MECHANISM OF CINEAMINATION OF CHLOROETHYNYLPYRAZOLES

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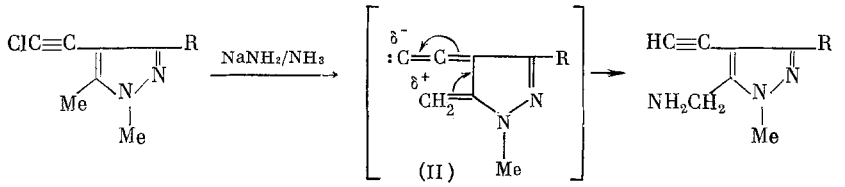
The cinesubstitution of the halogen in 4-chloroethynyl-5-methylpyrazoles (I) by the amino group in the presence of $NaNH_2$ in liquid ammonia has been described, and it has been suggested that the intermediate in this reaction is the vinylidenecarbene (II), formed by the α,ω-dehydrochlorination of (I) [1,2]

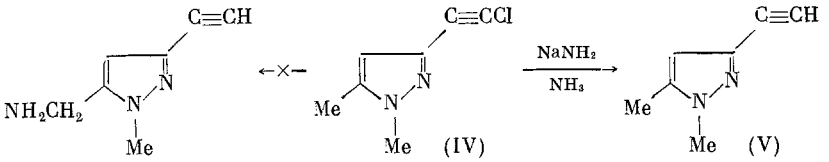


(I)
R = H (a), Me (b).

(II)

(III)

For α,ω-dehydrochlorination to occur, it is necessary that the electron pair at the center resulting from the deprotonation of the CH_3 group at C^5 should be conjugated with the chloroethynyl group. In the absence of such conjugation, dehydrochlorination will not occur, and hence cinesubstitution will not be possible. Accordingly, 3-chloroethynyl-1,5-dimethylpyrazole is not aminated by $NaNH_2$ in ammonia, but is simply dechlorinated to 3-ethynyl-1,5-dimethylpyrazole (V) in 65% yield



(IV) (V)

Undeniable proof of this mechanism would be trapping of the carbene (II) using an ethylene trap [3]. However, such trapping during the course of the amination would probably be prevented by the high rate of reaction of (II) with strong nucleophiles ($NaNH_2$ and NH_3). Attempts to trap (II) under the conditions used for the generation of related carbenes [4], specifically in cyclohexene (styrene) in the presence of t-BuOK and in the two-phase system 50% aq. KOH-cyclohexene (styrene) with the addition of the phase-transfer catalyst $PhCH_2NEt_3Cl$ or dibenzo[18]-crown-6 were unsuccessful. Most of (I) (80-90%) was recovered unchanged, perhaps as a result of a marked reduction in the acidity of the 5-CH_3 group in the weakly solvating medium [5]. Thus, the mechanism of the cineamination of 4-chloroethynyl-5-methylpyrazoles (I) remains unproved.

In this connection, following the observation that halogen could migrate from the side chain to the ring in chloroethynylhetarenes in NH_3 in the presence of $NaNH_2$, and the establishment of the mechanism of this reaction [6-8], doubts arose as to the correctness of the carbene mechanism for the cineamination reaction. An alternative route for the amination, analogous with the isomerization, could involve the transfer of "positivized" halogen from the chloroethynyl group to methyl (the TPH mechanism), followed by its substitution by the amino group. The present investigation has provided proof of the occurrence of this alternative.

