NATURAL AND SYNTHETIC MATERIALS WITH THE INSECT HORMONE ACTIVITY. XVIII.*

THE SYNTHESIS OF ALIPHATIC JUVENOIDS WITH tert-BUTOXYCARBONYL GROUP IN THE MOLECULE

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In connection with the study of structure-activity relationship in acyclic esters having juvenile hormone activity several pharnesoic acid derivatives have been prepared, the terminal part of the carbon atom chain of which was substituted by a tert-butoxycarbonylamino- or tert-butoxy-carbonyl group.

Recently, a series of synthetic substances (juvenoids[1,2]) has been described which possessed insect juvenile hormone activity. These substances cause developmental disturbances in insects leading in the majority of cases to sterility. The main work in this field is reviewed in several articles[3–9]. In our laboratories, among other problems, the dependence of the structure of juvenoids on their biological activity is being studied. In this connection the results of investigations with peptide-type juvenoids are very interesting[10,11]. These substances are remarkable for their exceptionally high specificity; they affect only the members of a single insect family (*Pyrrhocoridae* bugs). This strict specificity evidently depends on the structure of their molecule which is in some respects appreciably different from that of the common juvenoid types. A whole series of active substances of this type (*cf. I*) has the amino group of the central amino acid protected by a tert-butoxycarbonyl group[11]. Therefore, the question arose to what extent this part of the molecule of peptidic juvenoids is responsible for the juvenile hormone activity.

For this reason we prepared several analogues from the aliphatic series and investigated the change in juvenile hormone activity in dependence on structural changes.** The key reaction of their preparation was Kolbe's anodic synthesis which was already found useful earlier[13,14] and Wittig's reaction in Wadsworth–Emmons modification[15].

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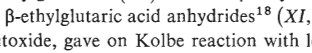
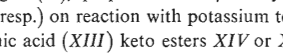
** This paper gives only the chemical results. Structure-activity relationships will be discussed elsewhere[12].

As the starting substance for the preparation of methyl 7-[(tert-butoxycarbonyl)-amino]-3-methyl-2-octenoate (*II*) we used DL-tert-butoxycarbonyl-β-aminobutyric[11] (*III*) and 5-methoxycarbonyl-4-methyl-4-pentenoic acids[14] (*IV*) which on Kolbe's reaction afforded ester *II* directly (Table I) in addition to other expected products of anodic coupling[16].

In the course of further work a series of diesters *V* and *VI*, and ester-amides *VII* and *VIII*, were prepared the basic skeleton of which differs from that of ester *II* in position 8 in which this substance has the —NH— group instead of the $—CH_2—$ group. The reaction sequence is represented in Scheme 1. tert-Butyl hydrogen β-methylglutarate (*IX*) and its β-ethylhomologue (*X*), prepared from β-methyl[17]- or β-ethylglutaric acid anhydrides[18] (*XI*, *XII*, resp.) on reaction with potassium tert-butoxide, gave on Kolbe reaction with levulinic acid (*XIII*) keto esters *XIV* or *XV*,



I



II

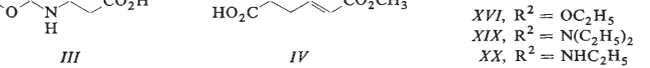
III

IV

$(C_2H_5O)_2P(O)CH_2COR^2$

XVI, $R^2 = OC_2H_5$
XIX, $R^2 = N(C_2H_5)_2$
XX, $R^2 = NHC_2H_5$

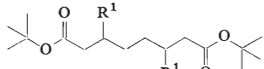
XVII, $R^1 = CH_3$
XVIII, $R^1 = C_2H_5$



IX, $R^1 = CH_3$
X, $R^1 = C_2H_5$

XIII

XIV, $R^1 = CH_3$
XV, $R^1 = C_2H_5$



V; $R^1 = CH_3$, $R^2 = OC_2H_5$
VI; $R^1 = C_2H_5$, $R^2 = OC_2H_5$

VII; $R^1 = CH_3$, $R^2 = N(C_2H_5)_2$
VIII; $R^1 = CH_3$, $R^2 = NHC_2H_5$

SCHEME 1

respectively. Wadsworth–Emmons reaction of these keto esters with triethyl phosphonoacetate[15] (*XVI*) afforded corresponding diesters *V* and *VI* respectively. In this case the Kolbe reaction of acid glutarates *IX* and *X* with the half-ester *IV* is not advantageous, due to the difficult separation of diesters *V* or *VI* from diesters *XVII* and *XVIII*, respectively, which are formed during this anodic synthesis by symmetrical coupling of two molecules of half-esters *IX* or *X*. In contrast to this both keto esters *XIV* and *XV* (Scheme 1) could be isolated from the reaction mixture easily and they could be utilised for the preparation of further derivatives. From keto ester *XIV* and the corresponding phosphonoacetamides[19] *XIX* and *XX*, ester-amides *VII* and

