# THE SYNTHESES OF JUVENOGEN DERIVATIVES OF 2-[4-(3-ETHOXY-3-METHYL-1-BUTOXY)BENZYL]-1-CYCLOHEXANOL

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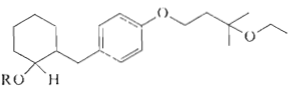
*Dedicated to Professor Holger Erdtman on the occasion of his 80th birthday.*

The syntheses of several juvenogen derivatives of both isomeric racemic 2-[4-(3-ethoxy-3-methyl--1-butoxy)benzyl]-1-cyclohexanols were described, in connection with the investigation of integrated protection of cultural plants against insect pests.

Recently, we published[1] the synthesis of a number of bioanalogues of insect juvenile hormones (juvenoids). As the most suitable candidates for subsequent transformation to juvenogen substances we chose from a series of substances prepared the isomeric pair of racemic *cis*- and *trans*-2-[4-(3-ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexanols (*I*, *II*). Both isomers displayed high absolute values of biological activity on selected insect species. From the chemical point of view the presence of the hydroxyl group was important since it enabled an easy conversion of alcohols *I* or *II* into juvenogen derivatives. The term juvenogen is used for compounds liberating products with a juvenile hormone activity under the effect of biotic or abiotic factors[2]. In this paper we concentrated on the syntheses of hydrophilic juvenogens which could probably be used as systemic "pro-pesticides" in the application to insect species which damage cultivated plants. For these reasons we used the biologically active alcohols *I* and *II* for the preparation of β-D-glucopyranosides, monoesters of succinic acid and finally even some analogues of glycerides. A part of the biological results has been published earlier[3], while some others will be published elsewhere.

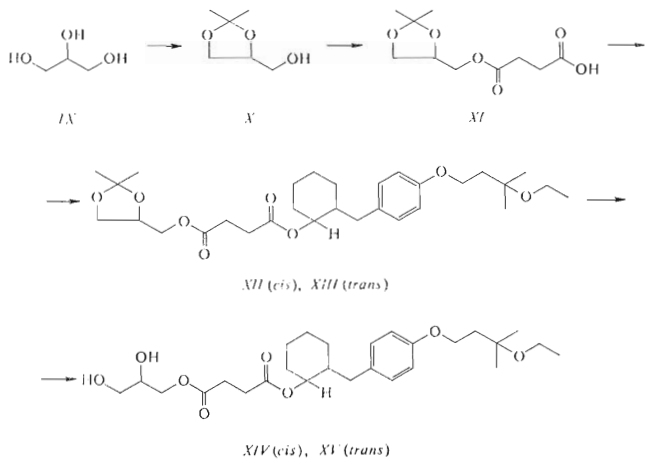
Both isomeric β-D-glucopyranosides *III* and *IV* were obtained by a modified Koenigs–Knorr method[4], consisting first in a reaction of isomeric *cis*- or *trans*--2-[4-(3-ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexanols (*I*, *II*) with 2,3,4,6-tetra--O-acetyl-α-D-glucopyranosyl bromide. Both obtained isomeric 2-[4-(3-ethoxy--3-methyl-1-butoxy)benzyl]-1-cyclohexyl-2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosides (*V*, *VI*) were deacetylated with methanolic sodium methoxide[5] affording the required derivatives *III* or *IV*, respectively.

The second type of juvenogens were the isomeric succinic acid esters *VII* and *VIII* obtained on reaction of isomeric alcohols *I* or *II* with succinic anhydride in pyridine



*I* (*cis*): R = H
*II* (*trans*): R = H
*III* (*cis*): R = β-D-glucopyranosyl
*IV* (*trans*): R = β-D-glucopyranosyl
*V* (*cis*): R = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl
*VI* (*trans*): R = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl
*VII* (*cis*): R = $COCH_2CH_2COOH$
*VIII* (*trans*): R = $COCH_2CH_2COOH$