The hypothetical TPH mechanism for the cineamination of (I) is shown below in two variations, the chain mechanism (A) and the nonchain mechanism (B):

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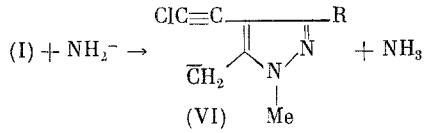
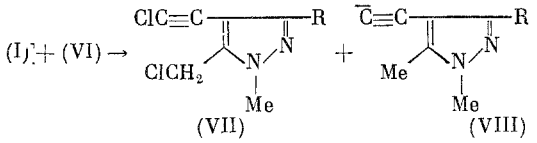
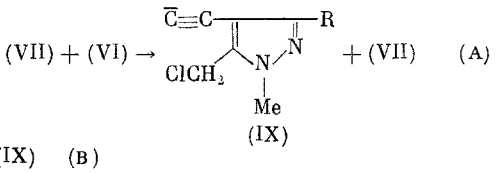




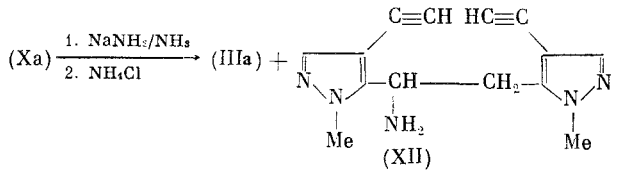


(VII) + (VIII) → 2 (IX) (B)

(in several steps, such as (VII) + (VIII) → (IX) + (I), etc.) R = H (a) or Me (b).

The Cl atom of the chloromethyl group is replaced by the amino group either in the anion (IX) or in (VII). In contrast to the carbene (II), the amination intermediates according to the TPH mechanism are stable compounds. We have synthesized the chloride (VIIa) and 4-ethynyl-5-chloromethyl-1-methylpyrazole (Xa), and examined their reactions in liquid ammonia.

Replacement of the Cl atom of the $ClCH_2$ group of the pyrazole (VIIa) in liquid ammonia in the absence of $NaNH_2$ occurs very slowly, and after 4.5 h 75% of (VIIa) was recovered unchanged. Since the cineamination of (Ia) requires only 15-20 min, replacement of the halogen of (VIIa) in this reaction could only occur by attack by amide anions. It would be natural to assume that the dichloride (VIIa) would react directly with excess $NaNH_2$ with ammonolysis of the chloromethyl group and dehalogenation of the chloroethynyl group to give the aminoacetylene (IIIa). Despite this, (VIIa) was found to react with 7 equiv. of $NaNH_2$ to give a complex mixture of products which did not contain (IIIa). The experimental findings could indicate that dehalogenation of the chloroethynyl group by amide anions occurs less efficiently than with pyrazolyl anions in the cineamination of (I), and the resulting 4-chloroethynyl-5-aminomethyl-1-methylpyrazole (XI) undergoes side reactions and is consumed. If it is further assumed that the rate of dechlorination by active dehalogenating agents is greater than the rate of replacement of Cl by NH_2, then (as shown in the scheme above), cineamination should proceed via the intermediate (IX) rather than (XI). Reaction of the chloromethylpyrazole (Xa) with $NaNH_2$ afforded the expected amine (IIIa) in 37% yield, together with an unknown product which, from its elemental analysis and IR and PMR spectra, was assigned the structure 1,2-di-(4'-ethynyl-1'-methylpyrazol-5'-yl)-1-aminoethane (XII) (47% yield)



In the reaction with $NaNH_2$, the initial concentration of (Xa) is apparently substantially greater than its equilibrium concentration in the amination of (Ia) (according to the TPH mechanism). The possibility cannot be excluded that the differences in the courses of the reactions of (Xa) in each instance is a result of this difference in concentration. We therefore studied the combined effects on the dichloride (VIIa) of $NaNH_2$ and the potentially active dechlorinating agent, viz., pyrazolyl anions. According to the TPH amination mechanism, anions (VI) (route A) or (VIII) (route B) function as acceptors of "positivized" halogen. With a twofold excess of 4-ethynyl-1,5-dimethylpyrazole (XIIIa), and $NaNH_2$ (VIIa), gave a mixture of the same products as in the absence of (XIIIa); (XIIIa) was regenerated to the extent of 83.5%, but (IIIa) was not formed even in trace amounts.

