SYNTHESIS OF SOME 6-OXA ANALOGUES OF ACYCLIC JUVENOIDS*

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Received May 30th, 1973

As analogues of the insect juvenile hormone, numerous esters and amides of 6-oxaalkenoic acids and 6 oxaalkadienoic acids have been prepared along with their chloro, epoxy, and alkoxy derivatives.

In connection with the recent synthesis and biological evaluation of some 5-oxa analogues of the insect juvenile hormone[1], we wish to report in the present paper the preparation** of the corresponding 6-oxa analogues (for previous reports see the Patent applications[1-4]), namely, of esters and amides of 6-oxa-2-alkenoic or 6-oxa-2,10--alkadienoic acids and their chloro, alkoxy, and epoxy derivatives.

Aliphatic branched saturated or unsaturated alcohols of a suitable number of carbon atoms have been used as the starting material. The acid-catalysed reaction of these alcohols with methyl vinyl ketone[5] afforded the corresponding β-alkoxyketones which were converted to esters of α,β-unsaturated 6-oxa acids by reaction with alkoxycarbonylmethylenetriphenylphosphorane[6,7] or dialkyl alkoxycarbonylmethanephosphonates[8], or, by the Reformatsky reaction with ethyl bromoacetate and the subsequent dehydration of the resulting β-hydroxy ester. The amides of α,β--unsaturated 6-oxa acids have been prepared either on treatment of β-alkoxy ketones with dialkyl N-alkyl- or N,N-dialkylaminocarbonylmethanephosphonates or by reaction of amines with chlorides of α,β-unsaturated 6-oxa acids. The 6-oxa acyl chlorides have been obtained by the action of thionyl chloride on the corresponding acids, prepared in turn by saponification of 6-oxa esters.

By the addition of hydrogen chloride or alcohols, or, by epoxidation, the esters and amides of 6-oxa-2,10-alkadienoic acids have been converted to the corresponding chloro, alkoxy, and epoxy derivatives.

* Part XX in the series Natural and Synthetic Materials with the Insect Hormone Activity; Part XIX: This Journal *39*, 587 (1974).

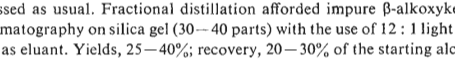
** The biological activity of the present substances will be reported elsewhere in collaboration with workers of the Entomological Institute, Czechoslovak Academy of Sciences, Prague.

EXPERIMENTAL

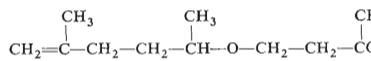
The IR spectra were measured in tetrachloromethane. The NMR spectra were taken in deuteriochloroform (tetramethylsilane as internal standard). Chemical shifts are expressed in δ (ppm) and the coupling constants in Hz. The column chromatography was performed on silica gel previously partially deactivated by shaking with 12% of water.

Preparation of β-Alkoxyketones *I*—*IV*

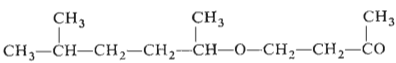
A mixture of the corresponding alcohol (0·5 g), red mercuric oxide (0·1 g), and boron trifluoride etherate (0·1 g) was heated up to 90—100°C, cooled down, treated with the corresponding alcohol (0·05 mol) and methyl vinyl ketone (0·05 mol), kept at room temperature for 30—60 h, and then processed as usual. Fractional distillation afforded impure β-alkoxyketone which was purified by chromatography on silica gel (30—40 parts) with the use of 12 : 1 light petroleum–ether solvent mixture as eluant. Yields, 25—40%; recovery, 20—30% of the starting alcohol.



I, R = H
II, R = CH_3



III



IV

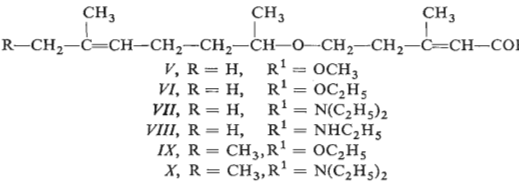
By this procedure, the following β-alkoxyketones were prepared: 6,10-dimethyl-5-oxa-9-undecen-2-one (*I*; from 6-methyl-5-hepten-2-ol); 6,10-dimethyl-5-oxa-9-dodecen-2-one (*II*; from 6-methyl-5-octen-2-ol), 6,9-dimethyl-5-oxa-9-decen-2-one (*III*; from 5-methyl-5-hexen-2-ol), and 6,9-dimethyl-5-oxa-2-decanone (*IV*; from 5-methyl-2-hexanol), see Table I.

