavenger as galvinoxyl.[13]

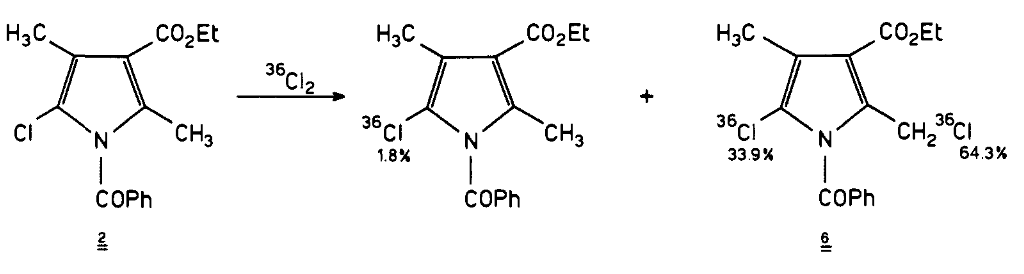
Furthermore, side-chain chlorination is roughly as fast as nuclear chlorination at the pyrrole ring and the *N*-benzoyl group is markedly rate depressing for both reactions.[9] All this evidence and the general analogy in behavior with the side-chain chlorination of highly reactive polyalkylbenzenes[10a] and 2,3-dimethylbenzothiophene[12] consistently suggest that the side-chain halogenation of the substrates herein investigated is electrophilic in nature. The general mechanism proposed for such nonconventional electrophilic reactions essentially consists of two main steps,[10a] i.e., the attack of the electrophile on the ring leading to the formation of a $\sigma$ adduct as an intermediate and the migration of chlorine or another moiety from nucleus to side chain.

Our product analyses, to be reported below, are consistent with the theory.

**Tracer Experiments.** The fate of chlorine in the reaction of pyrroles **1** and **2** was disclosed by tracer experiments with $^{36}Cl_2$. The results of two typical experiments are summarized in Table II and illustrated by eq 1 and 2 showing the distribution



(1)



(2)

**Table II.** Chlorination of Pyrroles **1** and **2** with $^{36}Cl_2$ in $CHCl_3$ at −25 °C in the Dark

| | **1**[a] | **2**[b] |
|---|---|---|
| overall conversion of $Cl_2$ to the side chain, % | 99.5[c] | 90.5[c] |
| radiochemical yield, % | 96.0[d] | 93.7[d] |
| % distribution of $^{36}Cl_2$: | | |
| side-chain chlorine | 91.8 | 64.3 |
| nuclear chlorine (exchange only) | 3.5[e] | 1.8[e] |
| nuclear chlorine (exchange in the side-chain substituted product) | 4.7[f] | 33.9[g] |
| overall nuclear chlorine | 8.2[h] | 35.7[h] |

[a] Pyrrole **1**, 0.74 mmol in 3 mL of $CHCl_3$; $^{36}Cl_2$, 0.36 mmol; initial radioactivity, 21.8 μCi; maximum expected radioactivity in chloroorganic products, 10.9 μCi. [b] Pyrrole **2**, 0.88 mmol in 5 mL of $CHCl_3$; $^{36}Cl_2$, 0.495 mmol; initial radioactivity, 29.7 μCi; maximum expected radioactivity in chloroorganic products, 14.85 μCi. [c] From chloride ion determinations. [d] Overall nuclear + side-chain chlorine. [e] Radioactivity determined for the recovered starting pyrrole after debenzoylative treatment with EtONa in EtOH. [f] Radioactivity determined in the side-chain substituted product after debenzoylative nucleophilic substitution with EtONa in EtOH. [g] Calculated from the overall nuclear chlorine[h] less the nuclear chlorine from exchange only.[e] [h] From radioactivity determinations of the ether extract.

