

PREPARATION OF DERIVATIVES OF ω -CYCLOHEXYL-2-ALKENOIC ACIDS*

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In connection with the study of structure-activity relationships in substances with juvenile hormone activity the preparation of esters of homologous series of ω -cyclohexyl-3,7-dimethyl- and ω -cyclohexyl-3,8-dimethyl-2-alkenoic acids has been described. Ethyl ester and diethylamide were prepared of the lowest member of this homologous series, 9-cyclohexyl-3,7-dimethyl-2-nonenic acid.

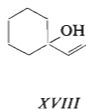
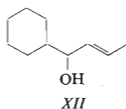
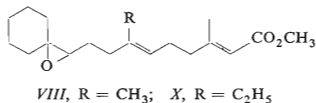
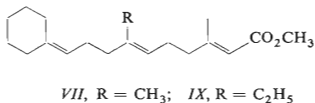
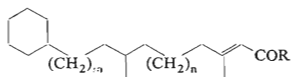
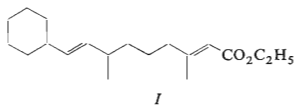
In recent years considerable attention has been devoted to the preparation of juvenile hormone analogues (juvenoids) as well as to their effect on insects¹⁻⁵. In our laboratories the relation between their structure and biological activity is also being investigated. It was observed that substantial changes in the effect of the compounds derived from farnesoic acid on various insect species take place not only in connection with structural changes of the α,β -unsaturated functional group and its surroundings, but also on alteration of the "terminal" part of the molecule of juvenoids^{3,5,6}.

For this reason we now prepared a series of 2-alkenoic acids the terminal part of which was formed by a cyclohexane ring. We supposed that in cases where the cyclohexyl substituent would increase the whole juvenoid molecule substantially serious changes might take place in the juvenile activity. In our effort to approach the optimal size and shape of the molecule of substances of this type we followed the effect of the length of the aliphatic chain and of the position of the central methyl group on activity. Final products, *I-VI*, are given in Table I. This paper gives chemical results only. Structure-activity relationships will be discussed elsewhere.

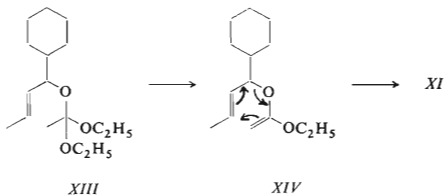
In the course of our work Findlay⁷ and Mori and coworkers⁸ described the preparation of juvenoids *VII-X*. These substances differ both in their structure and the method of preparation from substances described in this paper.

For the synthesis of substances *I, II, III* and *V* we used as the key intermediate ethyl 3-methyl-5-cyclohexyl-*trans*-4-pentenoate (*XI*) which was prepared by Claisen rearrangement of ethyl orthoacetate with 1-cyclohexyl-2-butenol⁹ (*XII*). This stereose-