Preparation of Esters *V*, *VI*, and *XIII*

A mixture of the β-alkoxyketone (0·01 mol), alkoxycarbonylmethylenetriphenylphosphorane (0·01 mol), benzoic acid (0·002 mol), and benzene (15—20 ml) was gently refluxed under nitrogen for 16 h. Another portions of alkoxycarbonylmethylenetriphenylphosphorane (0·005 mol) and benzoic acid (0·001 mol) were then added and the reflux continued for additional 20 h. The reaction mixture was then processed as usual and the crude product was purified by column chromatography on silica gel (30—40 parts) with the use of 12 : 1 light petroleum–ether solvent mixture as eluant. The initial chromatographic fractions afforded the individual *cis*-isomer, while the *trans*-isomer was contained in the final fractions. The ratio of the *cis*- to the *trans*-isomer was 1 : 2·0—2·5. Yields, 70—75%; recovery, 10% of the starting β-alkoxyketone.

By this procedure, the ketone *I* was converted by reaction with methoxycarbonylmethylenetriphenylphosphorane to methyl 3,7,11-trimethyl-6-oxa-2,10-dodecadienoate (*V*) and the treatment of ketones *I* and *IV* with ethoxycarbonylmethylenetriphenylphosphorane afforded ethyl

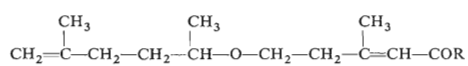
3,7,11-trimethyl-6-oxa-2,10-dodecadienoate (*VI*) and ethyl 3,7,10-trimethyl-6-oxa-2-undecenoate (*XIII*), resp., see Table I.



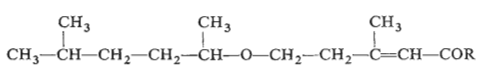
V, R = H, $R^1 = OCH_3$
VI, R = H, $R^1 = OC_2H_5$
VII, R = H, $R^1 = N(C_2H_5)_2$
VIII, R = H, $R^1 = NHC_2H_5$
IX, $R = CH_3$, $R^1 = OC_2H_5$
X, $R = CH_3$, $R^1 = N(C_2H_5)_2$

Preparation of Esters *VI*, *IX*, and *XI* and Amides *VII*, *VIII*, *X*, *XII*, and *XIV*

The dialkyl ester of the substituted alkylphosphonic acid (5·1 mmol) was added dropwise with stirring at 20—30°C under nitrogen to a suspension of sodium hydride (5·05 mmol) in 1,2-dimethoxyethane (10 ml), the resulting mixture stirred for 1 h, treated dropwise at 20—30°C with the β-alkoxyketone (5·0 mmol), and the whole mixture stirred at 20—50°C for 4—13 h. The course of the reaction was checked by thin-layer chromatography. When the starting ketone disappeared or when the composition of the reaction did not change any more, an usual work-up was performed and the crude product purified by column chromatography on silica gel (30—40 parts with the use of the following eluants: 12 : 1 light petroleum–ether in the chromatography of esters of 6-oxaacids and 4 : 1 light petroleum–ether with amides of 6-oxa acids). The ratio of the *cis*- to the *trans*-isomer was 1 : 2·5—3·0. Yields, 70—80%.



XI, R = OC_2H_5
XII, R = $N(C_2H_5)_2$



XIII, R = OC_2H_5
XIV, R = $N(C_2H_5)_2$
XV, R = NHC_2H_5

By this procedure, the ketones *I*, *II*, and *III* were converted by the action of diethyl ethoxycarbonylmethanephosphonate to the ester *VI*, ethyl 3,7,11-trimethyl-6-oxa-2,10-tridecadienoate (*IX*), and ethyl 3,7,10-trimethyl-6-oxa-2,10-undecadienoate (*XI*), resp. Reaction of diethyl N,N-diethylaminocarbonylmethanephosphonate with ketone *I*, *II*, *III*, and *IV* afforded the N,N-diethylamide of 3,7,11-trimethyl-6-oxa-2,10-dodecadienoic acid (*VII*), the N,N-diethylamide of 3,7,11-trimethyl-6-oxa-2,10-tridecadienoic acid (*X*), the N,N-diethylamide of 3,7,10-trimethyl-6-oxa-2,10-undecadienoic acid (*XII*), and the N,N-diethylamide of 3,7,10-trimethyl-6-oxa-2-undecenoic acid (*XIV*). By the reaction with diethyl N-ethylaminocarbonylmethanephosphonate, the β-alkoxyketone *I* was converted into the N-ethylamide of 3,7,11-trimethyl-6-oxa-2,10-dodecadienoic acid (*VIII*), see Table I.

