

CYCLIC ANALOGUES OF INSECT JUVENILE HORMONE*

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The preparation of some esters and amides of 3,7-dimethyl-9-(2-thienyl)-2,6-nonadienoic or 2-nonenic acid, as well as esters of 3,7-dimethyl-9-(2-thienyl)-2,4-nonadienoic acid is described.

In connection with more detailed investigation in the area of insect juvenile hormone, especially of the chemical structure and biological activity relationship, we have described the preparation of cyclic analogues of juvenile hormone, in which the oxiran ring of the original hormone was substituted by an oxolane ring¹⁻³. In this paper we describe the preparation of analogous compounds in which the thiophene nucleus substitutes the oxiran ring of the native hormone.**

For the preparation of derivatives of 3,7-dimethyl-9-(2-thienyl)-2,6-nonadienoic acid chloromethylthiophene was used as starting material which was converted by acetoacetate synthesis to 4-(2-thienyl)-2-butanone. This was submitted to a modified Wadsworth-Emmons procedure⁴, giving ethyl 3-methyl-5-(2-thienyl)-2-pentenoate, which was reduced with lithium aluminum hydride to the corresponding pentenol from which the 6-methyl-8-(2-thienyl)-5-octen-2-one (*I*) was prepared by acetoacetate synthesis *via* the corresponding bromide.

Derivatives of 3,7-dimethyl-9-(2-thienyl)-2,4-nonadienoic acid were prepared from 4-(2-thienyl)-2-butanone which was reduced with lithium aluminum hydride to corresponding alkanol. The bromide prepared from the latter was reacted with diethyl malonate to give ethyl 2-ethoxycarbonyl-3-methyl-5-(2-thienyl)pentanoate. This afforded by saponification and decarboxylation with subsequent esterification with diazomethane either methyl 3-methyl-5-(2-thienyl)pentanoate, or the corresponding ethyl ester was obtained by carbo-deethylation⁵ of the mentioned ethyl 2-ethoxycarbonyl-3-methyl-5-(2-thienyl)pentanoate. 3-Methyl-5-(2-thienyl)pentanol, which was obtained on reduction of the esters with lithium aluminum hydride, gave on oxida-

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** The biological activity of the substances prepared will be described elsewhere in collaboration with the scientists of the Entomological Institute, Czechoslovak Academy of Sciences, Prague.

EXPERIMENTAL

Column chromatographies were carried out on silica gel according to Pitra⁹ (prepared in the service laboratory of the Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague-Lysolaje), 60–120 μ particle size, extracted with a chloroform–methanol mixture 1 : 1 before use and activated at 120°C for 24 hours. The material was deactivated by addition of 12% of water. Neutral alumina, activity III (Reanal) was also used. Thin layer chromatography was carried out on silica gel G (Merck). The purity of the compounds or the content of isomers were determined by gas chromatography on a Pye Argon Chromatograph with ionisation detector (⁹⁰Sr) on columns with 10% LAC-6R-860, or 10% butanediol succinate, or 15% QF-1 on Chromosorb W as stationary phase. The mass spectra were measured on an A.E.I MS 902 spectrometer coupled with Pye Series 104, Model 64, gas chromatograph, and the infrared spectra on a UR-10 (C. Zeiss, Jena) instrument (in CCl₄).

4-(2-Thienyl)-2-butanone

Chloromethylthiophene¹⁰ (81.66 g, 615.8 mmol) was mixed with ethyl acetoacetate (100.18 g, 769.7 mmol) and a solution of sodium (14.16 g, 615.8 mgat) in ethanol (310 ml) was added to it dropwise at 2–4°C over 105 minutes. The mixture was stirred in a melting ice bath for 3 hours and then allowed to stand at room temperature for 48 hours and finally heated at 70°C under stirring for 3 hours. A 10% aqueous NaOH solution (940 ml) was then added dropwise during 45 min and the heating was continued for another 4 hours. The mixture was cooled and extracted with light petroleum. After the extract had been washed and dried over MgSO₄ it was distilled to give required ketone in 52.68% yield (49.98 g), b.p. 108–113.5°C/11 Torr. For C₈H₁₀OS (154.2) calculated: 62.30% C, 6.54% H, 20.79% S; found: 62.46% C, 6.66% H, 20.53% S. IR spectrum (cm⁻¹): 1723, 1585, 1540, 1411, 1358.