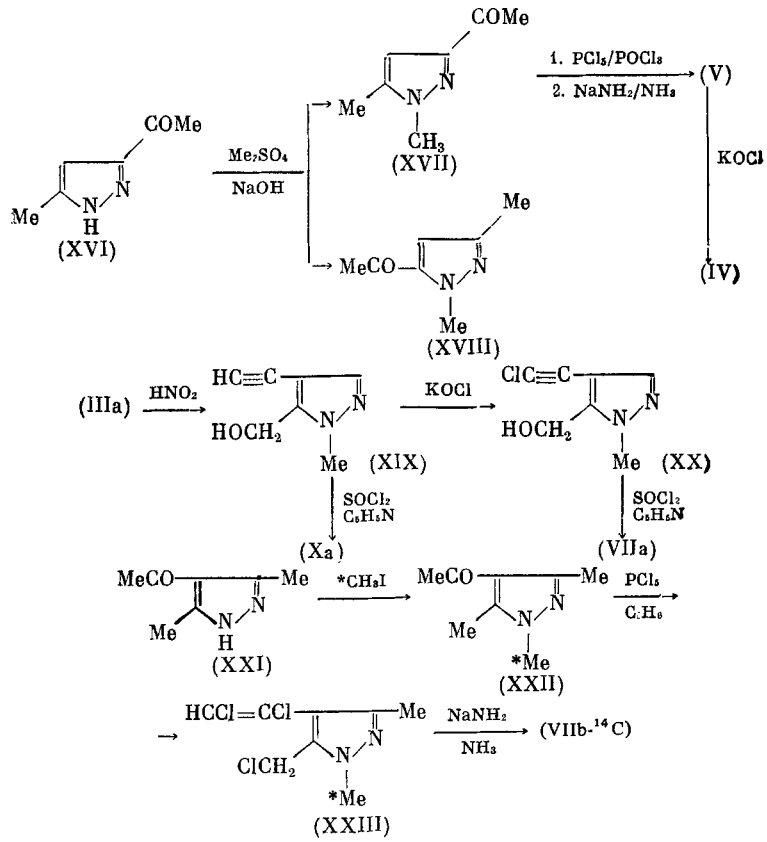
It follows that (VIII) is ineffective in the dechlorination of (VII), and the mechanism of the cineamination of (I) cannot be a chain TPH mechanism (route B).

The pyrazolylmethyl anion (VI) as an acceptor of "positivized" chlorine was modeled by its closest analog, 4-phenylethynyl-1-methylpyrazol-5-yl methyl anion (XIV). In this instance

also, however, none of the aminoacetylene (IIIa) was found in the complex mixture of products obtained from 4-phenylethynyl-1,5-dimethylpyrazole (XV), (VIIa), and $NaNH_2$ (1.5:1:7).

These findings do not support the TPH mechanism for the cineamination, but they do not prove that it does not occur, since the model anion (XIV) is not wholly equivalent to the anion (VIa). More convincing evidence would be the establishment of the participation or nonparticipation of the dichloride (VII) as a key intermediate directly involved in the cineamination process. For this reason, we aminated 4-chloroethynyl-1,3,5-trimethylpyrazole (Ib) in the presence of 2.5-5 mole% of 4-chloroethynyl-5-chloromethyl-1-methyl-^{14}C-3-methylpyrazole (VIIb-^{14}C). If the reaction proceeded via the TPH mechanism, the radioactive tag would inevitably be transferred to the final product (IIIb), but, if not, it would occur in byproducts formed from (VIIb-^{14}C) and excess $NaNH_2$. It turned out that the (VIIIb) obtained contained a total of about 5% of the activity of the tagged starting material, dichloride (VIIb-^{14}C). Thus, the TPH mechanism does not play an important part in the amination of 4-chloroethynyl-5-methylpyrazoles (I). The small inclusion of the tag in (IIIb) may be due to exchange of chlorine between (VIIb-^{14}C) and the likely carbene precursor, anion (VIb), formed in the initial α,ω-dehydrochlorination of (Ib).