(see ref.[6]). These half-esters *VII* and *VIII* were used for the synthesis of a further type of juvenogens – analogues of glycerides (Scheme 1). In this synthesis we started from 1,2,3-propanetriol (*IX*) from which we prepared 4-hydroxymethyl-2,2-dimethyl--1,3-dioxolane (*X*) by a known procedure[7]. The conversion of derivative *X* to analogues of 1,2,3-propanetriol *XIV* or *XV* (Scheme 1) requires a careful selection of reaction conditions. For the activation of the carbonyl group of the half-ester *XI* *in situ* we made use of the method published by Zaoral[8] which uses pivaloyl chloride



*IX* *X* *XI*

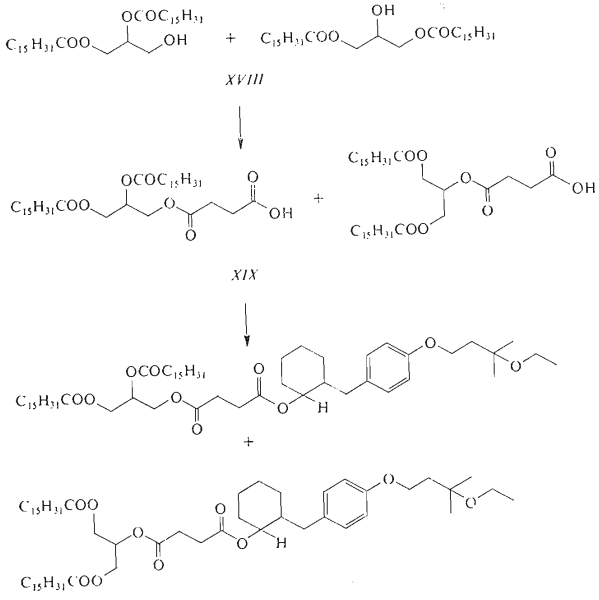
*XII* (*cis*), *XIII* (*trans*)

*XIV* (*cis*), *XV* (*trans*)

SCHEME 1

for the preparation of mixed anhydrides. Thus we obtained both isomeric products *XII* and *XIII* without a previous isolation of the intermediate *XI*. The required juvenogens *XIV* or *XV* were set free from corresponding acetonides *XII* or *XIII*, respectively, by splitting off the protecting groups on the hydroxyls using the ion exchange resin Amberlyst H−15 in methanol[9].

The synthesis of juvenogen glycerides *XVI* or *XVII* used as starting material the commercially available mixture of the racemates of 1,2- and 1,3-dipalmitoylglycerol (*XVIII*) in an approximate 1 : 2 ratio. The mixture *XVIII* was first reacted with succinic anhydride in pyridine and the obtained derivative *XIX* was converted by esterification[10] with N,N'-dicyclohexylcarbodiimide in the presence of 4-dimethylaminopyridine[11] to the isomeric juvenogen *XVI* or *XVII*, respectively. Each of the two isomers, however, represents a mixture of two racemic substances, depending



*XVIII*

*XIX*

*XVI* (*cis*), *XVII* (*trans*)

SCHEME 2

on the composition of the starting commercial mixture *XVIII*. The juvenogens prepared (Scheme 2) are potentially capable of imitating the function of native glycerides in the insect organism and thus supply new information on the method of storing and cleaving of fats in some insect species. In order to obtain preliminary information on the biological properties of these substances we did not consider it necessary to separate the two mixed products *XVI* or *XVII*. The identification of this mixture by IR spectrophotometry was unambiguous and it is presented in the experimental part of this study.

In this paper we have not studied the conformational changes of the saturated six-membered ring caused by the introduction of bulky substituents into position 1 of the isomers *I* or *II*. More detailed studies with alcohols *I*, *II* and further substances have already been published[1]. From them it followed that the six-membered ring assumed in the case of alcohols *I*, *II* and similar substances preferentially a chair conformation, with the benzyl group always in equatorial position. The hydroxyl group assumes then either an axial position (*cis*-isomers) or an equatorial position (*trans*-isomers). In the case of compounds *III*–*VIII* and *XII*–*XVII* the problem is more complex because the substituents in the positions 1 and 2 of the cyclohexane ring are equivalent with respect to their volume and the chair conformation need not be the most favourable one energetically.