**Table III.** Reaction of Pyrroles **3** and **4** with $Cl_2$ in $CH_2Cl_2$ at −20 °C in the Dark

| | | **3**[a] | | **4**[b] |
|---|---|---|---|---|
| pyrrole conversion, % | | 98.4[c] | | 95.9[d] |
| halogen composition in the recovered starting pyrrole, % | Br | 100[e] | Br | 100[e] |
| composition of the side-chain halogen in | Br | 0 | Br | 69.5 |
| the side-chain substituted products, % | Cl | 100 | Cl | 30.5 |
| composition of the nuclear halogen in the | Br | 98.3[f] | Br | 18[g] |
| side-chain substituted products | Cl | 1.7[f] | Cl | 67[g] |
| | | | Cl | 15[g] |

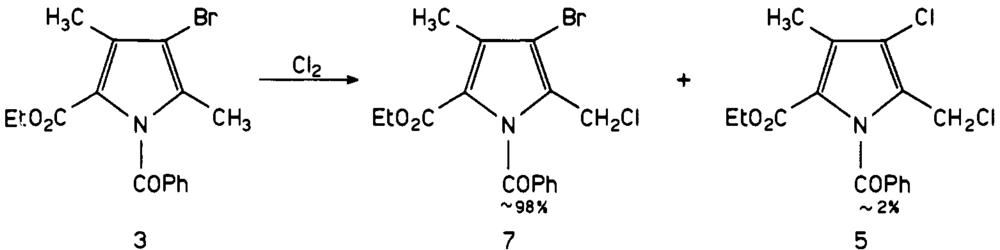
[a] Pyrrole **3**, 1.57 mmol in 20 mL of $CH_2Cl_2$; $Cl_2$, 8.50 mL of a 0.150 M solution. [b] Pyrrole **4**, 1.49 mmol in 20 mL of $CH_2Cl_2$; $Cl_2$, 3.90 mL of a 0.118 M solution. [c] As based on side-chain halogen determination. [d] As based on the recovery of the pyrrole **4**. Owing to the side reactions described in the Experimental Section, the total apparent side-chain halogen was found to be 107.8%. [e] Determination carried out after debenzoylative treatment with EtONa in EtOH. [f] Halogen analysis of the side-chain substituted products after debenzoylative nucleophilic substitution with EtONa in EtOH. [g] These figures refer to pyrroles **9**, **8**, and **6**, respectively, as based on NMR determinations.

of $^{36}Cl$ in the reaction products. Both substrates appear to undergo plain exchange without accompanying side-chain substitution as well as exchange and side-chain substitution at the α-methyl group. Exchange is limited with pyrrole **1** (overall 8.2%) and more extensive with pyrrole **2** (overall 35.7%), in agreement with the greater reactivity of the α, relative to the β, position with respect to electrophilic reagents.[14] Although a true α:β reactivity ratio cannot be assessed from these data, it is not surprising that the β position appears to be appreciably reactive in pyrrole **1** in line with the notion that the α:β reactivity ratio is lowest in pyrrole out of the five-membered heteroaromatic rings.[14] It will be noted that the side-chain chlorine picks up a major share (91.8%) of radioactivity in the reaction of pyrrole **1** despite the small extent of exchange, i.e., 4.7%. If we assume that the side-chain chlorine comes from a primary attack on ring carbon 4 followed by rearrangement, no more than 4.7% can be expected in the adjacent side chain. Therefore, the remaining $^{36}Cl$ must have a different origin. Starting from pyrrole **2**, the simultaneous presence of large amounts of $^{36}Cl$ at both nuclear and side-chain positions and the very limited extent of plain exchange (1.8%) suggest that chlorine could also originate from an α′-to-side-chain migration.

That side-chain halogen at an α-methyl group may derive from both the adjacent β and from the other α position is further supported by the behavior of pyrroles **3** and **4**.

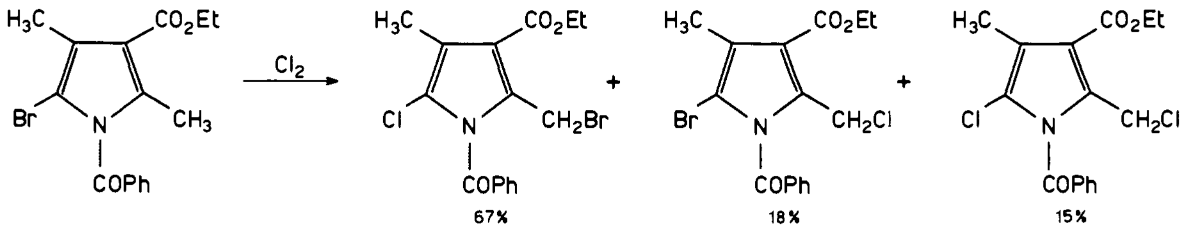
**The Halogen Element Effect.** Additional significant information was obtained with pyrroles **3** and **4** by investigating the effect of replacing Cl by Br with respect to pyrroles **1** and **2**. The results of two typical experiments are summarized in Table III and illustrated by eq 3 and 4. The reaction of **4** with $Cl_2$ unequivocally shows that bromine extensively undergoes an α′-to-α migration from nucleus (α′-position) to side chain (α position). It is closely similar to the reaction of the same substrate with hydrogen chloride in aprotic solvents leading to replacement of the nuclear Br by hydrogen and extensive migration of the halogen to the side chain.[15] These findings strongly support the hypothesis that on chlorination of **1** most of the side-chain chlorine comes from a primary attack of the electrophilic reagent at the α′-position occupied by the ethoxycarbonyl group. The behavior of **3** is also consistent with this peculiar change since most β-Br is *not* replaced by Cl in the reaction product.

