SYNTHESIS OF ANALOGS OF JUVENOIDS

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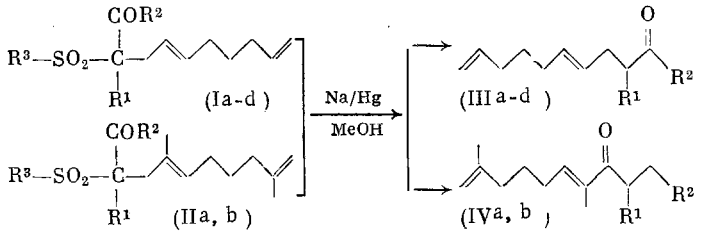
Active analogs of juvenile hormone (JH) are known in the unsaturated acid series, among which isoprenoid 2,4-dienoates have become of practical value [1-3]. The further search for active compounds in this series is undoubtedly expedient.

It seemed of interest to use telomers of 1,3-dienes with β-sulfono esters (Ia-d and IIa, b) [4, 5] for the synthesis of substances with potential juvenile hormone activity.

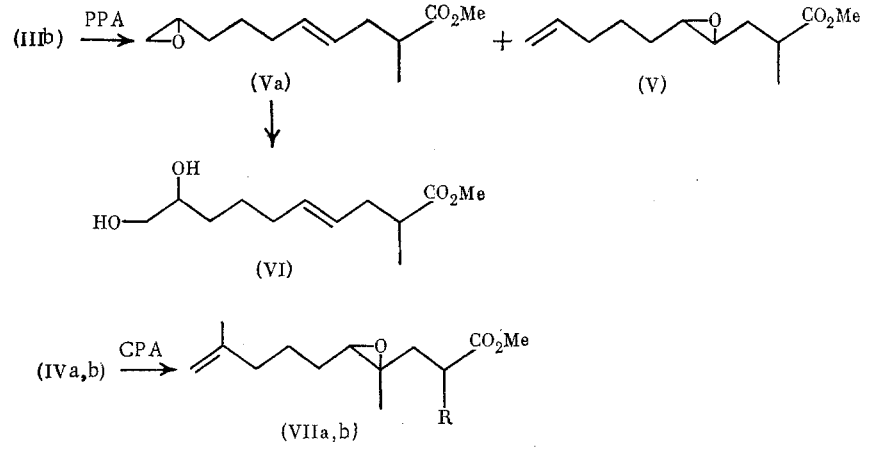
Desulfonation under the influence of Na amalgam by the method in [6] served as the first transformation. 4,9-Decadiene derivatives IIIa-d and IVa, b were obtained in 70-78% yields. The subsequent structural modifications were directed toward increasing the length of the hydrocarbon chain and introducing functional groups that are characteristic for JH and its active analogs.



$R^1 = H$, $R^2 = OMe$, $R^3 = Ph$ (Ia), (IIIa); $R^1 = Me$, $R^2 = OMe$, $R^3 = Ph$ (Ib), (IIIb);

$R^1 = Pr$, $R^2 = OMe$, $R^3 = p$-Tol (Ic), (IIIb); $R^1 = H$, $R^2 = Me$, $R^3 = Ph$ (Id), (IIId); $R^1 = H$, $R^2 = OMe$, $R^3 = Ph$ (IIa), (IVa); $R^1 = Me$, $R^2 = OMe$, $R^3 = p$-Tol (IIb), (IVb).

The epoxidation of esters IIIb and IVa, b was realized with perphthalic acid (PPA) and p-carbomethoxyperbenzoic acid (CPA).



R = H (IVa), (VIIa); Me (IVb), (VIIb).

The epoxidation of IIIb with PPA with subsequent chromatography on SiO_2 led to two products. One of them is epoxide V, the structure of which was confirmed by elementary and spectral analysis. The PMR spectrum contains signals at δ 2.31 and 4.50 ppm, which correspond to the protons attached to the C^4—C^5 atoms and the vinyl protons attached to the C^{10} atom. With respect to the results of elementary analysis, the second product corresponds