We use the terms "*cis*" or "*trans*-isomers" for the characterization of the relative configuration of 1,2-substituents on the cyclohexane ring.

## EXPERIMENTAL

Column chromatographies were carried out on silica gel (Herrmann, Koeln/Ehrenfeld). The reaction course and the purity of the compounds were checked by analytical thin-layer chromatography on silica gel G according to Stahl, "type 60" (Merck, Darmstadt). The IR spectra were measured in chloroform on a UR-20 (Carl Zeiss, Jena) instrument. The mass spectra were measured on an AEI MS-902 spectrometer. Elemental analyses were carried out in the analytical laboratory of this Institute.

2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl-β-D-glucopyranosides (*III*, *IV*)

Cadmium carbonate (0·85 g, 5 mmol) was added to a solution of alcohol *I* or *II* (0·63 g, 1·96 mmol) in toluene (30 ml) and 7 ml of toluene were distilled off. A solution of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (1·25 g; 3 mmol) in toluene (30 ml) was added to the mixture from which the reaction water was continuously eliminated by azeotropic distillation. Finally another 25 ml of toluene were added. When the reaction was terminated and toluene evaporated under reduced pressure a 1M-solution of sodium methoxide in methanol was added to the residue, until alkaline. After standing overnight methanol was evaporated under reduced pressure, the residue was diluted with water and extracted with a mixture of ethyl acetate and ether (1 : 1). Both isomers were obtained in a pure state after purification by column chromatography. The yields were 0·14 g (15%) of compound *III*, m.p. 30–35°C, or 0·26 g (27%) of compound *IV*,

m.p. 55—60°C, respectively. Infrared spectra for *III* and *IV* ($cm^{-1}$): 1 070, 1 179, 3 590; mass spectra for *III* and *IV*: $m/z$ = 436 ($M^+ - 46$), 107 (base peak). For $C_{26}H_{42}O_8$ (482·6) calculated: 64·70% C, 8·77% H; found: for *III* 64·92% C, 8·70% H, for *IV* 64·88% C, 8·66% H.

1-{2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl}-4-hydrogen]butanedioates (*VII, VIII*)

Succinic anhydride (0·1 g, 1 mmol) was added to a solution of alcohol *I* or *II* (0·3 g, 0·94 mmol) in pyridine (3 ml) and the mixture was heated at 60—80°C for several days. When the reaction was over pyridine was evaporated under reduced pressure and the residue purified by column chromatography. Both products were obtained pure in good yields, *i.e.* 0·35 g (90%) of compound *II*, or 0·3 g (76%) of compound *VIII*, m.p. 85—86°C. Isomer *VII*: Infrared spectrum ($cm^{-1}$): 1 072, 1 178, 1 248, 1 718, 1 724, 2 400—3 500; mass spectrum: $m/z$ = 420 ($M^+$), 320, 306, 302, 188, 107 (base peak). Isomer *VIII*: Infrared spectrum ($cm^{-1}$): 1 070, 1 177, 1 247, 1 720, 2 400—3 300; mass spectrum: $m/z$ = 420 ($M^+$), 374, 320, 306, 302, 188, 107 (base peak). For $C_{24}H_{36}O_6$ (420·5) calculated: 68·54% C, 8·63% H; found: for *VII* 68·51% C, 8·58% H, for *VIII* 68·67% C, 8·58% H.

1-{2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl}-4-[4-(2,2-dimethyl-1,3-dioxolan)yl]butanedioates (*XII, XIII*)