**Reaction Mechanism.** The above evidence suggests a reaction mechanism along the lines illustrated in Schemes I and



3 7 5

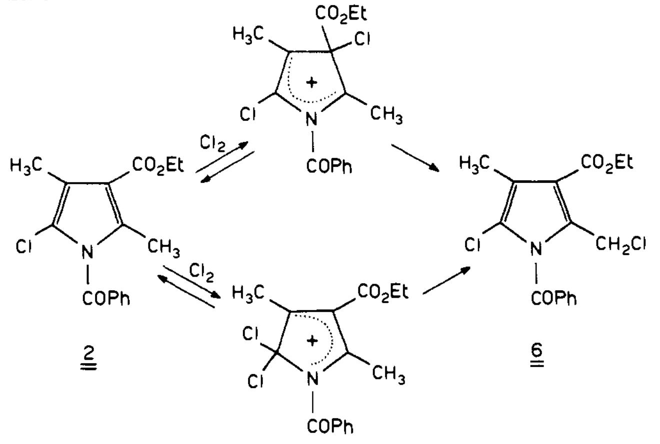
(3)



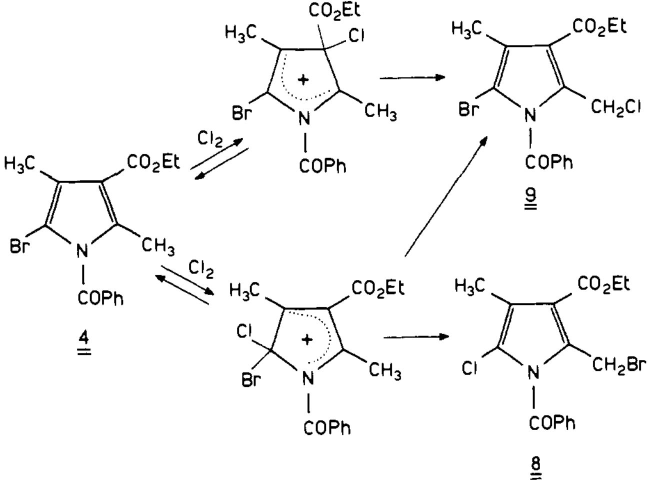
4 8 9 6

(4)

Scheme I



Scheme II



11 for pyrroles **2** and **4**, respectively. Pyrroles **1** and **3** have less tendency to utilize the reaction path via position $\beta$. With such substrates the side-chain substitution appears to derive nearly exclusively from a primary attack on an ethoxycarbonyl-bearing $\alpha$ position. Attack on the position bearing the $\beta$-methyl group is not excluded but there is no indication that chlorine is able to migrate from that position to the $\alpha$ side chain. Undoubtedly, the complete absence of any side-chain substituted product at the $\beta$-methyl group[16] stands for a very poor tendency of the halogen to migrate from a nuclear $\alpha$ to that side-chain $\beta$ position. It also confirms the ineffectiveness of a mechanism of the quinobenzylic type, an essentially homolytic path involving an in situ rearrangement from nucleus to side chain, under the conditions suitable for electrophilic nonconventional reactions.[17]