The pyrazoles (IV), (VIIa), (Xa), and (VIIb-^{14}C) used in this investigation were synthesized as follows:



EXPERIMENTAL

3-Acetyl-5-methylpyrazole (XVI). To 1.3 g of $MeCHN_2$ in 200 ml of ether at 0°C was added rapidly a cooled solution of 2.4 g of 1-chloro-1-butene-3-one [9] in 10 ml of ether, the mixture stirred for 4 h, and gaseous HCl passed through until precipitation was complete. The solid was filtered off, washed with ether, dissolved in 6 ml of water, and neutralized with Na_2CO_3. The product (XVI) was extracted with $CHCl_3$, yield 2.4 g (84%), mp 100-100.5°C (sub.) (cf. [10]).

3-Acetyl-1,5-dimethyl- and 5-Acetyl-1,3-dimethylpyrazole (XVII) and (XVIII). To a suspension of 19.6 g of (XVI) in 50 ml of 40% NaOH was added, at 25-27°C over 2 h, 27.0 g of Me_2SO_4. The mixture was stirred for 4 h at this temperature, diluted with 50 ml of water, and extracted with 500 ml of ether. Fractionation on a microcolumn under a water-pump vacuum

afforded 14.7 g (67.5%) of (XVII), mp 56-57°C (from light petroleum) (cf. [10]), and 4.0 g (18.3%) of (XVIII), mp 22-23°C (from light petroleum). Found: N 20.07%. $C_7H_{10}N_2O$. Calculated: N 20.28%. PMR spectrum (CCl_4, δ, ppm): 2.09, 2.28 (3-CH_3, $COCH_3$), 3.98 (NCH_3), 6.52 (4-H). IR spectrum (CCl_4, ν, cm^{-1}): 1680 (C=O).

3-Ethynyl-1,5-dimethylpyrazole (V). 4.1 g of (XVII) and 6.2 g of PCl_5 were heated in 14 ml of $POCl_3$ at 90-100°C for 20 h, until all the (XVII) had reacted. The $POCl_3$ was then distilled off, and the residue treated with 100 ml of ether and neutralized with aqueous NaOH. The ether layer was dried over K_2CO_3, and added to $NaNH_2$ (from 2.1 g of Na) in 200 ml of NH_3, the mixture stirred for 1 h, 10 g of NH_4Cl added, and the NH_3 removed. After removal of the ether, the residue was chromatographed on grade V alumina (ether—light petroleum, 1:1) to give 2.6 g (73%) of (V), mp 72-73°C (sub.). Found: N 23.20%. $C_7H_8N_2$. Calculated: N 23.31%. PMR spectrum ($CDCl_3$, δ, ppm): 2.12 (5-CH_3), 2.90 (HC≡C), 3.60 (NCH_3), 6.00 (4H). IR spectrum (CCl_4, ν, cm^{-1}): 2130 (C≡C), 3325 (HC≡C).

3-Chloroethynyl-1,5-dimethylpyrazole (IV). A mixture of 2.2 g of (V) and 162 ml of an alkaline solution of KOCl, obtained by passing chlorine into 12.5% aqueous KOH at 0°C and pH followed by dilution with an equal volume of 25% aqueous KOH, was stirred at 20°C for 12 h, then extracted with ether. Yield of (IV), 2.8 g (99%), mp 70-71°C (from light petroleum). Found: C 54.45; H 4.67; N 23.24%. $C_7H_7ClN_2$. Calculated: C 54.38; H 4.56; N 22.93%. PMR spectrum ($CDCl_3$, δ, ppm): 2.14 (5-CH_3), 3.62 (NCH_3), 6.00 (4-H). IR spectrum (CCl_4, ν, cm^{-1}): 2235 (C≡C).