A solution of dioxolane derivative *X* (0·182 g, 1 375 mmol) and succinic anhydride (0·15 g, 1·5 mmol) in pyridine (2 ml) was heated at 60—80°C for 4 h. After cooling a solution of pivaloyl chloride (0·18 g, 1·5 mmol) in benzene (3 ml) was added, the mixture was allowed to stand at room temperature for 2 h and a solution of alcohol *I* or *II* (0·4 g, 1·25 mmol) in benzene (2 ml) was added. This was then heated at 80°C for several days, the solvent evaporated and the residue purified by chromatography on a 50 fold amount of silica gel. Yield 0·285 g (43%) of product *XII* or 0·4 g (60%) of product *XIII*, respectively. Infrared spectra for *XII* and *XIII* ($cm^{-1}$): 990, 998 (*XII*), 1 002 (*XIII*), 1 032, 1 063, 1 075, 1 116, 1 161, 1 245, 1 371, 1 381, 1 740; mass spectra for *XII* and *XIII*: $m/z$ m 534 ($M^+$), 519, 420, 363, 303, 302, 188 (base peak), 107, 87, 59. For $C_{30}H_{46}O_8$ (534·7) calculated: 67·39% C, 8·67% H; found: for *XII* 67·49% C, 8·63% H, for *XIII* 67·37% C, 8·66% H.

1-{2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl}-4-(2,3-dihydroxypropyl)butanedioates (*XIV, XV*)

A solution of compound *XII* or *XIII* (0·1 g, 0·19 mmol) in methanol (3 ml) was heated at 45°C under stirring in the presence of the ion exchange resin Amberlyst H—15 (30 mg) for 8 h. The mixture was filtered, the solvent (methanol) evaporated under reduced pressure and the residue chromatographed. The products *XIV* or *XV* were obtained in a pure state in 0·09 g (97·5%) yield for compound *XIV* and 0·087 g (95%) yield for compound *XV*. Infrared spectra for *XIV* and *XV* ($cm^{-1}$): 1 050, 1 163, 1 244, 1 740, 3 430 (*XV*), 3 450 (*XIV*) mass spectra for *XIV* and *XV*: $m/z$ = = 494 ($M^+$), 420, 363, 302, 256, 188 (base peak). 107, 87, 59. For $C_{27}H_{42}O_8$ (494·6) calculated: 65·56% C, 8·56% H; found: for *XIV* 65·60% C, 8·58% H, for *XV* 65·47% C, 8·56% H.

Mixture of 1-{2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl}-
-4-[2,3-bis(palmitoyloxy)propyl]butanedioates and
2-{2-[4-(3-Ethoxy-3-methyl-1-butoxy)benzyl]-1-cyclohexyl}-
-4-[1,3-bis(palmitoyloxy)propyl]butanedioates (*XVI*, *XVII*)

A solution of compound *XVIII* (2·5 g, 4·4 mmol) and sucinic anhydride (0·45 g, 4·5 mmol) in pyridine (25 ml) was refluxed for 8 h and then poured onto ice. After acidification with dilute hydrochloric acid the organic phase was extracted with ether. The residue of the extract was chromatographed and 1 g (34%) of pure ester *XIX* was obtained. Infrared spectrum ($cm^{-1}$): 1 165, 1 730, 1 743, 2 300–3 400. For $C_{39}H_{72}O_8$ (669·0) calculated: 70·02% C, 10·85% H; found: 70·13% C, 10·83% H.

A solution of compound *XIX* (0·5 g, 0·75 mmol) and alcohol *I* or *II* (0·24 g, 0·75 mmol) in benzene (20 ml) was stirred in the presence of N,N'-dicyclohexylcarbodiimide (0·38 g, 0·75 mmol) and 4-dimethylaminopyridine (0·025 g, 0·2 mmol) for 2 h. When the reaction was over the mixture was shaken with a saturated sodium chloride solution and the organic layer was extracted with ether. The extract was evaporated and the residue chromatographed on a 50 fold amount of silica gel. Yield, 0·37 g (51%) of product *XVI* or 0·4 g (55%) of product *XVII*, respectively. Infrared spectra for *XVI* and *XVII* ($cm^{-1}$): 1 159, 1 246, 1 367, 1 381, 1 748; mass spectra for *XVI* and *XVII*: *m/z* m 970 ($M^+$), 924, 551, 550, 441, 303, 239, 188 (base peak). For $C_{59}.H_{102}O_{10}$ (971·4) calculated: 72·94% C, 10·58% H; found: for *XVI* 72·87% C, 10·50% H, for *XVII* 72·81% C, 10·50% H.

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