In polymethylbenzene systems ring positions occupied by halogen are far less available for attack by electrophilic chlorine than the other positions.[10c,d,f] The striking feature of the pyrrole substrates is the finding that the electrophile, such as molecular chlorine and proton,[15] is able to attach itself to positions occupied by electron-withdrawing substituents (Cl, Br, $CO_2Et$). The distinctly greater tendency of the electrophile to form a bond when the substituent is $CO_2Et$ rather than Cl or Br (see eq 1-4) can presumably be correlated to the lower $\sigma_I$ value for $CO_2Et$ (0.31 vs. 0.45 for Br and 0.47 for Cl). Furthermore, the electron-delocalized portion of the transition state leading to the cationic intermediate is expected to be more highly stabilized in the presence of more negative (or less positive) $\sigma^+$ substituents.[18]

The reaction of **4**, eq 4, provides evidence for the greater migration aptitude of Br relative to Cl from the geminal dihalogeno $\alpha'$ position of the intermediate $\sigma$ complex. This is so whether part of **9** comes from the $\sigma$ complex at the $\beta$ position or not and whether pyrrole **6** is formed from pyrrole **9** or not. The minimum migratory Br/Cl ratio would be $67/(18 + 15) = 2$, but could be appreciably higher than this.

Two minor reaction products deserve a separate comment. The $\beta$-chloro-$\alpha$-chloromethyl derivative **5** (less than 2%) from pyrrole **3** may form from the $\beta$-bromo-$\alpha$-chloromethyl derivative **7** (>98%) by subsequent Br/Cl nuclear exchange. Similarly, pyrrole **6** may derive from **4**, **8**, or **9** in a number of ways involving Br/Cl exchange prior to or after the side-chain process has taken place. These reactions have not been investigated any further.

In previous work the mechanism of the decomposition of the $\sigma$ adduct into the side-chain substituted product has been discussed at some length.[10a,b,e,12] Any halogen migration from ring to side chain should account for a proton loss at some stage and for the poor leaving group nature of the halogen as a cationic species. The latter point is supported by the mechanism of dipyrrylmethine formation[1] and by the present finding that plain nuclear halogen exchange in the pyrroles examined occurs to a very limited extent. The extensive formation of **8** from **4** would suggest an intramolecular migration of the bromo group of some sort. The migration could presumably occur via a tight ion pair resulting from an ionization of the C-Br bond of the $S_N1$ type. As a part of a program to obtain further information on the migration mechanism a subsequent paper will deal with direct evidence for the formation of the $\sigma$ adduct.

### Experimental Section

**General.** $^1H$ NMR spectra were obtained on a JEOL JNM-C60 HL spectrometer using tetramethylsilane as the internal standard. Chromatographic separations were carried out either on pretreated[1] silica gel (Merck, reinst) or on preparative silica 60 $F_{254}$ plates (Merck, 20 × 40 cm, layer thickness 2 mm). For the thin layer chromatographic analyses Merck $F_{254}$ silica plates were used. Radioactivity determinations were carried out on a Mark II (Nuclear Chicago) liquid scintillation spectrometer. Microanalyses were performed by the Laboratorio di Microanalisi of the Istituto Superiore di Sanità, Roma. Melting points are uncorrected. All experiments referred to as "in the dark" were carried out in a conventional darkroom (red lamp).

**Materials.** Benzene,[19] chloroform,[20] dichloromethane,[20] ethanol,[21] and ethyl acetate[22] were purified and dried as described in the given references. Diethyl ether ($Et_2O$) and tetrahydrofuran (THF) were distilled from the sodium ketyl of benzophenone and stored over sodium wire. Chlorine (Fluka, puriss.) was used as received; $^{36}Cl_2$ (specific activity 60 $\mu$Ci $mmol^{-1}$) was obtained from the Radiochemical Centre (Amersham, England). Stock solutions of chlorine in $CH_2Cl_2$ or $CHCl_3$ were prepared in Schlenk burets and stored under argon away from light. Galvinoxyl was prepared according to Kharasch and Joshi.[23]

**Pyrrole Derivatives. 1-Benzoyl-4-chloro-2-ethoxycarbonyl-3,5-dimethylpyrrole (1) and 1-benzoyl-2-ethoxycarbonyl-3,5-dimethylpyrrole (10)** were prepared as described previously.[9]

**1-Benzoyl-4-chloro-5-chloromethyl-2-ethoxycarbonyl-3-methylpyrrole (5).** This compound, which had been obtained previously[9] as a byproduct in the chlorination of **10**, was prepared as follows. A 0.525 M solution of chlorine in $CHCl_3$ (0.45 mL) was diluted with 5 mL of anhydrous $Et_2O$ and added dropwise under stirring to a solution of **1** (0.072 g, 0.236 mmol) in 15 mL of $Et_2O$ at −18 °C in the dark. After the addition was complete, the cooling bath was removed and the reaction mixture allowed to stand at room temperature for ca. 20 min. Any volatile material was then stripped off in vacuo and the residue, 0.085 g of a yellow oil, was chromatographed on 30 g of silica gel, benzene being the eluent, yield 0.083 g (90.5%), mp 45-46 °C (lit.[9] mp 45-46 °C).