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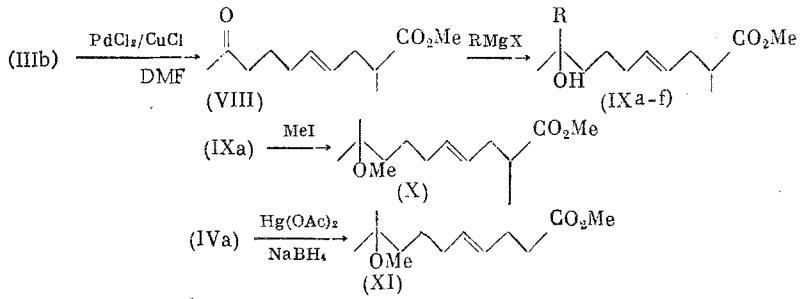
TABLE 1

Reagent	Reaction time, h	Reaction temp., °C	Yield, %	Literature method
tert-BuOK/DMSO	18	130	38	[9]
tert-BuOK/pyridine	18	115	40–50	[11]
MeONa/MeOH	18	65	–	[11]
$CaCO_3$/p-xylene	20	140	2	[12]
$CaCO_3$/PhMe	16	110	–	[12]
EtONa/EtOH	18	78	35	[13]
$NaNH_2/NH_3$	30	–70	–	[14]
KOH/H_2O	6	25	–	[15]
KOH/*t*-BuOH	10	120	–	[15]

to the composition $C_{12}H_{22}O_4$. The presence in the PMR spectrum of VI of a two-proton multiplet at δ 5.02 ppm and the absence in the IR and PMR spectra of signals that characterize a terminal methylene group indicate that the compound is the product of hydration of epoxide Va.

The action of CPA on esters IVa, b leads to the formation of C^4–C^5 monoxides VIIa, b. The four protons attached to the C^6 and C^3 atoms resonate at δ 2.20 ppm in the PMR spectrum of epoxy ester VIIa; a one-proton multiplet of the environment of the C^5 atom is observed at δ 2.70 ppm, and a CH_2=C singlet is observed at δ 5.52 ppm.

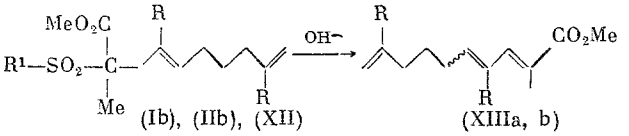
The corresponding hydroxy esters IXa-f were obtained by oxidation of ester IIIb by the method in [7] with subsequent reaction of VIII with Grignard reagents. Methoxy derivatives X and XI were obtained by standard methylation or reductive methoxymercuration [8]. Spec-



R = Me (IXa), Et (IXb), *i*-Bu (IXc), CH_2=CH (IXd), Ph (IXe), C_5H_{11} (IXg), CH≡C (IXf).

tral analysis confirmed their structures. Thus the IR spectrum of XI does not contain absorption bands at 890, 1640, and 3080 cm^{-1}, and the PMR spectrum does not contain a singlet at δ 4.67 ppm; this constitutes evidence for disappearance of the terminal C=C bond in ester IVb. On the other hand, a signal corresponding to three protons of an OCH_3 group appears at δ 3.13 ppm; the signal at 1.95 ppm corresponds to four allyl protons, and a signal of methyl protons of a $(CH_3)_2CO$ grouping is located at δ 1.08 ppm.

In order to obtain compounds with a conjugated 2,4-diene structure we searched for the optimum method for the elimination of sulfinic acid fragments from β-arylsulfonyl and β-alkylsulfonyl esters. It is apparent from Table 1 that we were unable to accomplish the elimination of the RSO_2 group by means of a number of methods. Thus, according to [12], aliphatic sulfones split out sulfinic acids when they are treated with $CaCO_3$ in refluxing toluene. Better results were obtained when tert-BuOK in pyridine was used, in which case the products were obtained in 40-50% yields. However, in this case ester XIIIb was a mixture of E,Z-isomers, which we were unable to separate. The shift of the signal in the IR spectrum from 1740 to 1710 cm^{-1} constitutes evidence for the presence of a conjugated system. A one-proton multiplet appears in the PMR spectrum at δ 5.91 ppm. The UV spectrum contains two absorption maxima at λ 235 nm (ε 9260) and λ 220 nm (ε 8140).