Preparation of Esters *VI* and *XIII* by the Reformatsky Reaction

Ethyl bromoacetate (0·011 mol) was added dropwise to a mixture of the β-alkoxyketone (0·01 mol), activated zinc dust (0·0105 g-at), and benzene (20 ml). When the spontaneous reaction was over, the reaction mixture was refluxed for 2 h and processed as usual. The crude hydroxy acid ester was dissolved in benzene (10 ml) and the solution added dropwise into a mixture of phosphorus oxychloride (0·012 mol) and pyridine (0·077 ml) in benzene (15 ml). The whole mixture was allowed to stand for 1 h, heated at 50–80°C for 1 h, and poured onto ice. The usual isolation afforded the crude ester which was purified by column chromatography on silica gel. Yields, 40–50%.

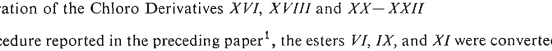
By this procedure, the ketones *I* and *IV* afforded the esters *VI* and *XIII*, resp.

Preparation of Amides *VII*, *XIV*, and *XV* from Acyl Chlorides

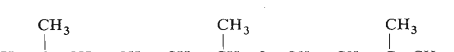
By a procedure reported in the preceding paper[1] and in similar yields, the esters *VI* and *XIII* were converted to the amide *VII*, the amide *XIV*, and the N-ethylamide of 3,7,10-trimethyl--6-oxa-2-undecenoic acid (*XV*).

Preparation of the Chloro Derivatives *XVI*, *XVIII* and *XX–XXII*

By a procedure reported in the preceding paper[1], the esters *VI*, *IX*, and *XI* were converted to ethyl 11-chloro-3,7,11-trimethyl-6-oxa-2-dodecenoate (*XVI*), ethyl 11-chloro-3,7,11-trimethyl-6-oxa--2-tridecenoate (*XX*), and ethyl 10-chloro-3,7,10-trimethyl-6-oxa-2-undecenoate (*XXII*), resp. From the amides *VII* and *X*, there was prepared the N,N-diethylamide of 11-chloro-3,7,11-trimethyl-6-oxa-2-dodecenoic acid (*XVIII*) and the N,N-diethylamide of 11-chloro-3,7,11-trimethyl-6-oxa-2-tridecenoic acid (*XXI*)



XVI, R = H, $R^1 = OC_2H_5$, X = Cl
XVII, R = H, $R^1 = OC_2H_5$, $X = OC_2H_5$
XVIII, R = H, $R^1 = N(C_2H_5)_2$, X = Cl
XIX, R = H, $R^1 = N(C_2H_5)_2$, $X = OC_2H_5$
XX, $R = CH_3$, $R^1 = OC_2H_5$, X = Cl
XXI, $R = CH_3$, $R^1 = N(C_2H_5)_2$, X = Cl



XXII, $R = OC_2H_5$, X = Cl

Preparation of Epoxy Derivatives *XXIII–XXVI*

By a procedure reported in the preceding paper[1], the esters *VI* and *IX* and the amides *VII* and *X* were converted to ethyl 10,11-epoxy-3,7,11-trimethyl-6-oxa-2-dodecenoate (*XXIII*), ethyl 10,11--epoxy-3,7,11-trimethyl-6-oxa-2-tridecenoate (*XXV*), the N,N-diethylamide of 10,11-epoxy-

