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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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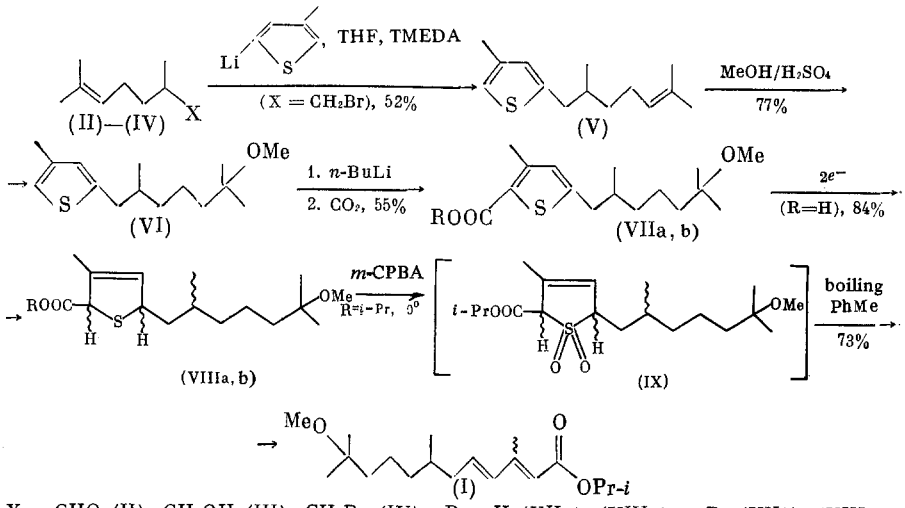

X = CHO (II), CH_2OH (III), CH_2Br (IV); R = H (VIIa), (VIIIa), *i*-Pr (VIIb), (VIIIb).

Each of the isomers was converted into its isopropyl ether (VIIIb) with 2-diazopropane, then oxidized with 2 mole-eq. of m-chloroperbenzoic acid (m-CPBA). At the oxidation stage, in addition to the expected sulfolenes (IX), the aromatization product (VIIb), identified spectroscopically, was obtained in 20% yield. Since the chromatographic purification of the unstable sulfolenes (IX) was attended by considerable losses, the mixture of oxidation products was subjected directly to thermolysis.

The thermolysis of cis- and trans-2,5-dialkylsulfolenes, being an electrocyclic process, occurs stereospecifically to form the E,E- and Z,E-1,4-disubstituted butadienes, respectively [7, 8]. We found that each of the isomers of (VIIIb), following oxdation with m-CPBA and boiling in toluene, gave high yields of the diene (I) as a 2E,4E/2Z,4E mixture in a ratio of ≈1:1. This ratio was determined by comparing the completely identical PMR spectra of the product with those described [2, 3] for the individual isomers of (I). Further, according to GLC, one of the components of the mixture, with the higher retention time, coincided with an authentic sample of methoprene. Labelling studies with the mixture of acids (VIIIa) formed on electrolysis gave the same ratio of isomers of (I).

The formation in all these cases of an approximately equal mixture of isomers of (I) formally indicates the complete loss of stereospecificity in the conversion of the sulfolenes (IX), having an ester group at C^2, into the corresponding 1,3-dienes. However, in this experiment the isomeric sulfones (IX) could not be isolated in the pure state. For this reason, it is not possible to decide unambiguously whether an equilibrium epimerization of the ester group occurs at the stage of oxidation of the sulfides (VIIIb), or whether there is in fact a loss of stereospecificity in this electrocyclic reaction as a result of the presence of an electron-accepting substituent in (IX).

Hence, the substituted thiophene-2-carboxylic acid (VIIa) has been converted in three steps, including electrochemical reduction, into a mixture of methoprene (I) and its 2Z,4E-isomer in an overall yields of more than 60%.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument. PMR spectra were measured on a Tesla BS-497 spectrometer (100 MHz) in CCl_4, relative to TMS. GLC was carried out on an LKhM-8MD chromatograph, column 2 m × 3 mm with 15% Carbowax 20M on Chromatone N-AW-HMDS, flame ionization detector, carrier gas nitrogen. For TLC, plates with a bound layer of Silufol SiO_2 were used. Mass spectra were measured on a Varian MAT CH-6 (70 eV). Electrochemical reductions were carried out in a cell fitted with a porous glass electrode using a P-5827 potentiostat. Cathode, mercury (~30 cm^2); anode a Pt grid; reference electrode, saturated calomel electrode; catholyte, 25 ml of 2 M LiOH containing 1.7 mmole of the compound. Electrolysis was carried out for 8 h in an argon atmosphere, at 25°C and a potential of −2.2 to −2.3 V.