Ethyl 3-Methyl-5-(2-thienyl)-2-pentenoate

The above ketone (24.68 g, 160 mmol) and diethyl ethoxycarbonylmethylphosphonate (39.49 g, 176 mmol) were dissolved in dry ethanol (224 ml) and a solution of sodium (4.05 g, 176 mgat) in ethanol (105 ml) was added dropwise and under stirring to it over 60 minutes, taking care that the temperature should not exceed 30°C (see⁴). The mixture was stirred for 2 hours and allowed to stand overnight. Ethanol was distilled off *in vacuo* at 40°C and the residue was poured into water acidified with 1M-H₂SO₄ (90 ml). The product was extracted with light petroleum and the extract washed with water, 1M-KHCO₃ and water to neutrality. After drying over MgSO₄ and evaporation the required ester was obtained; b.p. 111°C/0.3 Torr–118.5°C/0.4 Torr. Yield, 31.04 g (86.5%). For C₁₂H₁₆O₂S (224.3) calculated: 64.25% C, 7.19% H, 14.29% S; found: 63.95% C, 7.10% H, 14.45% S. IR spectrum (cm⁻¹): 1751, 1720, 1585, 1540, 1223, 1179, 1150.

3-Methyl-5-(2-thienyl)-2-pentenol

A solution of the preceding pentenoate (32.08 g, 143 mmol) in ether (50 ml) was added dropwise over 105 minutes to a stirred solution of LiAlH₄ (3.26 g, 85.8 mmol) in ether (500 ml) (prepared under argon by one hour's refluxing and cooling down), keeping the temperature below –17.5°C. The stirring was continued for another 90 minutes in the very slowly warming up cooling bath (after 90 minutes the inner temperature was –14.5°C), and then for another 150 minutes at room temperature. Water was then added dropwise (3.26 ml) followed by a 15% aqueous NaOH solution (3.26 ml) and water (9.78 ml)¹¹, and after a short while of stirring the precipitated salts

were filtered off under suction and washed with ether. The filtrate was washed and dried over Drierite and then distilled through a Vigreux column (10 cm) to afford the required pentenol, b.p. 104.5°C/0.05 Torr—107.5°C/0.08 Torr in 72.0% yield (18.78 g) in addition to 2.17 g of a fore-run and a residue. For $C_{10}H_{14}OS$ (182.3) calculated: 65.89% C, 7.74% H, 17.59% S; found: 65.95% C, 7.69% H, 17.31% S. IR spectrum (cm^{-1}): 3620, 3350, 1668, 1640, 1581, 1538, 1002.

1-Bromo-3-methyl-5-(2-thienyl)-2-pentene

The above pentenol (20.71 g, 113.6 mmol) in pyridine (1.12 g, 14.41 mmol) was dissolved in a mixture of light petroleum (50 ml) and ether (20 ml), and PBr_3 (12.30 g, 45.4 mmol) in light petroleum (11 ml) was added to it dropwise under stirring at -30 to $-22^\circ C$ over 20 minutes. The stirring was continued for another 100 minutes at $-25^\circ C$ to $-22^\circ C$ and the mixture was poured onto ice and the product extracted with light petroleum. The extract was washed with 1M- $KHCO_3$ and water, dried over Drierite and the solvent evaporated *in vacuo* from a water bath at $30^\circ C$. Yield, 23.29 g (83.6%) of crude bromide which was worked up immediately.

6-Methyl-8-(2-thienyl)-5-octen-2-one (I)

A solution of sodium (2.73 g, 118.7 mgat) in ethanol (60 ml) was added dropwise and under stirring into a mixture of crude bromide from the preceding experiment (23.29 g, 95 mmol) and ethyl acetoacetate (16.07 g, 123.5 mmol) at -17.5° to $-12^\circ C$. The addition lasted 30 minutes and the stirring was continued at -10 to $-6^\circ C$ for 3 hours and at room temperature for another 3 hours. After standing overnight the mixture was heated at $80^\circ C$ for one hour and a 10% NaOH solution (150 ml) was added to it dropwise at the same temperature over 45 minutes. After 4 hours stirring at $80^\circ C$ the mixture was cooled and extracted with light petroleum. The extract was washed and dried over $MgSO_4$ and distilled through a Vigreux column to yield ketone I, b.p. $108^\circ C/0.04$ Torr— $109.5^\circ C/0.02$ Torr, in 77.5% yield (16.36 g). For $C_{13}H_{18}OS$ (222.3) calculated: 70.22% C, 8.16% H, 14.42% S; found: 70.06% C, 8.20% H, 14.16% S. IR spectrum (cm^{-1}): 1720, 1582, 1539, 1358.