4-Ethynyl-5-hydroxymethyl-1-methylpyrazole (XIX). To 5.0 g of (IIIa) in 20 ml of 50% aqueous acetic acid was added with ice-cooling over 40 min a saturated aqueous solution of 2.7 g of $NaNO_2$. When evolution of N_2 had ceased, the mixture was heated on a boiling water bath for 15 min, cooled, 15 g of KOH in 5 ml of water added followed by 6 ml of MeOH, stirred for 2 h at 20°C, neutralized with aqueous HCl and extracted with ether, to give 5.0 g (99%) of (XIX), mp 101.5-102°C (from C_6H_6). Found: C 61.82; H 5.79; N 20.72%. $C_7H_8N_2O$. Calculated: C 61.75; H 5.92; N 20.58%. PMR spectrum [$(CD_3)_2CO$, δ, ppm]: 3.42 (HC≡C), 3.78 (NCH_3), 4.50 (OH), 4.62 (CH_2), 7.36 (3-H). IR spectrum ($CHCl_3$, ν, cm^{-1}): 2125 (C≡C), 3315 (H—C≡C), 3608 (OH).

4-Chloroethynyl-5-hydroxymethyl-1-methylpyrazole (XX) was obtained in a similar way to the chloroacetylene (IV), reaction time 3 h, yield 85%, mp 117-118°C (from benzene). Found: C 49.28; H 4.15; N 20.64%. $C_6H_7ClN_2O$. Calculated: C 49.28; H 4.14; N 20.78%. PMR spectrum ($CDCl_3$, δ, ppm): 3.75 (NCH_3), 4.42 (OH), 4.55 (CH_2), 7.33 (3-H). IR spectrum (CCl_4, ν, ppm): 2230 (C≡C).

4-Ethynyl-5-chloromethyl-1-methylpyrazole (Xa). To 0.72 g of (XIX) and 0.44 g of dry pyridine in 5 ml of $CHCl_3$ was added with ice-cooling over 1 h 0.66 g of $SOCl_2$ in 1.5 ml of $CHCl_3$. The mixture was stirred for 30 min, heated to the boil for 30 min, and stirring continued for a further 40 min. After cooling, the mixture was diluted with 20 ml of ether, the solid filtered off, and the residue after removal of the solvent was recrystallized from hexane to give 0.65 g (79.5%) of (Xa), mp 101-102°C. Found: C 54.22; H 4.60; Cl 22.95%. $C_7H_7ClN_2$. Calculated: C 54.38; H 4.56; Cl 22.93%. PMR spectrum ($CDCl_3$, δ, ppm): 3.12 (HC≡C), 3.85 (NCH_3), 4.59 (CH_2), 7.19 (3-H). IR spectrum (CCl_4, ν, cm^{-1}): 2125 (C≡C), 3120 (HC≡C).

Similarly, from 0.30 g of (XX) there was obtained 0.31 g 93%) of (VIIa)„ mp 83-84°C (from light petroleum). Found: C 44.40; H 3.20; Cl 37.42%. $C_7H_6Cl_2N_2$. Calculated: C 44.47; H 3.20; Cl 37.51%. PMR spectrum [$(CD_3)_2CO$, δ, ppm]: 3.80 (NCH_3), 4.52 (CH_2), 7.34 (3-H). IR spectrum (CCl_4, ν, cm^{-1}) 2218, 2244 (C≡C).

4-Acetyl-1-methyl-^{14}C-3,5-dimethylpyrazole (XXII). In a conical flask fitted with a magnetic stirrer, a dropping funnel with a side-tube for the equalization of pressure, and a dry ice reflux condenser, was placed 9.6 g of KOH in 5.6 ml of water and 50 ml of ethanol, and 8.1 g of (XXI) added with stirring. The mixture was stirred for 30 min, and 8.6 g of $^{14}CH_3I$ in 15 ml of ether was added over 1.5 h at 35°C. The mixture was boiled for 3 h, diluted with 150 ml of ether, filtered, and evaporated to give 4.4 g [49.5% on (XXI), 48% on radiocarbon)] of (XXII), mp 68-69°C (cf. [11]).