**Ethyl 2,4-dimethylpyrrole-3-carboxylate (11)** was obtained by protodecarboxylation of 4-ethoxycarbonyl-3,5-dimethylpyrrole-2-carboxylic acid[24] as follows: 10.6 g (0.05 mol) of this acid was dissolved in warm 95% EtOH (430 mL) and treated with 37% HCl (75 mL) by gradual addition; the resulting mixture was refluxed for 1 h and, after cooling, neutralized with aqueous $Na_2CO_3$. The alcohol was then removed under reduced pressure and the precipitate formed extracted with $CHCl_3$. From the extracts an oily, dark solid was obtained which was recrystallized from $Et_2O$-petroleum ether (bp 30-50 °C), mp 74-75 °C (lit.[25] mp 75-76 °C), yield 5.4 g (77%). This procedure was preferred over the usual thermal decarboxylation, being simpler and giving better yields.

**1-Benzoyl-3-ethoxycarbonyl-2,4-dimethylpyrrole (12).** Compound **11** (5.0 g, 30 mmol) was dissolved in 400 mL of dry THF and added dropwise at room temperature under nitrogen to 1.2 g (30 mmol) of KH.[26] After the evolution of hydrogen had ended, freshly distilled benzoyl chloride (4.2 g, 30 mmol) was added at once. After 1 h of stirring at room temperature, the mixture was transferred into a separatory funnel and thoroughly shaken with water and $CH_2Cl_2$. The usual workup afforded a yellow, waxy product which was purified by chromatography, a mixture of benzene and ethyl acetate (99:1 v/v) being the eluent: mp 63.5-64 °C; yield 5.25 g (65%); $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 (t, 3 H, $J = 6.75$ Hz, $\beta$-$CO_2CH_2CH_3$), 2.19 (s, 3 H, $\beta$-$CH_3$), 2.79 (s, 3 H, $\alpha$-$CH_3$), 4.32 (q, 2 H, $J = 6.75$ Hz, $\beta$-$CO_2CH_2CH_3$), 6.55 (br s, 1 H, $\alpha$-H), 7.57 (m, 5 H, $COC_6H_5$). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.69; H, 6.22; N, 5.04.

In a similar way **1-benzoyl-4-bromo-2-ethoxycarbonyl-3,5-dimethylpyrrole (3)** was prepared in 59% yield starting from ethyl 4-bromo-3,5-dimethylpyrrole-2-carboxylate:[27] mp 63.5-64 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (t, 3 H, $J = 7.3$ Hz, $\alpha$-$CO_2CH_2CH_3$), 2.22 (s, 3 H, $\alpha$-$CH_3$), 2.31 (s, 3 H, $\beta$-$CH_3$), 3.87 (q, 2 H, $J = 7.3$ Hz, $\alpha$-$CO_2CH_2CH_3$), 7.45 (m, 5 H, $COC_6H_5$). Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; Br, 22.82; N, 4.00. Found: C, 54.87; H, 4.60; Br, 22.74; N, 4.03.

**1-Benzoyl-5-chloro-3-ethoxycarbonyl-2,4-dimethylpyrrole (2).** A stirred solution of **12** (1.0 g, 3.3 mmol) in 140 mL of $CH_2Cl_2$, cooled at −78 °C, was treated in the dark under nitrogen with 3.3 mmol of $Cl_2$ in 100 mL of the same solvent over a 5-h period. Any volatile material was then removed under reduced pressure at room temperature and the residue was chromatographed (120 g of silica gel, benzene). A first fraction yielded 56 mg (5%) of a waxy product which was assigned the structure of 1-benzoyl-5-chloro-2-chloromethyl-3-ethoxycarbonyl-4-methylpyrrole (**6**). A second fraction yielded **2** (0.5 g, 50%) as a white, crystalline powder; mp 64-65 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (t, 3 H, $J = 6.75$ Hz, $\beta$-$CO_2\ CH_2CH_3$), 2.24 (s, 3 H, $\beta$-$CH_3$), 2.47 (s, 3 H, $\alpha$-$CH_3$), 4.30 (q, 2 H, $J = 6.75$ Hz, $\beta$-$CO_2CH_2CH_3$), 7.75 (m, 5 H, $COC_6H_5$). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.57. Found: C, 62.78; H, 5.32; N, 4.50.