4-(2-Thienyl)-2-butanol

4-(2-Thienyl)-2-butanone (34.93 g, 226.5 mmol) was added dropwise under stirring to a solution of $LiAlH_4$ (3.01 g, 56.6 mmol) in ether (300 ml), prepared by 30 minutes' refluxing and cooling. The addition was carried out under argon, over 40 minutes, keeping the solvent mildly boiling. The mixture was then stirred at room temperature for 75 minutes and under reflux for another 60 minutes. After cooling the mixture was decomposed by dropwise addition of water (3 ml), 15% aqueous NaOH (3 ml) and water (9 ml)¹¹, and the separated salts were filtered off under suction and washed with ether. The filtrate was washed and dried over $MgSO_4$ and distilled. Yield, 30.14 g (85.2%) of the required alcohol, b.p. $116.8-118.7^\circ C/11$ Torr. For $C_8H_{12}OS$ (156.2) calculated: 61.50% C, 7.74% H, 20.52% S; found: 61.83% C, 7.58% H, 20.28% S. IR spectrum (cm^{-1}): 3629, 3610, 1582, 1539, 1123.

2-Bromo-4-(2-thienyl)butane⁷

Dry bromine (31.87 g, 199.4 mmol) was added dropwise under argon into a stirred solution of triphenylphosphine (52.30 g, 199.4 mmol) in dimethylformamide (182 ml) over 20 minutes, keeping the temperature below $50^\circ C$. After 15 minutes' stirring at room temperature the above

prepared alcohol (28.32 g, 181.3 mmol) was added dropwise at 40–50°C over 20 minutes to the preceding mixture and the stirring was continued for 2 hours at room temperature. The mixture was distilled in a vacuum (10 Torr) up to 180°C temperature of the bath. The distillate was poured into water, extracted with light petroleum, the extract was washed and dried over MgSO_4 . Distillation gave the bromo derivative of b.p. 113–115.5°C/9.5 Torr in 76.0% yield (30.20 g). A part of the distillate was chromatographed on silica gel for analysis, using light petroleum for elution, and then distilled. For $\text{C}_8\text{H}_{11}\text{BrS}$ (219.1) calculated: 43.84% C, 5.06% H, 36.47% Br, 14.63% S; found: 44.14% C, 4.97% H, 36.70% Br, 14.48% S. IR spectrum (cm^{-1}): 3070, 3050, 1538. Mass spectrum: major component: $\text{M}^+ = 218$, base peak m/e 97 (thiapyrilium), with corresponding fragmentation; minor component: $\text{M}^+ = 218$.

Ethyl 2-Ethoxycarbonyl-3-methyl-5-(2-thienyl)pentanoate

Ethyl malonate (6.83 g, 42.7 mmol) was added dropwise, under stirring, over 5 minutes to a solution of sodium (0.91 g, 39.4 mgat) in ethanol (24 ml) kept under argon. Dry NaJ (0.5 g) was then added followed, over 5 minutes, by the preceding bromo derivative (7.19 g, 32.8 mmol, dropwise addition). The mixture was stirred at room temperature for 15 minutes and at 80°C (internal temperature) until all of the bromo derivative had reacted, following the reaction course by TLC in light petroleum–acetone 9 : 1. The precipitated salts were filtered off and washed, the filtrate was distilled *in vacuo* to eliminate ethanol, then diluted with water, acidified with acetic acid and extracted with ether. The extract was washed until neutral and dried over MgSO_4 , filtered and distilled. The residue was distilled in a Hickman flask with glass wool to give the required ester, boiling at 128°C/0.009 Torr–145°C/0.008 Torr (bath temperature). Yield 6.65 g (67.9%). According to TLC the product contained traces of the starting bromo derivative and 4-(2-thienyl)-2-butanol as impurities.