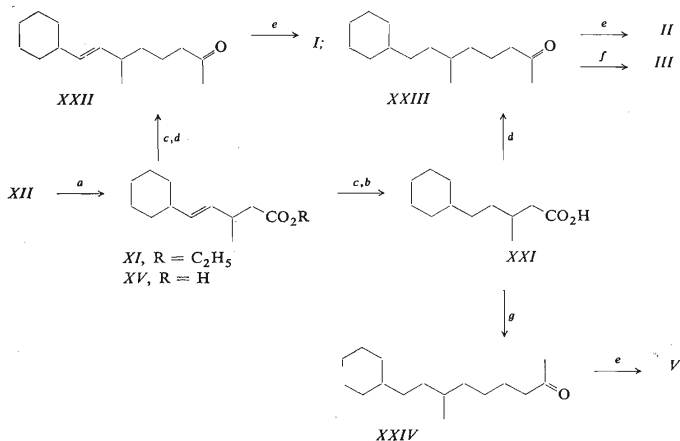
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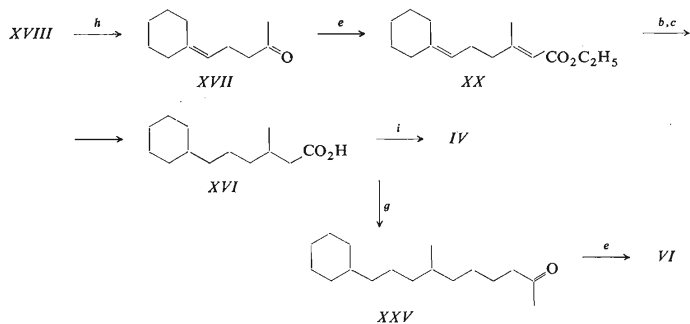
lective reaction^{10,11} in which a temporary formation of the mixed orthoacetate *XIII* takes place, followed by the formation of ketene acetal *XIV* that rearranges to the final unsaturated *trans* ester *XI* (Scheme 1), gave practically pure *trans* isomer in good yield. The *trans* configuration of the double bond in the product of this reaction is indicated by the IR band at 970 cm⁻¹ in ester *XI*, 971 cm⁻¹ band in 3-methyl-5-cyclohexyl-*trans*-4-pentenoic acid (*XV*) formed by its saponification, and at 970 cm⁻¹ in the final product *I*. Neither is the PMR spectrum of acid *XV* in disagreement with this conclusion. The analysis of ester *XI* by gas chromatography has shown that the *cis* isomer is formed in this reaction in a less than 1% yield.



SCHEME 1



SCHEME 2



SCHEME 3

Legends to Schemes 2 and 3

a, triethyl orthoacetate, propionic acid,
b, H_2 , PtO_2 , ethanol,
c, OH^- ,
d, levulinic acid, anodic coupling,
e, $(\text{C}_2\text{H}_5\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ (XIX),

f, $(\text{C}_2\text{H}_5\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CON}(\text{C}_2\text{H}_5)_2$ (XXVI),
g, acetylbutyric acid, anodic coupling,
h, diethyl acetylmalonate,
i, $\text{HO}_2\text{C} \cdot \text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)=\text{CH} \cdot \text{CO}_2\text{CH}_3$ (XXVII), anodic coupling.

We carried out the synthesis of juvenoids *IV* and *VI* via the 3-methyl-6-cyclohexylhexanoic acid (*XVI*). For its preparation we took 5-cyclohexylidene-2-pentanone (*XVII*) as starting material, which we prepared – similarly as Colonge and Brunie¹² did – from 1-vinylcyclohexanol (*XVIII*) by Carroll reaction¹³, using ethyl acetylmalonate¹⁴ instead of the poorly reactive ethyl acetoacetate. The Wadsworth–Emmons reaction¹⁵ of this ketone *XVII* with triethyl phosphonoacetate (*XIX*) afforded unsaturated ester *XX*. Its hydrogenation and saponification gave acid *XVI*. The final products were prepared by combination of Kolbe anodic coupling and Wadsworth–Emmons reaction in a manner similar to previous work^{16,17}. During the second of the two reactions a modification described by Hejno and Jarolím¹⁸ was found convenient. The reaction Schemes 2 and 3 illustrate the main features of the preparations of single products given in Table I.

EXPERIMENTAL

Analytical thin layer chromatography was carried out on silica gel G (Merck) and the substances were detected by spraying with ethanolic phosphomolybdic acid solution. Column chromatography was carried out on silica gel (Gebr. Herrmann Köln-Ehrenfeld, GFR), or on neutral alumina (Woelm, act. III, according to Brockmann). The purity of the products was checked by gas chromatography on a Perkin Elmer F 11 apparatus provided with a FID. The PMR spectra were measured on a Varian HA-100 machine in deuteriochloroform with tetramethylsilane as internal reference. The mass spectra were measured on an AEI MS-902 spectrometer.