**1-Benzoyl-5-chloro-2-chloromethyl-3-ethoxycarbonyl-4-methylpyrrole (6).** To a stirred solution of **2** (0.4 g, 1.3 mmol) in $CH_2Cl_2$ (4.5 mL) 3.3 mL of a 0.33 M solution of $Cl_2$ in the same solvent was added at −25 °C in the dark. The progress of the reaction was followed by testing (starch-iodide paper) for residual chlorine in the vapor phase over the reaction mixture. As soon as the reaction was complete, any volatile material was removed under reduced pressure at room temperature and the residue—a violet, oily solid—was chromatographed (50 g of silica gel, benzene). Product **6** was eluted first: 0.22 g, 59%; $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 (t, 3 H, $J = 6.75$ Hz, $\beta$-$CO_2CH_2CH_3$), 2.24 (s, 3 H, $\beta$-$CH_3$), 4.38 (q, 2 H, $J = 6.75$ Hz, $\beta$-$CO_2CH_2CH_3$), 5.15 (s, 2 H, $\alpha$-$CH_2Cl$), 7.57 (m, 5 H, $COC_6H_5$). Anal. Calcd for $C_{16}H_{15}Cl_2NO_3$: C, 56.48; H, 4.44; N, 4.11. Found: C, 55.89; H, 4.40; N, 4.32. This compound was a low-melting solid which could neither be recrystallized nor stored because of its rapid transformation into polypyrrolic compounds. A second fraction yielded 35 mg (8%) of the starting material. Polypyrrolic compounds (not examined) were also formed.

**1-Benzoyl-5-bromo-3-ethoxycarbonyl-2,4-dimethylpyrrole (4).** A solution of bromine (0.19 mL, 3.7 mmol) in anhydrous $Et_2O$ (3 mL) was added over 5 min to a stirred ether solution of **12** (1.0 g, 3.7 mmol, in 25 mL of $Et_2O$) at −20 °C in the dark. After 1-h stirring at −20 °C, the reaction mixture was brought to dryness under reduced pressure at room temperature. The crude product was recrystallized from EtOH; mp 80-81 °C; yield 0.9 g (70%); $^1H$ NMR ($CDCl_3$) $\delta$ 1.39 (t, 3 H, $J = 7.2$ Hz, $\beta$-$CO_2CH_2CH_3$), 2.25 (s, 3 H, $\beta$-$CH_3$), 2.46 (s, 3 H, $\alpha$-$CH_3$), 4.36 (q, 2 H, $J = 7.2$ Hz, $\beta$-$CO_2CH_2CH_3$). 7.67 (m, 5 H, $COC_6H_5$). Anal. Calcd for $C_{16}H_{16}BrNO_3$: C, 54.87; H, 4.60; Br, 22.82; N, 4.00. Found: C, 54.45; H, 4.56; Br, 22.68; N, 3.89.

**Chlorination Experiments (with Ordinary $Cl_2$ and with $^{36}Cl_2$).** The chlorination experiments with pyrroles **1** and **2** were carried out in the apparatus shown in Figure 1. A vial provided with a break-seal and containing a known amount of chlorine was sealed to side arm A. From 3 to 5 mL of a ca. 0.1 M solution of the pyrrole in $CHCl_3$ or $CH_2Cl_2$ was placed in B and the apparatus connected to a vacuum line. The solution was then thoroughly outgassed by repeated freeze-pump-thaw cycles before sealing off the vessel. The break-seal tip in side arm A was subsequently broken (dark room) thus allowing the chlorine gas to condense into the well-shaken pyrrole solution maintained at ca. −40 °C. When mixing was complete, the apparatus was immersed into a cooling bath at −25 °C and left standing for ca. 3 h, after which it was connected again to the vacuum line; the seal in B was broken and any volatile material (HCl and solvent) removed by a bulb-to-bulb distillation. The residue was taken up in anhydrous $Et_2O$, subjected to bulb-to-bulb distillation once again, and finally analyzed as described below.