Methyl 3-Methyl-5-(2-thienyl)pentanoate

The preceding ethyl ester (35.01 g, 117.3 mmol) was saponified by standing with a KOH solution (20 g) in water (20 ml) and methanol (200 ml) for 72 hours. Methanol was then distilled off *in vacuo* and the non acid material was extracted with ether (four times). The aqueous phase was acidified with diluted H_2SO_4 (1 : 5) to Congo red and the acid was extracted with ether. After washing the extract and drying over MgSO_4 and evaporation the residue (20.68 g) was mixed with crushed glass (particle size 0.5–1 mm; 2.5 g) and heated gradually at 145–160°C, first under mildly reduced pressure and then in full vacuum of a water pump (12 Torr). The heating was continued under a reflux condenser for 45 minutes. After cooling the residue was extracted with ether, the glass filtered off and the filtrate extracted with a NaOH (5 g) solution in water (100 ml). Ether was separated and the aqueous phase reextracted with ether. The aqueous phase was acidified with dilute H_2SO_4 (1 : 5) to Congo red and the acid extracted with ether. The extract was washed and dried over MgSO_4 , then filtered and the filtrate concentrated. The residue (15.36 g) was esterified with diazomethane prepared in the conventional manner from N-nitrosomethylurea (20 g) in ether (200 ml), under the effect of 40% KOH (60 ml). After a conventional work-up the required ester was obtained, b.p. 100°C/0.007 Torr–104°C/0.008 Torr, yield 14.09 g (56.6%). For $\text{C}_{11}\text{H}_{16}\text{O}_2\text{S}$ (212.3) calculated: 62.23% C, 7.60% H, 15.10% S; found: 62.08% C, 7.46% H, 14.63% S. Mass spectrum: $\text{M}^+ = 212$; base peak m/e 97 (thiapyrilium) with a corresponding fragmentation, containing a small amount of an admixture of the same mass. IR spectrum (cm^{-1}): 1741, 1538, 1201, 1166.

Ethyl 3-Methyl-5-(2-thienyl)pentanoate⁶

A mixture of ethyl 2-ethoxycarbonyl-3-methyl-5-(2-thienyl)pentanoate (6.55 g, 22.29 mmol) and dry NaCN (2.18 g, 44.57 mmol) was mixed with dimethyl sulfoxide (25 ml) and stirred at 160°C for 7 hours. After cooling the mixture was poured into water (200 ml) containing 3 g (50 mmol) of acetic acid and extracted with light petroleum. The extract was washed with 1M-KHCO₃ and water, and dried over MgSO₄. Distillation gave crude ester boiling at 100°C/0.07 Torr—118°C/0.05 Torr (bath temperature) (3.74 g), which was chromatographed on silica gel (140 g, light petroleum-ether 98 : 2). Distillation of the fractions containing a single compound according to TLC (light petroleum-ether 95 : 3) from a Hickman flask filled with glass wool gave the required pentanoate, boiling at 98°C/0.009 Torr—128°C/0.005 Torr (bath temperature). Yield 3.22 g (63.8%). For C₁₂H₁₈O₂S (226.3) calculated: 63.68% C, 8.02% H, 14.16% S; found: 64.03% C, 7.99% H, 14.32% S. IR spectrum (cm⁻¹): 1740, 1166.

3-Methyl-5-(2-thienyl)pentanol

This was prepared analogously with 4-(2-thienyl)-2-butanol from methyl 3-methyl-5-(2-thienyl)-pentanoate (13.87 g, 65.3 mmol) and LiAlH₄ (1.86 g, 49 mmol) in ether (150 ml). On distillation it gave the alcohol, b.p. 114—118°C/0.25 Torr, in 84.0% yield (10.11 g). For C₁₀H₁₆OS (184.3) calculated: 65.17% C, 8.75% H, 17.40% S; found: 64.99% C, 8.58% H, 17.18% S. IR spectrum (cm⁻¹): 3635, 1538, 1057.