2,6-Dimethylhept-5-en-1-al (II). To a stirred solution of the Grignard reagent obtained from 1.2 g (50 mg·atom) of Mg and 9.55 g (50 mmole) of 2-bromo-6-methylhept-5-ene [11] in 75 ml of THF was added over 10 min at 25°C under argon 3.66 g (50 mmole) of DMF. The mixture was kept for 30 min at 25°C, then diluted with ether and decomposed with saturated NH_4Cl. The

organic layer was separated, washed with H_2O, dried over $MgSO_4$, evaporated, and the residue distilled in vacuo to give 4.76 g (68%) of (II) [12], bp 79-80°C (20 mm), n_D^{20} 1.4492. PMR spectrum (δ, ppm): 1.03 d (J = 7 Hz, 3H, CH_3), 1.59 and 1.68 br.s. (6H, CH_3), 1.2-2.4 m (5H, HC^2, HC^3, HC^4), 5.04 br.t. (J = 7 Hz, 1H, HC=C), 9.52 d (J = 1.5 Hz, 1H, CHO).

2,6-Dimethylhept-5-en-1-ol (III). A solution of 7 g (50 mmole) of (II) in 25 ml of MeOH was treated over 30 min at 25°C with 1.25 g (33 mmole) of $NaBH_4$, and after 30 min the mixture was diluted with twice its volume of water, neutralized with AcOH, and extracted with ether. The extract was dried over $MgSO_4$, and the residue after removal of the solvent was distilled in vacuo to give 5.2 g (73%) of (III) [13], bp 98-100°C (15 mm), n_D^{20} 1.4552. IR spectrum (ν, cm^{-1}): 740, 825, 990, 1045, 1070, 1375, 1450, 2850-2950, 3345. PMR spectrum (δ, ppm): 0.87 d (J = 6 Hz, 3H, CH_3), 1.59 and 1.66 br.s. (6H, CH_3), 1.2-2.1 m (5H, HC^2, HC^3, HC^4), 3.40 br.d. (J = 6 Hz, 2H, CH_2O), 5.04 br.s. (J = 7 Hz, 1H, HC=C).

1-Bromo-2,6-dimethylhept-5-ene (IV). To a solution of 7.1 g (50 mmole) of (III) and 15 ml of pyridine in 40 ml of ether was added, with stirring at 25°C over 30 min, 11.5 g (60 mmole) of p-TsCl, and the mixture was boiled for 6 h. It was then diluted with water, neutralized with conc. HCl, the ether layer separated, and the aqueous layer extracted with ether. The combined ethereal solutions were worked up in the usual way to give 12 g (about 40 mmole) of the crude tosylate of alcohol (III), which was dissolved in 30 ml of DMF. This was stirred with 9 g (80 mmole) of NaBr for 5 h at 50°C, then diluted with water and extracted with ether. The extract was worked up in the usual way to give 7.5 g of material which was chromatographed on 100 g of SiO_2. Elution with hexane gave 5.84 g (57%) of (IV) was a colorless liquid, bp 91-93°C (14 mm), n_D^{20} 1.4745. IR spectrum (ν cm^{-1}): 620, 650, 815, 1230, 1375, 1450, 2850-2960. PMR spectrum (δ, ppm): 0.99 d (J = 6.5 Hz, 3H, CH_3), 1.57 and 1.65 br.s. (6H, CH_3), 1.2-2.1 m (5H, HC^2, HC^3, HC^4), 3.27 d (J = 5 Hz, 2H, HC^1), 5.03 br.t. (J = 6.5 Hz, 1H, HC=C). Found: C 52.90; H 8.24; Br 38.78%. M^+ 205. $C_9H_{16}Br$. Calculated: C 52.68; H 8.35; Br 38.94%; mol. wt. 205.2.