4-Chloroethynyl-5-chloromethyl-1-methyl-^{14}C-3-methylpyrazole (VIIb-^{14}C). A mixture of 3.04 g of (XXII) and 16.7 g of PCl_5 in 20 ml of dry benzene was boiled for 7 h, and kept overnight. Benzene was removed from the reaction mixture under reduced pressure, and the residue diluted with 150 ml of ether and neutralized with 20% aqueous NaOH. The ethereal layer

was separated and dried over K_2CO_3, and the resulting solution of (XXIII) (cf. [12]) was added over 1-2 min at −70°C to $NaNH_2$ (from 0.55 g of Na) in 200 ml of NH_3. The mixture was stirred for 15 min, 3.0 g of NH_4Cl added, and the NH_3 evaporated. The ethereal solution of (VIIb-^{14}C) was filtered through a thin layer of anhydrous Al_2O_3, the solvent removed, 3 ml of light petroleum added to the residue, cooled to 0°C, and the solid filtered off and washed with cold light petroleum. Sublimation at 80°C (1 mm) gave 0.41 g (10%) of (VIIb-^{14}C), mp 81-82°C (cf. [12]).

Attempts to Generate Carbene (IIb) from 4-Chloroethynyl-1,3,5-trimethylpyrazole (Ib). a) To a suspension of 0.92 g of t-BuOK in 8 ml of t-BuOH was added under nitrogen, over 45 min, 1.10 g of (Ib) [1, 12] in 2 ml of styrene, and the mixture was stirred for 2 h at 0°C. After removal of styrene and distillation of the residue in vacuo (100°C/1 mm), 0.9 g (91%) of (Ib) was recovered.

b) A mixture of 0.20 g of (Ib), 0.37 g of styrene, 2.5 mg of $PhCH_2NEt_3Cl$, 3 ml of benzene, and 10 ml of 50% aqueous KOH was stirred for 48 h at 20°C, under nitrogen. The IR spectra of samples removed at intervals failed to show the presence of stretching vibrations of the allene group. There was recovered 0.16 g (80%) of (Ib).

Dechlorination of 3-Chloroethynyl-1,5-dimethylpyrazole (IV). A mixture of 1.58 g of (IV) and 20 ml of dry ether was added rapidly to $NaNH_2$ (from 1.65 g of Na) in 150 ml of NH_3, stirred for 20 min, and 7.7 g of NH_4Cl added. Chromatography on grade V alumina in $CHCl_3$ afforded 0.78 g (63.5%) of (V), mp 72-73°C.

Reaction of 4-Chloroethynyl-5-chloromethyl-1-methylpyrazole (VIIa) with $NaNH_2$. a) Under the dechlorination conditins used for (IV), (VIIa) afforded a complex mixture of unstable products which contained no (IIIa) (by TLC).

b) Sodamide (from 160 mg Na) and 240 mg of (XIIIa) [12] in 120 ml of NH_3 was stirred for 10 min, and after 50 min 189 mg of (VIIa) in 10 ml of dry ether was added. Following decomposition, the reaction mixture contained degradation products of (VIIa) and unreacted (XIIIa) (200 mg, 83.5%).

c) A mixture of 280 mg of (VIIa), 440 mg of (XV) [5], and $NaNH_2$ (from 230 mg of Na) in 120 ml of NH_3 was stirred for 15 min. Chromatography on grade V alumina led to the recovery of 150 mg (34.1%) of (XV), mp 73-74°C; (IIIa) was not found in the reaction products.

Reaction of 4-Ethynyl-5-chloromethyl-1-methylpyrazole (Xa) with $NaNH_2$. Reaction of 204 mg of (Xa) with $NaNH_2$ (from 212 mg of Na) was carried out as described for (IV). Chromatography on silica gel (benzene–methanol, 1:1) gave 65 mg (36.5%) of (IIIa) and 79 mg (47.3%) of (XII), mp 131-132°C. Found: C 66.09; H 5.89; N 27.67%. $C_{14}H_{15}N_5$. Calculated: C 66.38; H 5.97; N 27.65%. PMR spectrum (C_5D_5N, δ, ppm): 1.92 (NH_2), 3.13, 3.27 (HC≡C), 3.20 d (CH_2), 3.57, 3.60 (NCH_3), 4.50 t (CH), 7.50 (3-H). IR spectrum ($CHCl_3$, ν, cm^{-1}): 2123 (C≡C), 3317 (HC≡C), 3390 (NH_2).