3-Methyl-5-(2-thienyl)pentanal⁶ (II)

Dry CrO₃ (12 g, 120 mmol, dried in vacuum over P₂O₅) was added into a solution of pyridine (18.98 g, 240 mmol) in dichloromethane (300 ml, dried over P₂O₅) under stirring which was continued at room temperature for 30 minutes. The preceding pentanol (3.69 g, 20 mmol) in dichloromethane (4 ml) was then added under Ar and the stirring was continued while the course of the reaction was controlled by TLC (light petroleum-acetone 9 : 1). After one hour the starting alcohol disappeared. The dichloromethane solution was decanted from the dark reaction products and the residue in the flask was washed with ether (3 times with 135 ml). The combined dichloromethane and ether solutions were washed gradually with 5% NaOH solution (three 200 ml portions), 5% HCl (two 100 ml portions), 5% aqueous NaHCO₃ (200 ml), and saturated NaCl to neutrality, and the solution was dried over MgSO₄. Distillation from a Hickman flask containing glass wool gave the aldehyde, boiling at 90°C/0.008 Torr—100°C/0.0065 Torr (bath temperature) in a 80.7% yield (3.16 g). For C₁₀H₁₄OS (182.3) calculated: 65.89% C, 7.74% H, 17.59% S; found: 65.54% C, 7.70% H, 17.53% S. IR spectrum (cm⁻¹): 1730, 1582, 1539, 1515.

1-Bromo-3-methyl-5-(2-thienyl)pentane

This was prepared⁷ in a manner analogous to that of the preparation of 2-bromo-4-(2-thienyl)-butane from 3-methyl-5-(2-thienyl)pentanol (6.14 g, 33.32 mmol), triphenylphosphine (10.49 g, 39.98 mmol) and bromine (6.39 g, 39.98 mmol) in dimethylformamide (40 ml), with the difference that the mixture was not distilled, but extracted many times with light petroleum, the extract washed until neutral, dried over MgSO₄ and the light petroleum distilled off, finally in a vacuum. Thus, crude bromo derivative was obtained (10.19 g) which contained a considerable amount of triphenylphosphine oxide, which was used for further reaction.

6-Methyl-8-(2-thienyl)-2-octanone (*III*)

Ethyl acetoacetate (5.64 g, 43.31 mmol) was added dropwise under stirring and over 10 minutes to a solution of sodium (0.92 g, 39.98 mgat) in ethanol (24 ml), NaJ (0.25 g) was added to it, followed by dropwise addition of crude bromide from the preceding experiment (10.19 g) over 10 minutes. The mixture was stirred for 30 minutes and allowed to stand at room temperature for 64 hours. The reaction mixture was then heated at 80°C for 11.5 hours, 10% aqueous NaOH (53 ml) was then added dropwise over 10 minutes and the heating was continued for another 4 hours. After cooling the mixture was diluted with water and extracted with light petroleum. After washing of the extract and drying over MgSO₄ the crude product obtained was chromatographed on silica gel (240 g, light petroleum–acetone 97.5 : 2.5). According to TLC (light petroleum–acetone 95 : 5) the pure fractions gave on distillation from a Hickman flask filled with glass wool the ketone boiling at 115°C/0.007 Torr–130°C/0.004 Torr (bath temperature) in 54.2% yield (4.05 g), calculated per 3-methyl-5-(2-thienyl)pentanol. For C₁₃H₂₀OS (224.35) calculated: 69.59% C, 8.99% H, 14.29% S; found: 66.46% C, 8.46% H, 13.85% S. Mass spectrum: M⁺ = 224; base peak *m/e* 97 (thiapyrylium) with corresponding fragmentation, in addition to a small amount of a compound of M⁺ = 302; base peak *m/e* 175 (bromothiapyrylium). IR spectrum (cm⁻¹): 1720, 1540, 1538, 1410, 1360. The substance could not be purified from an impurity containing bromine.