2-(2',6'-Dimethylhept-5'-enyl)-4-methylthiophene (V). To a solution of the 2-lithio-derivative, prepared as in [14] from 4.9 g (50 mmole) of 3-methylthiophene [15], 45 ml of a 1.1 M solution of n-BuLi (50 mmoles), and 5.1 g (50 mmole) of TMEDA in 50 ml of THF was added over 30 min with stirring at −15°C under argon a solution of 4.1 g (50 mmole) of (IV) in 20 ml of THF. After 1 h, the mixture was warmed to 20°C, and after 2 h it was decomposed with water and diluted with ether. The organic layer was separated, worked up in the usual way, and the residue (7.8 g) chromatographed on 500 g of SiO_2. Elution with hexane gave 5.8 g (52%) of (V) as a colorless oil, bp 102-103°C (1.5 mm), n_D^{20} 1.5082, pure according to GLC (160°C). IR spectrum (ν, cm^{-1}): 505, 745, 795, 890, 1040, 1380, 1425, 2850-2970. PMR spectrum (δ, ppm): 0.93 d (J = 6 Hz, 3H, CH_3), 1.55, 1.63, and 2.12 br.s. (9H, CH_3), 1.2-2.3 m (5H, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$), 2.56 (J = 5 and 6 Hz, 2H, $HC^{1'}$), 4.98 br.t. (J = 7 Hz, 1H, $HC^{5'}$), 6.40 s. (1H, HC^3), 6.47 s (1H, HC^5). Found: C 75.54; H 9.95; S 14.30%; M^+ 222. $C_{14}H_{22}S$. Calculated: C 75.61; H 9.97; S 14.42%; mol. wt. 222.4.

2-(6'-Methoxy-2',6'-dimethylheptyl)-4-methylthiophene (VI). A solution of 5.56 g of (V) and 1.3 ml of conc. H_2SO_4 in 70 ml of MeOH was boiled for 4 h, then neutralized with 5% $NaHCO_3$, evaporated, and the residue extracted with ether. The extract was worked up in the usual way to give 5.8 g of product, which was chromatographed on 250 g of SiO_2. Elution with a mixture of hexane and ether (20:1) gave 4.9 g (77%) of (VI) as a colorless oil, bp 114-115°C (2 mm), n_D^{20} 1.4940. IR spectrum (ν, cm^{-1}): 500, 760, 795, 1090, 1160, 1365, 1380, 1465, 2830-2965. PMR spectrum (δ, ppm): 0.88 d (J = 6 Hz, 3H, CH_3), 1.05 s (6H, CH_3), 1.2-1.9 m (7H, $HC^{2'}$, $CH^{3'}$, $HC^{4'}$, $HC^{5'}$), 2.36 br.s. (3H, CH_3), 2.56 d.d. (J = 5 and 6 Hz, 2H, $HC^{1'}$), 3.04 s (3H, OCH_3), 6.38 br.s. (2H, HC^3, HC^5). Found: C 70.63; H 10.82; S 12.48%; M^+ 254. $C_{15}H_{26}OS$. Calculated: C 70.81; H 10.30; S 12.60%; mol. wt. 254.4.

5-(6'-Methoxy-2',6'-dimethylheptyl)-3-methylthiophene-2-carboxylic Acid (VIIa). A solution of the 5-dithio derivative, prepared by boiling for 1 h under argon 2.54 g (10 mmole) of (VI) in 15 ml of ether and 8.9 ml of a 1.15 M solution of n-BuLi in ether (10 mmole), was poured onto dry ice (2 g) in 15 ml of THF. The residue after removal of excess CO_2 was treated with H_2O, and extracted with ether. The aqueous layer was acidified with conc. HCl to pH 1, extracted with ether, and the extract worked up in the usual way to give 2 g of material which was chromatographed on 100 g of SiO_2. Elution with hexane–ether (4:1) gave 1.64 g (55%) of (VIIa) as a colorless oil, R_f 0.36 (hexane–ether, 3:2). IR spectrum (ν, cm^{-1}): 760, 840, 925, 1080, 1270, 1375, 1460, 1660, 1700, 2800-2975. PMR spectrum (δ, ppm): 0.92 d (J = 7 Hz, 3H, CH_3), 1.08 s (6H, CH_3), 1.2-1.8 m (7H, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$, $HC^{5'}$), 2.48 br.s. (3H, CH_3),

2.64 d.d. (J = 4.5 and 6.5 Hz, 2H, $HC^{1'}$), 3.08 s. (3H, OCH_3), 6.53 s (1H, HC^4). Found: C 64.08; H 8.55; S 10.61%. $C_{16}H_{26}O_3S$. Calculated: C 64.39; H 8.78; S 10.74%.