R^1 = Ph, R = H (Ib), (XIIIa); R^1 = *p*-Tol, R = Me (IIb), (XIIIb); R^1 = Et, R = H (XII), (XIIIa)

TABLE 2. Physicochemical Constants and Results of Elementary Analysis of the Compounds Obtained

Compound	Yield, %	n_D^{20}	bp, °C (1 mm)	Found, %		Empirical formula	Calc., %	
				C	H		C	H
(IIIa)	78	1,4752	55	72,61	9,71	$C_{11}H_{18}O_2$	72,49	9,95
(IIIb)	78	1,4501	69	73,10	10,54	$C_{12}H_{20}O_2$	73,42	10,27
(IIIc)	75	1,4538	56	74,90	11,53	$C_{14}H_{24}O_2$	74,95	10,78
(IIId)	75	1,4767	–	76,98	10,96	$C_{11}H_{18}O_3$	79,46	10,91
(IVa)	70	1,4573	70	74,01	10,28	$C_{13}H_{22}O_2$	74,24	10,54
(IVb)	70	1,4582	72	74,42	10,77	$C_{14}H_{24}O_2$	74,95	10,78
(V)	55	1,4501	–	67,29	9,20	$C_{12}H_{20}O_3$	67,89	9,50
(VIIa)	55	–	25	68,29	9,09	$C_{13}H_{22}O_3$	68,99	9,80
(VIIb)	55	–	38	69,59	10,52	$C_{14}H_{24}O_3$	69,86	10,07
(VIII)	90	1,4567	104	68,23	9,52	$C_{12}H_{20}O_3$	67,89	9,49
(IXa)	64	1,4571	89	68,44	10,51	$C_{13}H_{24}O_3$	68,38	10,59
(IXb)	58	1,4578	–	69,66	10,07	$C_{14}H_{26}O_3$	69,38	10,81
(IXc)	66	1,4590	–	71,20	11,32	$C_{16}H_{30}O_3$	71,06	11,18
(IXd)	65	1,4680	106	70,51	10,01	$C_{14}H_{24}O_3$	69,96	10,07
(IXe)	60	1,4821	–	74,35	8,95	$C_{18}H_{26}O_3$	74,44	9,02
(IXf)	64	1,4602	120	71,64	11,57	$C_{17}H_{32}O_3$	71,78	11,34
(IXg)	85	1,1646	115	70,41	9,40	$C_{14}H_{22}O_3$	70,55	9,68
(X)	70	–	–	69,03	10,47	$C_{14}H_{26}O_3$	69,38	10,81
(XI)	60	1,4519		69,03	10,81	$C_{14}H_{26}O_3$	69,38	10,81
(XIIIa)	45	–	–	70,90	13,00	$C_{12}H_{18}O_2$	70,94	13,3
(XIIIb)	45	–	–	74,38	11,67	$C_{14}H_{27}O_2$	74,0	11,94

Compounds Ia-d, IIIa, b, and V-XI were tested for biological activity, and VIII displayed JH activity in the case of the large mealworm.

EXPERIMENTAL

The IR spectra of films of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with a Tesla BS-487 spectrometer at 60 MHz relative to hexamethyldisiloxane. Analysis by gas-liquid chromatography (GLC) was carried out with a Khrom-41 chromatograph with a flame-ionization detector, a 1.2-m-long column packed with SE-30, and He as the carrier gas.

Methyl trans-4,9-Decadienoate (IIIa). A 5.68-g (40 mmole) sample of Na_2HPO_4 was added to a solution of 3.22 g (10 mmole) of Ia in 50 ml of MeOH, after which 8 g of 6% Na/Hg was added at 0°C, and the mixture was stirred for 2 h. The MeOH was evaporated, the residue was dissolved in H_2O, and the aqueous solution was extracted with ether. The extract was dried with $MgSO_4$, the ether was removed by distillation, and the oily residue was distilled in vacuo to give 1.4 g (78%) of ester IIIa. IR spectrum (ν, cm^{-1}): 920, 1645, 3085 (CH_2=C); 975, 1000, 3010 (trans-CH=CH); 1260, 1745 (CO_2Me). PMR spectrum (δ, ppm): 1.35 m (2H, CH_2), 1.93 m (6H, CH_2C=C), 2.28 m (2H, CH_2CO_2), 3.58 s (3H, CH_3), 4.86 m (2H, CH_2=C), and 5.36 m (3H, CH=C). Compounds IIIb-d and IVa, b were similarly obtained. The characteristics and yields are presented in Table 2.