Methyl 3,7-Dimethyl-9-(2-thienyl)-2,6-nonadienoate (*IVa*)

A solution of sodium (0.253 g, 11 mgat) in methanol (6 ml) was added into a solution of compound I (2.22 g, 10 mmol) and dimethyl methoxycarbonylmethylphosphonate (2.00 g, 11 mmol) (prepared similarly as diethyl ethoxycarbonylmethylphosphonate according to¹², b.p. 95.5 to 103.5°C/0.3 Torr) in methanol (14 ml) dropwise over 10 minutes. After 5.5 hours' stirring at room temperature and standing overnight methanol was evaporated *in vacuo* at 30°C, the mixture diluted with water (300 ml) containing 1M-H₂SO₄ (6 ml) and extracted with light petroleum. The crude product, obtained from the extract by its washing and drying over MgSO₄, was chromatographed on silica gel (130 g, light petroleum–methyl acetate (97.5 : 2.5). Combination of the fractions identical according to TLC (in light petroleum–methyl acetate (95 : 5) and their distillation from a Hickman flask gave 2 fractions, differing in the ratio of isomers; *IVa*₁ boiling at 140–150°C/0.007 Torr (bath temp.), yield 1.89 g (67.9%), and *IVa*₂ boiling at 130–140°C : 0.007 Torr (bath), yield 0.05 g (1.8%); total yield 1.94 g (69.7%). For C₁₆H₂₂O₂S (278.4) calculated: 69.00% C, 7.97% H, 11.52% S; found: 69.10% C, 7.94% H, 11.65% S. IR spectrum (cm⁻¹): 1711, 1651, 1590, 1581, 1436, 1226, 1155, 1149.

Ethyl 3,7-Dimethyl-9-(2-thienyl)-2,6-nonadienoate (*IVb*)

This was prepared analogously with *IVa* from ketone I (2.22 g, 10 mmol), and diethyl ethoxycarbonylmethylphosphonate¹² (2.47 g, 11 mmol) in ethanol. The crude product was chromatographed on silica gel (135 g, light petroleum–ethyl acetate 97 : 3). By combining the fractions which were identical according to TLC (light petroleum–ethyl acetate 95 : 5) 2 fractions were obtained differing in the ratio of isomers present in them: *IVb*₁, boiling at 145–160°C/0.006 Torr (bath), yield 2.13 g (72.8%) and *IVb*₂, boiling at 140–150°C/0.006 Torr (bath), yield 0.14 g (4.8%); total yield 2.27 g (77.6%). For C₁₇H₂₄O₂S (292.4) calculated: 69.82% C, 8.27% H, 10.96% S; found: 70.16% C, 8.20% H, 10.86% S. IR spectrum (cm⁻¹): 1717, 1649, 1590, 1581, 1222, 1153, 1145.

Ethyl 3,7-Dimethyl-9-(2-thienyl)-2-nonenolate (*VIa*)

This was prepared in an analogous manner with *IVb* from *III* (1.91 g, 8.5 mmol), diethyl ethoxycarbonylmethylphosphonate¹² (2.10 g, 9.35 mmol) and a solution of sodium (0.22 g, 9.35 mgat) in ethanol. The crude product was chromatographed on silica gel (130 g, light petroleum-ether 98 : 2). After combination of the fractions which were identical according to TLC (light petroleum-abs. ether 9 : 1) two fractions were obtained, differing in the ratio of isomers: *VIa*₁, boiling at 142–150°C/0.006 Torr (bath), yield 0.17 g (5.8%) and *VIa*₂ boiling at 142–150°C/0.006 Torr (bath), yield 1.56 g (53.0%); total yield 1.73 g (58.75%). For C₁₇H₂₆O₂S (294.4) calculated: 69.34% C, 8.90% H, 10.89% S; found: 69.16% C, 8.81% H, 10.87% S. IR spectrum (cm⁻¹): 1715, 1650, 1540, 1233, 1175, 1149.

Isopropyl 3,7-Dimethyl-9-(2-thienyl)-2,6-nonadienoate (*IVc*)