Ethyl 3-Methyl-5-cyclohexyl-*trans*-4-pentenoate (*XI*)

A mixture of 1-cyclohexyl-2-butenol⁹ (*XII*; 8.70 g), triethyl orthoacetate (65.0 g), and propionic acid (0.30 g) was heated at 135–140°C for one hour under simultaneous distillation off of ethanol. The reaction mixture was then submitted to fractional distillation. The crude ester *XI* obtained was purified chromatographically on a hundred-fold amount of alumina. Elution with light petroleum containing 10% of ether gave a pure product (5.20 g), b.p. 135–138°C/12 Torr, n_D^{24} 1.4598, and the main IR bands at 970, 1176, 1696, and 1735 cm^{-1} . For $\text{C}_{14}\text{H}_{24}\text{O}_2$ (224.3) calculated: 74.95% C, 10.78% H; found: 74.71% C, 10.69% H.

3-Methyl-5-cyclohexyl-*trans*-4-pentenoic Acid (*XV*)

Ester *XI* (1.21 g) was saponified by 2 hours' refluxing in a solution of 0.5 g of sodium hydroxide in 20 ml of 50% ethanol. The reaction mixture was worked up in the conventional manner to give acid *XV* (0.70 g) of b.p. 130–134°C/0.2 Torr, and IR bands at 971, 1714 and 2500–3400 cm^{-1} . For $\text{C}_{12}\text{H}_{20}\text{O}_2$ (196.3) calculated: 73.43% C, 10.27% H; found: 73.39% C, 10.26% H. PMR spectrum: 1.05 p.p.m. (3 H, d, $J = 6.5$, $-\text{CH}_3$), 2.61 p.p.m. (1 H, m, $-\text{CH}-\text{CH}_3$), 5.36 p.p.m. (2 H, m, $J_{\text{vic}} \sim 15$, *trans* olefinic H); n_D^{24} 1.4720.

3-Methyl-5-cyclohexylpentanoic Acid (*XXI*)

A solution of acid *XV* (1.00 g) in methanol (15 ml) was hydrogenated at atmospheric pressure on PtO_2 (0.10 g). After elimination of the catalyst by filtration and evaporation of the solvent the crude residue of the acid was distilled to afford a product (0.80 g) of b.p. 142–145°C/0.5 Torr, and n_D^{24} 1.4629. The preparation of *XXI* by hydrogenation of the aromatic analogue is described in literature¹⁹.

TABLE I

Properties of Compounds I—VI (mixtures of geometrical isomers on the double bond conjugated with the carboxyl group)

Products B.p., °C (Torr)	Reaction Components	IR Spectrum cm ⁻¹	Formula (mol. w.)	Calculated/Found	
				% C (mass spectrum, M ⁺)	% H
I 132—136 (0.5)	XIX	970, 1 151, 1 224	C ₁₉ H ₃₂ O ₂ (292.5)	78.03	11.03
	XXII	1 651, 1 721		78.27	11.08
				(292 m/e)	
II 128—130 (0.2)	XIX	1 148, 1 221, 1 650	C ₁₉ H ₃₄ O ₂ (294.5)	77.49	11.64
	XXIII	1 719		77.37	11.59
III 196—200 (12)	XIX	1 629, 1 650	C ₂₁ H ₃₉ NO (321.5)	(321 m/e)	
	XXVI				
IV 147—150 (0.2)	XVI	1 153, 1 224, 1 649	C ₁₉ H ₃₄ O ₂ (294.5)	77.49	11.64
	XXVII	1 720		77.29	11.33
				(294 m/e)	
V 155—158 (0.2)	XIX	1 152, 1 224, 1 437	C ₁₉ H ₃₄ O ₂ (294.5)	(294 m/e)	
	XXIV	1 649, 1 720			
VI 165—167 (0.5)	XIX	1 153, 1 225, 1 436	C ₂₀ H ₃₆ O ₂ (308.5)	(308 m/e)	
	XXV	1 650, 1 720			

5-Cyclohexylidene-2-pentanone¹² (XVII)