Amination of 4-Chloroethynyl-1,3,5-trimethylpyrazole (Ib) in the Presence of 4-Chloroethynyl-5-chloromethyl-1-methyl-^{14}C-3-methylpyrazole (VIIb-^{14}C). To $NaNH_2$ (from 0.55 g of Na) in 150 ml of NH_3 was added 1000 mg of (Ib) and 60 mg of (VIIb-^{14}C) (activity 19,022 counts/sec), and the mixture stirred for 20 min. Chromatography followed by sublimation (100°C/1 mm) afforded 785 mg (89.5%) of (IIIb), mp 76-76.5°C (cf. [1,2]), activity 819 counts/sec.

CONCLUSIONS

4-Chloroethynyl-5-chloromethyl derivatives are not intermediates in the cineamination of 4-chloroethynyl-5-methylpyrazoles with $NaNH_2$ in liquid ammonia. Experimental evidence thus enables one of two alternative mechanisms for this reaction, involving the initial intermolecular transfer of halogen to the 5-methyl group, to be rejected.

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SYNTHESIS OF METHOPRENE VIA ELECTROREDUCTION OF THE THIOPHENE RING

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The discovery of the juvenile hormones, and the elucidation of their functions in the vital processes of insects, has led in recent years to numerous studies of the synthesis of these hormones and analogs thereof (juvenoids), which are in many instances more active than the naturally occurring compounds [1]. Certain juvenoids have already found practical use as hormonal pesticides, for example methoprene (I) [2, 3], which is used to control the larvae of mosquitos and flies. A typical feature of the farnesane (I) molecules is the presence therein of the 2E,4E-diene fragment. We here report a new synthesis of methoprene, using a method which we have developed [4, 5] for the electrochemical preparation of 2,5-dihydrothiophenecarboxylic acids, together with the method described in the literature [6-8] for the stereospecific thermolysis of 2,5-dihydrothiophene sulfones to 1,3-dienes.

The starting material used was the 2,4-disubstituted thiophene (V), obtained by alkylating 2-lithio-4-methylthiophene with the bromide (IV) in the presence of N,N'-tetramethylethylenediamine (TMEDA). The bromide (IV) was in turn synthesized in two stages from the known aldehyde (II) and alcohol (III), as described in the experimental section. Methoxylation of the terminal isopropylidene group in (V) was effected in MeOH solution in the presence of conc. H_2SO_4 [9]. Carboxylation of the ether (VI) in the usual way afforded the acid (VIIa), the structure of which was established by spectroscopy. (See scheme on following page.)

Electrochemical reduction of (VIIa) at a mercury cathode in 2 M LiOH [5] gave a mixture of two isomeric 2,5-dihydroacids (VIIIa) in a ratio of ~3:2. These isomers, separated chromatographically on SiO_2, had PMR spectra which differed both in the positions and the shapes of the signals for the HC^2 and HC^5 protons, the signal with greater multiplicity at δ 4.1-4.2 ppm being assigned to the HC^5 proton in both isomers. The chemical shifts with respect to the low-field HC^2 signal were different in the two isomers (δ 4.29 and 4.34 ppm). On the basis of these observations, and literature data for a series of 2,5-dihydrothiophenes [6, 8-10], it was not considered possible to make a rigorous assignment of the geometry of these isomers (VIIIa). In the present case, such assignment is further complicated by the occurrence of diastereoisomerism involving the methyl group at $C^{2'}$ of the side chain. This is shown by the signal for $\underline{C}H_3$-$C^{2'}$, δ 0.89 ppm, present in each (VIIIa) isomer as an overlapping doublet, J = 6 Hz.

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