Diisopropyl isopropoxycarbonylmethylphosphonate (3.33 g, 12.25 mmol) prepared analogously as diethyl ethoxycarbonylmethylphosphonate according to¹² (b.p. 94.5–97°C/0.22 Torr) was added dropwise under stirring into a suspension of NaH (0.30 g, 10 mmol of 80%) in peroxide-free 1,2-dimethoxyethane (20 ml). After one hour's stirring at room temperature compound *I* (2.22 g, 10 mmol) was added dropwise over 5 minutes and the stirring was continued for 30 minutes at room temperature and 4 hours at 50–60°C. After cooling the mixture was poured into water (300 ml) acidified with 1M-H₂SO₄ (6 ml) and extracted with light petroleum. The residue obtained from the extract after washing and drying over MgSO₄ was chromatographed on silica gel (130 g, light petroleum-acetone 98 : 2). The fractions which were identical according to TLC (light petroleum-ethyl acetate 94 : 6) were combined and distilled from a Hickman flask with glass wool to give 2 fractions differing in the ratio of isomers; *IVc*₁ boiling at 140–152°C/0.007 Torr (bath), yield 1.64 g (53.5%), and *IVc*₂ boiling at 140–165°C/0.006 Torr (bath.), yield 0.28 g (9.1%); total yield 1.92 g (62.6%). For C₁₈H₂₆O₂S (306.5) calculated: 70.54% C, 8.55% H, 10.46% S; found: 70.65% C, 8.51% H, 10.45% S. IR spectrum (cm⁻¹): 1711, 1649, 1580, 1539, 1225, 1158, 1146.

Monoethylamide of 3,7-Dimethyl-9-(2-thienyl)-2,6-nonadienoic Acid (*IVd*)

This was prepared in the same manner as *IVc* from ketone *I* (2.22 g, 10 mmol) and diethyl monoethylaminocarbonylmethylphosphonate¹³ (2.73 g, 12.25 mmol). The crude product was chromatographed on silica gel (130 g, light petroleum-acetone 85 : 15). The fractions which were identical according to TLC (light petroleum-acetone 75 : 25) were combined and evaporated *in vacuo* (10 Torr) at 98°C to give two fractions, differing in the ratio of isomers: *IVd*₁ (0.57 g, 19.6%) and *IVd*₂ (1.97 g, 67.6%), total yield 2.54 g (87.1%). For C₁₇H₂₅NOS (291.4) calculated: 70.05% C, 8.65% H, 4.81% N, 11.00% S; found: 69.66% C, 8.55% H, 4.70% N, 11.04% S. IR spectrum (cm⁻¹): 3455, 1668, 1640, 1539, 1505.

Diethylamide of 3,7-Dimethyl-9-(2-thienyl)-2,6-nonadienoic Acid (*IVe*)

This was prepared in the same manner as *IVd* from ketone *I* (2.22 g, 10 mmol) and diethyl diethylaminocarbonylmethylphosphonate¹⁴ (3.08 g, 12.25 mmol). The crude amide was chromatographed on silica gel (180 g, light petroleum-acetone 9 : 1). The fractions identical according to TLC (light petroleum-acetone 4 : 1) were combined and evaporated *in vacuo* at 10 Torr and 98°C, to give 2 fractions differing in the ratio of isomers: *IVe*₁ (2.31 g, 72.3%) and *IVe*₂ (0.68 g, 21.3%); total yield 2.99 g (93.6%). For C₁₉H₂₉NOS (319.5) calculated: 71.42% C, 9.15% H, 4.38% N, 10.04% S; found: 71.29% C, 9.07% H, 4.38% N, 9.84% S. IR spectrum (cm⁻¹): 1650, 1629, 1540.

Dimethyl 2-Methyl-3-methoxycarbonyl-2-propenylphosphonate

About one tenth of the amount of the total employed trimethyl phosphite (39.69 g, 319.87 mmol) was added to methyl 4-bromo-3-methyl-2-butenonate (56.13 g, 290.7 mmol) and the mixture was heated in a bath until incipient rearrangement (100–105°C). The rest of the phosphite was then added dropwise so that the reaction would proceed at a convenient rate. The heating was continued at 145°C, for another hour, the volatile material was evaporated *in vacuo* and the residue distilled. The fraction boiling at 92–135°C/0.35 Torr was collected which was redistilled through a Vigreux column, to afford the required phosphonate, b.p. 108–115°C/0.008 Torr, in 60.9% yield (39.35 g).

Methyl 3,7-Dimethyl-9-(2-thienyl)-2,4-nonadienoate (*Va*)

This was prepared analogously as *IVc* from aldehyde *II* (1.82 g, 10 mmol) and the preceding phosphonate (2.78 g, 12.5 mmol), with the difference that the mixture after addition of the aldehyde was stirred only at room temperature for 4.5 hours, and then allowed to stand overnight. The crude product was chromatographed on silica gel (130 g, light petroleum–ether 96 : 4). Distillation of the fractions which were identical according to TLC (light petroleum–ether 96 : 4) from a Hickman flask with glass wool gave the ester, boiling at 160°C/0.006 Torr–170°C/0.004 Torr (bath temperature), in 74.3% yield (2.07 g). For $C_{16}H_{22}O_2S$ (278.4) calculated: 69.02% C, 7.97% H, 11.52% S; found: 69.23% C, 8.03% H, 11.58% S. IR spectrum (cm^{-1}): 1720, 1640, 1613, 1609 sh, 1540, 1242, 1159.