A mixture of alcohol¹² XVIII (2.50 g) and ethyl acetylmalonate²⁰ (6.65 g) was heated at 120 to 130°C for one hour and at 170—180°C for an additional two hours. After cooling to 40°C the mixture was diluted with methanol (25 ml), additioned with a 20% sodium hydroxide solution (10 ml), and heated at 100°C for two hours. Methanol was evaporated *in vacuo* and the residue diluted with water (30 ml) and extracted with ether (3 × 15 ml). The combined extracts were worked up in the usual manner. The obtained residue was chromatographed on a hundred-fold amount of alumina using a mixture of light petroleum and 20% of ether as eluent. Pure ketone XVII (1.51 g) was thus obtained, b.p. 145—147°C/80 Torr. IR spectrum: 1670, 1710 cm⁻¹.

PMR spectrum: 1.52 p.p.m. (6 H, m, $\text{CH}_2\text{—CH}_2\text{—C=}$); 2.11 p.p.m. (3 H, s, $\text{CH}_3\text{—C=O}$);

2.40 p.p.m. (2 H, m, $\text{CH}_2\text{—C=O}$); 2.10 p.p.m. (4 H, m, $\text{—CH}_2\text{—C=}$); 5.02 p.p.m. (1 H, t,

$J = 7 \text{ Hz}$, $\text{—CH}_2\text{—C=CH—}$). For C₁₁H₁₈O (166.3) calculated: 79.46% C, 10.92% H; found: 79.69% C, 10.76% H.

Wadsworth–Emmons Reaction¹⁸

To a solution of ketone (8.0 mmol) and phosphonoacetate XIX (8.4 mmol) in ethanol (7 ml) a solution of 8.4 mmol of sodium in 5 ml of ethanol was added dropwise at a temperature not exceeding 40°C. The mixture was allowed to stand at room temperature and the reaction course was followed by thin-layer chromatography. In the case of ketone described in this paper the reaction took 6 hours. The reaction mixture was concentrated at 50 Torr pressure and extracted with pentane. The combined pentane extracts were worked up in the usual manner. The crude product was purified by chromatography on a hundred-fold amount of alumina, using a mixture of 10% of ether in light petroleum for elution, and by vacuum distillation.

Ethyl 3-Methyl-6-cyclohexylidene-2-hexenoate (XX)

Ester XX was prepared from ketone XVII (1.50 g) by Wadsworth–Emmons reaction with phosphonoacetate XIX (1.91 g). It had b.p. 149–151°C/15 Torr. IR spectrum: 1149, 1222, 1650 and 1719 cm⁻¹. For C₁₆H₂₄O₂ (236.3) calculated: 76.22% C, 10.24% H; found: 76.41% C, 10.19% H.

3-Methyl-6-cyclohexylhexanoic Acid (XVI)

Hydrogenation of ester XX (3.80 g) on 5% Pd/CaCO₃ (0.70 g) in methanol (25 ml) at atmospheric pressure gave after elimination of the solvent under reduced pressure the saturated ester which was saponified by 2 hours' boiling with sodium hydroxide (1.00 g) solution in 75% methanol. The acidic fraction of this reaction mixture was obtained in the conventional manner. After evaporation of ether and distillation 2.75 g of acid XVI were obtained, b.p. 186–189°C/12 Torr. IR spectrum: 1700 and 2500–3500 cm⁻¹. For C₁₃H₂₄O₂ (212.3) calculated: 73.53% C, 11.39% H; found: 73.83% C, 11.27% H.

Kolbe's Anodic Syntheses

These were carried out in a manner described earlier^{16,17}. Thus from single intermediates (cf. reaction Schemes 2 and 3) the following ketones were obtained by this procedure: XXII (mass spectrum: M⁺ = 222 m/e), XXIII (mass spectrum: M⁺ = 224 m/e), XXIV (mass spectrum: M⁺ = 238 m/e), and XXV (mass spectrum: M⁺ = 252 m/e).

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