TABLE I

Elemental Analyses and Boiling Points of Alkoxy Compounds *I*–*XXVI*

Compound	Formula m.w.	Calculated/Found % C	% H	% Cl	% N	B.p.[a] °C/Torr
I	$C_{12}H_{22}O_2$ 198·3	72·68 72·71	11·19 11·09	—	—	125–130 10
II	$C_{13}H_{24}O_2$ 212·3	73·54 73·81	11·39 11·48	—	—	132–138 12
III	$C_{11}H_{20}O_2$ 184·3	71·69 71·69	10·94 10·98	—	—	125–130 18
IV	$C_{11}H_{22}O_2$ 186·3	70·92 70·95	11·91 11·91	—	—	100–107 12
V	$C_{15}H_{26}O_3$ 254·4	70·82 70·64	10·30 10·15	—	—	95–98 0·007
VI	$C_{16}H_{28}O_3$ 268·4	71·60 71·81	10·51 10·75	—	—	105–112 0·009
VII	$C_{18}H_{33}NO_2$ 295·5	73·17 73·33	11·26 11·20	—	4·74 4·84	126–134 0·009
VIII	$C_{16}H_{29}NO_2$ 267·4	71·86 71·62	10·93 11·12	—	5·24 5·27	—
IX	$C_{17}H_{30}O_3$ 282·4	72·30 72·43	10·71 10·76	—	—	115–120 0·009
X	$C_{19}H_{35}NO_2$ 309·5	73·73 73·65	11·40 11·37	—	4·53 4·52	135–140 0·009
XI	$C_{15}H_{26}O_3$ 254·4	70·82 70·93	10·30 10·48	—	—	97–105 0·009
XII	$C_{17}H_{31}NO_2$ 281·4	72·55 72·68	11·10 11·28	—	4·98 5·15	123–128 0·009
XIII	$C_{15}H_{28}O_3$ 256·4	70·27 70·43	11·01 10·85	—	—	88–93 0·009
XIV	$C_{17}H_{33}NO_2$ 283·5	72·03 71·94	11·73 11·77	—	4·94 4·93	120–125 0·009
XV	$C_{15}H_{29}NO_2$ 255·4	—	—	—	5·49 5·35	—
XVI	$C_{16}H_{29}ClO_3$ 304·9	—	—	11·63 11·83	—	—
XVII	$C_{18}H_{34}O_4$ 314·5	68·75 68·52	10·90 10·71	—	—	125–130 0·009

TABLE I
(*Continued*)

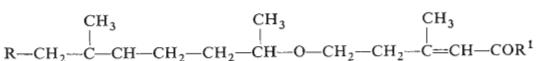
Compound	Formula m.w.	Calculated/Found % C	% H	% Cl	% N	B.p.[a] °C/Torr
XVIII	$C_{18}H_{34}ClNO_2$ 331·9	—	—	10·68 10·69	4·22 4·15	—
XIX	$C_{20}H_{39}NO_3$ 341·5	—	—	—	4·10 4·06	155—160 0·009
XX	$C_{17}H_{31}ClO_3$ 318·9	—	—	11·12 10·91	—	—
XXI	$C_{19}H_{36}ClNO_2$ 345·9	—	—	10·25 10·24	4·05 3·97	—
XXII	$C_{15}H_{27}ClO_3$ 290·8	—	—	12·19 12·35	—	—
XXIII	$C_{16}H_{28}O_4$ 284·4	67·57 67·56	9·92 9·64	—	—	115—120 0·009
XXIV	$C_{18}H_{33}NO_3$ 311·4	69·41 69·01	10·68 10·89	—	4·50 4·56	—
XXV	$C_{17}H_{30}O_4$ 298·4	68·42 68·28	10·13 10·08	—	—	130—135 0·01
XXVI	$C_{19}H_{35}NO_3$ 325·5	70·11 70·18	10·84 11·09	—	4·30 4·41	—

[a] Bath temperature.

-3,7,11-trimethyl-6-oxa-2-dodecenoic acid (*XXIV*), and the N,N-diethylamide of 10,11-epoxy--3,7,11-trimethyl-6-oxa-2-tridecenoic acid (*XXVI*), resp.

Preparation of Alkoxy Derivatives *XVII*, and *XIX*

By a procedure reported in the preceding paper[1], the ester *VI* was converted to ethyl 3,7,11,11--tetramethyl-6,12-dioxa-2-tetradecenoate (*XVII*) and the amide *VII* was transformed to the N,N-diethylamide of 3,7,11,11-tetramethyl-6,12-dioxa-2-tetradecenoic acid (*XIX*).



XXIII, R = H, $R^1 = OC_2H_5$
XXIV, R = H, $R^1 = N(C_2H_5)_2$
XXV, R = CH_3, $R^1 = OC_2H_5$
XXVI, R = CH_3, $R^1 = N(C_2H_5)_2$

Characterisation of Compounds

The structure of the present compounds (Table I) was confirmed by elemental analysis, combined in some cases with IR and NMR spectra.