Diisopropyl 2-Methyl-3-isopropoxycarbonyl-2-propenylphosphonate

A mixture of triisopropyl phosphite (54.5 g, 262 mmol) and about one tenth of the required amount of isopropyl 4-bromo-3-methyl-2-butenonate (58.0 g, 262 mmol) was heated to the temperature at which the rearrangement began (145°C). The remaining butenoate was then added dropwise over one hour. After another hour of heating at 150°C the volatile material was evaporated *in vacuo* (up to 120°C/13 Torr) and the residue distilled to give the required phosphonate, b.p. 110–113.8°C/0.008 Torr in 75% yield (60.27 g).

Isopropyl 3,7-Dimethyl-9-(2-thienyl)2,4-nonadienoate (*Vb*)

It was prepared in the same manner as *Va*, from aldehyde *II* (1.82 g, 10 mmol) and the preceding phosphonate (3.83 g, 12.5 mmol), with the difference that for the formation of the ylide the phosphonate had to be heated with NaH at 40–45°C for 45 minutes. The crude product was chromatographed on silica gel (230 g, light petroleum–ether 98 : 2). The fractions which were identical according to TLC in light petroleum–ether 19 : 1 (triple development) were distilled from a Hickman flask filled with glass wool to yield 2 fractions differing by the ratio of isomers: *Vb*₁, boiling at 138–145°C/0.004 Torr (bath), yield 1.20 g (39.2%), and *Vb*₂, boiling at 135 to 158°C/0.004 Torr (bath), yield 0.12 g (3.9%); total yield, 1.32 g (43.1%). For $C_{18}H_{26}O_2S$ (306.5) calculated: 70.54% C, 8.55% H, 10.46% S; found: 70.34% C, 8.51% H, 10.49% S. IR spectrum (cm^{-1}): 1711, 1640, 1615, 1539, 1511, 1240, 1160 and further aromatic bands.

Monoethylamide of 3,7-Dimethyl-9-(2-thienyl)-2-nonenic Acid (*Vib*)

This was prepared similarly as *IVd* from ketone *III* (1.79 g, 7.89 mmol) diethyl monoethylamino-carbonylmethylphosphonate¹³ (2.20 g, 9.86 mmol) and NaH (0.24 g, 7.89 mmol). The crude product was chromatographed on silica gel (130 g, light petroleum–acetone 98 : 2). The fractions

which were identical according to TLC (light petroleum-acetone 85 : 15) were combined, evaporated in vacuum at 98°C and 10 Torr, to give two fractions differing in the ratio of the isomers: Vib_1 in 9.93% yield (0.23 g), and Vib_2 in 74.29% yield (1.72 g); total yield 1.95 g (84.22%). As the analysis of Vib_2 was not satisfactory the substance was rechromatographed on alumina, activity III (100 g, light petroleum-ether 1 : 1), and the pure fractions were combined, concentrated and distilled from a Hickman flask with glass wool. The required amide 1.42 g was obtained, boiling at 170–180°C/0.003 Torr (bath temperature). For $C_{17}H_{27}NOS$ (293.5) calculated: 69.57% C, 9.28% H, 4.77% N, 10.93% S; found: 68.85% C, 9.34% H, 4.75% N, 10.71% S. Mass spectrum: the major component is the *cis* and *trans* amide, $M^+ = 293$, base peak m/e 97 (thiapyrilium) with the corresponding fragmentation. According to high-resolution measurement its composition was $C_{17}H_{27}NOS$, but it was contaminated with the amide of $M^+ = 371$, base peak m/e 175 (bromothiapyrilium) and a negligible amount of the amide of $M^+ = 449$, base peak m/e 253 (dibromothiapyrilium). IR spectrum (cm^{-1}): 1675, 1645, 1539, 1504, 694.

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