Methyl 2-Methyl-4,5-epoxy-9-decenoate (V). An 11.6-ml (5.1 mmole) sample of 11.3% perphthalic acid (PPA) was added to a solution of 1 g (5.1 mmole) of ester IIIb in 5 ml of ether, and the mixture was stirred at 25°C for 5 h. The ether was evaporated, and the product was chromatographed on SiO_2 in a hexane–ethyl acetate system (7:1) to give 60 mg (55%) of monoxide V. IR spectrum (ν, cm^{-1}): 925, 1650, 3080 (CH_2=CH); 1260, 1745 (CO_2Me). PMR spectrum (δ, ppm): 1.12 m (3H, CH_3), 1.44 m (2H, CH_2), 1.98 m (5H, CH_2C=C, CH_2COC, CH), 2.58 m (1H, CHCOC), 3.58 s (3H, OCH_3), and 4.90 m (CH_2=C).

Methyl 4,9-Dimethyl-4,5-epoxy-9-decenoate (VIIa). A 1.181-g sample of 80% p-carbomethoxyperbenzoic acid (CPA) was added to a solution of 1 g (4.76 mmole) of ester IVa in 20 ml of CCl_4, and the mixture was maintained at 25°C. The CCl_4 was removed by distillation, and the residue was chromatographed on SiO_2 in a hexane–ethyl acetate system (7:1) to give 0.590 mg (55%) of VIIa. IR spectrum (ν, cm^{-1}): 890, 1650, 3080 (CH_2=C); 1280, 1740 (CO_2Me). PMR spectrum (δ, ppm): 1.22 s (3H, CH_3), 1.43 m (2H, CH_2), 1.67 s (3H, CH_3), 1.95 m (2H, CH_2C=C), 2.20 m (4H, CH_2COC), 2.70 m (HCOC), 3.63 s (3H, OCH_3), and 5.52 s (2H, CH_2=C).

Compound VIIb was similarly obtained.

Methyl 2-Methyl-9-oxo-trans-4-decenoate (VIII). Oxygen was passed through a mixture of 997 mg (5 mmole) of $PdCl_2$, 5.43 g (54 mmole) of CuCl, and 3 ml of H_2O in 25 ml of di-

methylformamide (DMF) for 1 h, after which 9.5 g (48 mmole) of ester IIIb was added to the catalyst prepared in this way, and the mixture was stirred for 6 h until 0.6 liter of O_2 had been absorbed. The mixture was then treated with 3% HCl and extracted with CH_2Cl_2. The extract was dried with $MgSO_4$, the CH_2Cl_2 was removed by distillation, and the residue was distilled in vacuo to give 9.5 g (90%) of VII. IR spectrum (ν, cm^{-1}): 965, 1000, 3010 (trans-CH=CH); 1250, 1750 (CO_2Me); 1720 (C=O). PMR spectrum (δ, ppm): 1.02 m (3H, CH_3), 1.16 m (2H, CH_2), 1.58 m (4H, $CH_2C=C$), 2.08 s (3H, $CH_3C=O$), 2.33 m (3H, $CH_2C=O$, CH), 3.65 s (3H, OCH_3), and 5.35 m (2H, CH=C).

Methyl 2,9-Dimethyl-9-hydroxy-trans-4-decenoate (IXa). A 720-mg (6.6 mmole) sample of MeI was added to 260 mg (6.6 mmole) of Mg in 15 ml of ether, after which a solution of 0.7 g (3.3 mmole) of VIII in 5 ml of ether was added dropwise at 0°C to the resulting Grignard reagent, and the mixture was stirred for 1 h. It was then treated with a saturated solution of NH_4Cl and extracted with ether. The extract was dried with $MgSO_4$, and the ether was evaporated. Chromatography of the residue on G brand SiO_2 (40/100) in a benzene–ethyl acetate system (10:1) gave 502 mg (64%) of hydroxy ester IXa. IR spectrum (ν, cm^{-1}): 980, 3040 (trans-CH=CH); 1245, 1740 (CO_2Me); 3500 (OH). PMR spectrum (δ, ppm): 1.14 d (3H, CH_3), 1.44 m (3H, CH_3), 2.00–2.64 m (10H, $2CH_2C=C$, $2CH_2$, OH, CH), 3.67 s (3H, OCH_3), 5.42 q (2H, CH=CH) Compounds VIIIb-f were similarly obtained.