The purity of compounds and the ratio of the *cis*- to the *trans*-isomer was determined by gas chromatography under conditions reported in the preceding paper[1].

The IR spectra of β-alkoxyketones *I*, *II*, and *III* contained absorption bands indicating the presence of a —CO—CH_3 group (1 718—1 720 cm^{-1}, 1 358—1 360 cm^{-1}) and the ethereal oxygen atom (1 102—1 105 cm^{-1}, 1 078—1 080 cm^{-1}, 1 136—1 138 cm^{-1}). The structure of the ketone *I* was confirmed by the NMR spectrum: $C_{(6)}$—CH_3 1·105 (d), $J = 6$ (3 H); $C_{(2)}$ 2 × —CH_3 1·59 (s) (3 H), 1·66 (s) (3 H); 2 $H_{(4)}$ + 2 $H_{(5)}$ 1·8—2·1 (m) (2 H), 1·2—1·5 (m) (2 H); $C_{(10)}$—CH_3 2·16 (s) (3 H); 2 $H_{(9)}$ 2·63 (t), $J = 6$ (2 H); $H_{(6)}$ + 2 $H_{(8)}$ 3·25—3·75 (m) (3 H); $H_{(3)}$ 5·10 (m) (1 H).

The IR spectra of esters *VI* and *XIII* exhibited absorption bands attributable to the ester group in conjugation with a double bond (round 1 715 cm^{-1}, 1 650 cm^{-1}, 1 150 cm^{-1}) and absorption bands belonging to the ethereal oxygen atom (1 080 cm^{-1}, 1 096—1 098 cm^{-1}). The structure of the ester *VI* was confirmed by the NMR spectrum: $C_{(7)}$—CH_3 1·15 (d), $J = 6·5$ (3 H); $C_{(11)}$ 2 × —CH_3 1·60 (bs) (3 H), 1·68 (bs) (3 H); 2 $H_{(9)}$ 1·7—2·15 (m) (2 H); $C_{(3)}$—CH_3 2·18 (d), $J = 1·5$ (3 H); 2 $H_{(8)}$ 2·49 (t), $J = 7$ (2 H); 2 $H_{(5)}$ + $H_{(7)}$ 3·2—3·75 (m) (3 H); $H_{(10)}$ 5·09 (m) (1 H); $H_{(2)}$ 5·70 (m) (1 H); —$COOC_2H_5$. —CH_2— 4·15 (q), $J = 7$ (2 H), —CH_3 1·26 (t), $J = 7·0$ (3 H).

The IR spectra of amides *VII* and *XIV* exhibit absorption bands due to the N,N-disubstituted amidic group in conjugation with a double bond (1 652 cm^{-1}, 1 630 cm^{-1}) and an absorption band of the ethereal oxygen atom (997—999 cm^{-1}). The structure of the amide *VII* was confirmed by the NMR spectrum: $C_{(7)}$—CH_3 1·08 (d), $J = 6·5$ (3 H); 2 × —CH_3 (ethylic) 1·11 (t), $J = 6·7$ (6 H); 2 $H_{(8)}$ 1·35 (m) (2 H); $C_{(11)}$ 2 × —CH_3 1·58 (s), $J = 1·0$ (3 H), 1·66 (3 H); $C_{(3)}$—CH_3 1·86 (d), $J = 1·6$ (3 H); 2 $H_{(9)}$ 2·01 (m) (2 H); 2 $H_{(4)}$ 2·57 (t) (2 H); 2 $H_{(5)}$ + $H_{(7)}$ + + 2 × —CH_2— (ethylic) 3·20—3·75 (m) (7 H); $H_{(10)}$ 5·08 (m) (1 H); $H_{(2)}$ 5·85 (bs) (1 H).

Elemental analyses were performed in the Analytical Department (Dr J. Horáček, Head) of this Institute by Mrs V. Rusová, Mrs E. Šípová, Mrs L. Pejchová, and Mr V. Štěrba. The IR spectra were measured by Mr P. Formánek and interpreted by Dr J. Smolíková. The NMR spectra were measured and interpreted by Dr M. Synáčková and Dr P. Sedmera. The technical assistance of Miss D. Stiborová is gratefullly acknowledged.

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Translated by J. Pliml.