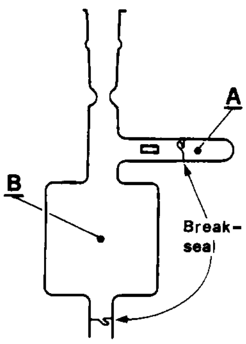


Figure 1. Chlorination reactor.

As for pyrroles **3** and **4**, chlorination was performed in the dark under dry argon by dropwise addition of an appropriate volume of a freshly titrated $Cl_2$ solution to the solution of the pyrrole held at −20 °C. At the end of the reaction, the mixture was brought to dryness in vacuo and the residue treated as described above before analysis.

**Product Analysis. General Procedure.** For the product analyses to be reliable the $\alpha$-halogenomethylpyrroles were converted into the less reactive $\alpha$-ethoxymethyl derivatives as quickly as possible. The residue from the bulb-to-bulb distillation was dissolved in anhydrous $Et_2O$ and treated with an excess (ca. 20-fold) of freshly prepared EtONa (ca. 1 M solution in absolute EtOH). This treatment also removes the *N*-benzoyl group quantitatively.[28] After 6-min stirring at room temperature, the mixture was cooled to −18 °C and treated with water (3-5 mL) and the excess alkali exactly neutralized with sulfuric acid (0.3-0.7 M). Blank experiments showed that nuclear halogen does not react with ethoxide under these conditions. The two layers were then separated and washed twice with the fresh solvents and the washings combined to the respective solutions. The halide ion content of the aqueous solutions (side-chain halogen) was determined argentometrically (in the experiments with $^{36}Cl_2$ also radiometrically) and the composition of the ether solution by PLC, 7:3 benzene-hexane being the eluent. In the experiments with $^{36}Cl_2$ the radioactivity of the whole ether solution as well as of some of the chromatographically isolated compounds was measured; in those involving bromine-containing substrates the compounds isolated from the ether solution were analyzed for the nuclear halogen by elemental analysis. In some cases the composition of the reaction mixture was also checked by NMR spectroscopy prior to treatment with ethanolic sodium ethoxide. Radioactivity determinations were found to be accurate to ±4.5%, argentometric halide ion determinations to ±1%.

**Chlorination of 1.** As shown by the data in Table IV, chlorination of **1** in $CH_2Cl_2$ or $CHCl_3$ quantitatively affords **5**, which can be converted into the corresponding debenzoylated $\alpha$-ethoxymethyl derivative in nearly quantitative yield. Also, the recovery of unreacted (debenzoylated) starting material was always quantitative. The results of product analysis of a typical chlorination experiment using $^{36}Cl_2$ are presented in Table II.

**Chlorination of 2.** The radioactivity of nuclear chlorine in product **6** and in unreacted **2** was measured on the whole ether solution and on the debenzoylated **2** as isolated from the same solution (or a portion thereof) by PLC. Neither the isolation of product **6** nor that of the corresponding debenzoylated ethoxymethyl derivative could be used for analytical purposes because of their fast decomposition.

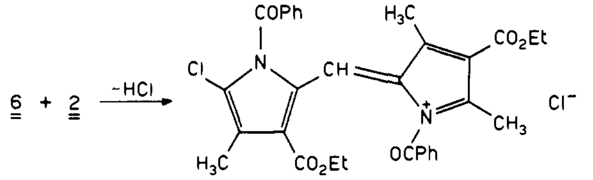
The analytical results are reported in Table II. In order to better appreciate these data, it should be noted that the reaction of **2** with chlorine to give **6** is followed by condensation reactions of the product with itself or with unreacted **2**. Although such subsequent reactions are slowed down by the presence of the *N*-benzoyl group, the time

**Table IV.** Chlorination of **1** at −25 °C in the Dark

| **1**, mmol | $Cl_2$, mmol | side-chain substituted product analysis: isolated product[a] mmol | isolated product[a] % yield | side-chain chlorine[b] % yield |
|---|---|---|---|---|
| 0.236 [c] | 0.236 | 0.235[d] | 99.6 | 98.7 |
| 0.582[e] | 0.318 | 0.316 | 99.4 | 98.4 |
| 0.464[f] | 0.245 | 0.243 | 99.2 | 101.2 |