5-(6'-Methoxy-2',6'-dimethylheptyl)-3-methyl-2,5-dihydrothiophene-2-carboxylic Acid (VIIIa). The acid (VIIa) (0.51 g) was electrolyzed under the conditions given above. The catholyte was isolated, acidified with conc. HCl to pH 1, extracted with ether, and the residue (0.5 g), after removal of the ether, was chromatographed on 30 g of SiO_2. Elution with hexane—ether (7:3) gave 0.21 g of (VIIIa) and 0.13 g of its isomer as colorless oils with R_f 0.26 and 0.22, respectively (hexane—ether, 3:2), and 90 mg of a 1:1 mixture of the two (by PMR), overall yield 94%. (VIIIa), R_f 0.26, IR spectrum (ν, cm^{-1}): 680, 730, 825, 875, 930, 1080, 1175, 1280, 1380, 1460, 1710, 2850-2970. PMR spectrum (δ, ppm): 0.87 d and 0.92 d (J = 6.5 Hz, 3H, CH_3), 1.13 s (6H, CH_3), 1.2-1.7 m (9H, $HC^{1'}$, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$, $HC^{5'}$), 1.80 br.s (3H, CH_3), 3.12 s (3H, OCH_3), 4.12 m (1H, HC^5), 4.29 m (1H, HC^2), 5.53 m (1H, HC^4). (VIIIa), R_f 0.22, IR spectrum (ν, cm^{-1}): 760, 790, 845, 1080, 1180, 1215, 1255, 1380, 1460, 1710, 2850-2970. PMR spectrum (δ, ppm): 0.86 d and 0.89 d (J = 6.5 Hz, 3H, CH_3), 1.08 s (6H, CH_3), 1.1-1.6 m (9H, $HC^{1'}$, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$, $HC^{5'}$), 1.79 br.s (3H, CH_3), 3.09 s (3H, OCH_3), 4.2-4.4 m (2H, HC^2, HC^5), 5.48 m (1H, HC^4).

Isopropyl 11-Methoxy-3,7,11-trimethyldodeca-2,4E-1-dienoate (I) and Isopropyl 5-(6-Methoxy-2,6-dimethylheptyl)-3-methylthiophene-2-carboxylate (VIIb). To a solution of 0.42 g (1.4 mmole) of acid (VIIIa) with R_f 0.26 in 5 ml of ether was added at 0°C with stirring 2 ml of 2 M 2-diazopropane [16] in ether (2 mmole), and after 30 min the mixture was evaporated in vacuo. The resulting ester (VIIIb) was dissolved without further purification in 7 ml of CH_2Cl_2, and treated with 0.48 g (2.8 mmole) of m-CPBA. After stirring for 12 h at 0°C, the mixture was filtered and the solid washed with CH_2Cl_2. The combined filtrates were washed with saturated sodium carbonate solution, dried over $MgSO_4$, evaporated under reduced pressure, and the residue (0.45 g) chromatographed on 40 g of SiO_2. Elution with hexane gave 0.32 g (73%) of an oily mixture of isomers of (I) [2,3], 2E/2Z ≈ 1:1 (PMR, GLC, 170°C), R_f 0.32 (hexane—ether, 9:1). PMR spectrum (250 MHz, δ, ppm): 0.92 d and 0.96 d (J = 6 Hz, 3H, CH_3), 1.09 s (6H, CH_3), 1.28 d (J = 6 Hz, 6H, $C\underline{H}_3CHC\underline{H}_3$), 1.3-1.7 m (8H, HC^6, HC^8, HC^9, HC^{10}), 1.98 br.s and 2.23 br.s (3H, CH_3-C^3, Z- and E-isomers, respectively), 1.9-2.3 m (1H, HC^7), 3.12 s (3H, OCH_3), 5.11 t (J = 6 Hz, 1H, $CH_3C\underline{H}CH_3$), 5.53 br.s and 5.62 br.s (1H, HC^2, Z- and E-isomers, respectively), 6.05 m and 7.57 br.d ($J_{4,5}$ = 16 Hz, 2H, HC^4, HC^5) ($CDCl_3$).