Methyl 2,9-Dimethyl-9-methoxy-trans-4-decenoate (X). A mixture of 500 mg (2.19 mmole) of IXa in 4 ml of MeI, 1.11 mg (8.19 mmole) of $CaSO_4$, and 828 mg (356 mmole) of Ag_2O was stirred at 25°C for 18 h, after which it was chromatographed on SiO_2 (100/160) in an ethyl acetate–$CHCl_3$ system (1:1) to give 280 mg (50%) of methoxy ester IX. IR spectrum (ν, cm^{-1}): 975, 1000, 3030 (trans-CH=CH); 1150 (OCH_3); 1250, 1745 (CO_2Me). PMR spectrum (δ, ppm): 1.08 d (3H, CH_3), 1.21 m (6H, $2CH_3$), 1.37 q (2H, CH_2), 1.80–2.40 m (5H, $4CH_2C=C$, CH), 3.11 s (3H, OCH_3), 3.61 s (3H, CO_2CH_3), and 5.38 m (2H, CH=CH).

Methyl 4,9-Dimethyl-9-methoxy-trans-4-decenoate (XI). A suspension of 1.05 g of $Hg(OAc)_2$ was added to a cooled (with ice water) solution of 1 g (4.76 mmole) of ester IVa in 15 ml of absolute MeOH, and the mixture was stirred at 5°C for 1 h and at 20°C for 2 h. A solution of 2 g of NaOH, 2.5 ml of H_2O, and 0.7 g of $NaBH_4$ was then added at 5°C, and the mixture was stirred at 5°C for 1 h. It was then poured into water, and the aqueous mixture was extracted with ether. The ether extract was washed with water and dried with $MgSO_4$, the ether was removed by distillation, and the product was chromatographed on SiO_2 in a hexane–ethyl acetate system (7:1) to give 0.69 g (60%) of methoxy ester XI. IR spectrum (ν, cm^{-1}): 890, 3020 (trans-CH=C); 1250, 1750 (CO_2Me). PMR spectrum (δ, ppm): 0.98 m (2H, CH_2), 1.08 s (6H, $2CH_3$), 1.20 m (2H, CH_2), 1.37 q (2H, CH_2CO), 1.58 m (2H, CH_2CO), 1.95 m (4H, $2CH_2C=C$), 2.31 s (3H, CH_3), 3.13 s (3H, OCH_3), 3.63 s (3H, OCH_3), and 5.13 m (2H, CH=CH).

Methyl 2-Methyl-2,4-E,Z-9-decatrienoate (XIIIa). A solution of 1.67 g (5 mmole) of sulfono ester Ib in 10 ml of pyridine was added dropwise in a stream of argon to 2.26 g (20 mmole) of freshly prepared tert-BuOK in 50 ml of absolute pyridine, and the reaction mixture was stirred at 115°C for 18 h. It was then poured into water, and the aqueous mixture was acidified and extracted with ether. The extract was dried with $MgSO_4$, the ether was removed by distillation, and the product was chromatographed on SiO_2 (100/160) in a hexane–ether system (7:1) to give 0.36 g (40%) of ester XIIIa. IR spectrum (ν, cm^{-1}): 920, 1650, 3080 ($CH_2=CH$); 980, 1600, 2990 (trans-CH=CH); 1250, 1710 (CO_2Me). PMR spectrum (δ, cm^{-1}): 1.28 m (5H, CH_3, CH_2) and 1.93 m (4H, $2CH_2$).

Methyl 2,4,9-Trimethyl-2,4-E,Z-9-decatrienoate (XIIIb). This compound was obtained by a procedure similar to that used to prepare XIIIa. IR spectrum (ν, cm^{-1}): 890, 1650, 3080 ($CH_2=C$); 820, 1600, 1620 (CH=CH conjugation); 1250, 1715 (CO_2Me). PMR spectrum (δ, cm^{-1}): 0.8 s (6H, $2CH_3$), 1.16 m (4H, $2CH_2$), 1.58 s (3H, CH_3), 5.43 s (2H, $CH_2=C$), 5.05 (CH=C), and 5.91 (CH in conjugation).

CONCLUSIONS

Structural analogs of juvenile hormone, viz., derivatives of C_{10}–C_{14} aliphatic unsaturated acids, were synthesized on the basis of telomers of butadiene and isoprene with β-sulfono esters and β-keto sulfones.

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