[a] Isolated, unless noted otherwise, as ethyl 4-chloro-5-ethoxymethyl-3-methylpyrrole-2-carboxylate: mp 109–110 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (t, 3 H, $J = 7.02$ Hz, $\alpha'$-$CH_2OCH_2CH_3$), 1.37 (t, 3 H, $J = 7.02$ Hz, $\alpha$-$CO_2CH_2CH_3$), 2.30 (s, 3 H, $\beta$-$CH_3$), 3.53 (q, 2 H, $J = 7.02$ Hz, $\alpha'$-$CH_2OCH_2CH_3$), 4.34 (q, 2 H, $J = 7.02$ Hz, $\alpha$-$CO_2CH_2CH_3$), 4.50 (s, 2 H, $\alpha'$-$CH_2OCH_2CH_3$), 9.62 (br s, 1 H, NH). Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.98; H, 6.67; N, 5.42. [b] By argentometric determination of the chloride ion in the aqueous phase. [c] In 3 mL of $CH_2Cl_2$. [d] Isolated as such; treatment with $EtO^-$ afforded the debenzoylated ether in 99.1% yield. [e] In 5 mL of $CH_2Cl_2$. [f] In 4 mL of $CHCl_3$.

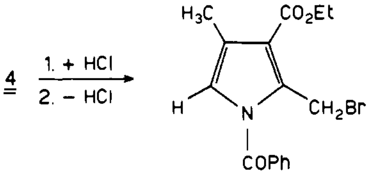
required by the workup procedures and PLC analysis does not allow the isolation of product **6** in yields any better than 60% or lower. A useful result of PLC analysis is that recovery of the excess **2** used in the chlorination experiments is markedly less than expected and shows that the condensation of **6** with unreacted **2** (eq 5) is more likely to occur than the self-condensation reaction. This means that any radiochemical losses caused by this reaction concern exclusively the side-chain chlorine of **6** since the nuclear chlorine atom of **2** undergoing displacement (eq 5) is made only slightly radioactive by a limited degree of exchange (Table II). The fact that the radiochemical yield is found to be as high as 93.7% (Table II) shows that the analytical procedure used for side-chain chlorine is fast enough to keep the radiochemical loss (as HCl) within reasonably low limits (no greater than 6.3%).



(5)

**Chlorination of 3.** In this case, PLC of the ether solution allowed separation and quantitative recovery of debenzoylated **3** and of the debenzoylated ethoxymethyl derivatives of the reaction products. The results of nuclear halogen analysis together with that of side-chain halogen are reported in Table III.

**Chlorination of 4.** This reaction is complicated by the occurrence of consecutive condensation reactions analogous to those referred to in the chlorination of **2** and of a parallel reaction involving **4** and the HCl formed[15] which increases both the side-chain bromine and the number of the possible oligomerization reactions. In order to keep these side reactions to a minimum, immediately after chlorine was used up the reaction mixture was evaporated under vacuum. An accurate determination was only possible for the side-chain halogen and the halogen present in the unreacted **4**, because the chemical lability of the debenzoylated ethoxymethyl derivatives of the reaction products prevented their isolation and separation. A qualitative and roughly quantitative analysis of the composition of the reaction mixture was made by NMR spectroscopy on an exactly known aliquot of the ether solution prior to treatment with EtONa (Table III).



**Effects of Light and Radical Scavengers.** Because of the very high reactivity of the pyrrole derivatives examined, a batchwise procedure, similar to that described previously,[29] was adopted in order to measure reaction percents at given times. Unfortunately, the lowest accessible percents by this procedure were no less than 80. The apparatus was a modification of the one reported previously[29] using two pressure-equalizing funnels (for successive rapid additions to the reaction vessel), one of which was thermostated. Both pressure-equalizing arms were provided with stopcocks in order to minimize the volume above the reaction mixture and to prevent moisture from reaching the reaction mixture. In the funnels were placed the chlorine solution and 5 mL of a saturated solution of KI in 50% aqueous ethanol. All the experiments were carried out at −28 ± 0.5 °C (MK 70 ultracryostat) and run at least in triplicate. Concentrations were corrected for solvent contraction.[30] The batch experiments were repeated at varying reaction times. Typical data for pyrrole **1** are collected in Table I.

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