Elution with hexane—ether (9:1) gave 90 mg (20%) of (VIIb) as a pale yellow oil, R_f 0.28 (hexane—ether, 9:1). IR spectrum (ν, cm^{-1}): 770, 830, 1090, 1265, 1380, 1470, 1705. PMR spectrum (δ, ppm): 0.90 d (J = 7 Hz, 3H, CH_3), 1.08 s (6H, CH_3), 1.32 d (J = 6 Hz, 6H, $C\underline{H}_3CHC\underline{H}_3$), 1.2-1.8 m (7H, $HC^{2'}$, $HC^{3'}$, $HC^{4'}$, $HC^{5'}$), 2.43 br.s (3H, CH_3), 2.60 d.d (J = 4.5 and 7 Hz, 2H, $HC^{1'}$), 3.08 s (3H, OCH_3), 5.08 t (J = 6 Hz, 1H, $CH_3C\underline{H}CH_3$), 6.50 s (1H, HC^4). Found: C 66.48; H 9.75; S 9.61%. M^+ 341. $C_{19}H_{32}O_3S$. Calculated: C 66.82; H 9.74; S 9.56%; mol. wt. 341.5.

Similarly, 0.21 g of acid (VIIIa) with R_f 0.22 afforded 0.15 g (70%), and 0.1 g of the mixtures (~1:1) of isomers of (VIIIa) afforded 62 mg (68%) of mixed isomers of (I), 2E/2Z ≈ ≈ 1:1, identical (PMR and GLC) with that described above.

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CONCLUSIONS

The synthesis of the juvenoid methoprene and its 2Z,4E isomer (as a ~1:1 mixture) has been accomplished, one of the steps being the electrochemical reduction of a 3,5-dialkylthiophene-2-carboxylic acid.

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SYNTHESIS AND SPATIAL STRUCTURE OF 4,6-DISUBSTITUTED 2-BORO-1,3,5-DIOXAPHOSPHORINANES

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It has been shown that on passing from N-methylpiperidine [1] to N-methyl-1,3-diazane [2], -1,3,5-triazane [3], -1,3-oxazane [4], and -1,3,5-azadithiane [5], the equilibrium is considerably shifted toward the conformer with an axially oriented methyl group. This is due to the transfer of electron density from the orbital of the unshared electron pair of the N atom to the extended orbital of the C—X bond, where X is N, O, or S [6]. This effect is also observed in phosphorus heterocycles. On passing from S-methyl- and 5-phenylphosphorinanes [7, 8] to the corresponding 1,3,5-dioxaphosphorinanes [9, 10], there is an increase in the equilibrium amount of the conformer (stereoisomer) with an axially oriented substituent at the P atom. In compounds with P and N atoms in the 1,3-positions, the substituent at the N atom assumes the axial orientation [11]. The conformational behavior of phosphorus heterocycles with heteroatoms in the 1,3-positions may be rationalized in terms of $n-\pi^*$ donor—acceptor interactions.

In connection with this rationalization, the conformational equilibrium of unsubstituted and stereoisomeric substituted 2-bora-1,3,5-dioxaphosphorinanes was of interest, since the boron atom should enhance the acceptor properties of the extended orbital of the C—O bond [6], resulting in an increase in the axial preference of the substituent at the P atom. It has previously been shown that the conformational equilibrium in 2,5-diphenyl-2-bora-1,3,5-dioxaphosphorinane is almost wholly shifted toward the conformer with axial orientation of the Ph substituent (96%, according to DM data) [12]. We here report a study of the equilibria in stereoisomers of 4,6-disubstituted-2,5-diphenyl-2-bora-1,3,5-dioxaphosphorinanes.

The synthesis of phosphorus-containing esters of phenylboric acid was effected by reacting α-hydroxyalkyl derivatives of phenylphosphine with phenylboric anhydride. Di(hydroxymethyl)-, di(α-hydroxyethyl)-, di(α-hydroxyisobutyl)-, and di(hydroxybenzyl)phenylphosphine afforded, respectively, 2,5-diphenyl-2-bora-1,3,5-dioxaphosphorinane (I), 2,5-diphenyl-4,6-dimethyl-2-bora-1,3,5-dioxaphosphorinane (II), 2,5-diphenyl-4,6-diisopropyl-2-bora-1,3,5-dioxaphosphorinane (III), and 2,4,5,6-tetraphenyl-2-bora-1,3,5-dioxaphosphorinane (IV). Compound (I) has been synthesized by other methods [12, 13], but (II)-(IV) are new (see scheme at top of next page).

The reaction of phosphorus-containing diols with phenylboric anhydride involves nucleophilic substitution at the boron atom and, in this respect, it resembles the reaction of diols with aldehydes. The latter was used for the synthesis of 5-phenyl-1,3,5-dioxaphosphorinanes,

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