TABLE I
Products of the Synthesis

Product	Reaction components	B.p., °C 0·5 Torr n_D^{23}	IR Spectrum cm^{-1}	Formula (mol. w.)	Calculated/Found		
					% C	% H	% N
XIV[a]	*IX*	89–92	1 150, 1 360, 1 381	$C_{13}H_{24}O_3$	68·38	10·59	—
	XIII	1·4369	1 720, 1 728	(228·3)	68·42	10·73	—
XV	*X*	92–95	1 150, 1 160, 1 368	$C_{14}H_{26}O_3$	69·38	10·81	—
	XIII	1·4375	1 393, 1 721	(242·4)	69·08	10·77	—
V	*XIV*	125–6	1 150, 1 173, 1 225,	$C_{17}H_{30}O_4$	68·42	10·13	—
	XVI[b]	1·4532	1 371, 1 395, 1 645, 1 729	(298·4)	68·56	9·77	—
VII	*XIV*	110–12	1 149, 1 170, 1 368	$C_{19}H_{35}NO_3$	—	—	4·30
	XIX[c]	1·4675	1 393, 1 630, 1 650 1 728	(325·5)	—	—	4·31
VIII[d]	*XIV*	120–22	1 150, 1 173, 1 370,	$C_{17}H_{31}NO_3$	—	—	4·71
	XX[c]	1·4630	1 395, 1 504, 1 635, 1 645, 1 670, 1 730, 3 450	(297·4)	—	—	4·87
VI	*XV*	108–10	1 150, 1 170, 1 223,	$C_{18}H_{32}O_4$	69·19	10·32	—
	XVI[b]	1·4560	1 369, 1 393, 1 650, 1 723	(312·4)	69·39	10·34	—
II[e]	*III*[f]	—	1 150, 1 369, 1 391,	$C_{15}H_{27}NO_4$	—	—	4·91
	IV[g]	1·4633	1 500, 1 650, 1 710, 1 720, 3 440	(285·4)	—	—	4·88

[a] Mass spectrum: mol. ion M^+ ∅, further: 172 *m/e* (M^+ — isobutylene), 155 *m/e* (M^+ — isobutylene — OH), 154 *m/e* (M^+ — isobutylene — H_2O); [b] see[15]; [c] see[19]; [d] mass spectrum: mol. ion $M^+ = 297$ *m/e*, further: 241 *m/e* (M^+ — isobutylene), 224 *m/e* (M^+ — isobutylene — OH); [e] mass spectrum: mol. ion $M^+ = 285$ *m/e*, further: 229 *m/e* (M^+ — isobutylene), 184 *m/e* (M^+ — butoxycarbonyl); 144 *m/e* ($CH_3CH{=}N^{(+)}H.CO_2C_4H_9$); [f] see[11]; [g] see[14].

VIII were prepared in this way. A review of the substances prepared by this method as well as of their analytical data is given in Table I.

EXPERIMENTAL

Analytical thin-layer chromatography was carried out on silica gel G (Merck), detection by spraying with an ethanolic phosphomolybdic acid solution. Column chromatography was carried out on silica gel Woelm, deactivated by addition of 10% of water per adsorbent weight, or on neutral alumina Woelm (activity III according to Brockmann).

Anodic Syntheses

A solution of tert-butyl hydrogen β-alkylglutarate (25 mmol) and levulinic acid (40 mmol) in methanol (30 ml), in which 50 mg of sodium were dissolved, was electrolysed at 24 V and 35–45° C. The end of the electrolysis was indicated by the pH change of the reaction mixture (to alkaline region). After evaporation of the bulk of the methanol the product was extracted with ether and chromatographed on a 150-fold amount of silica gel. By elution with a light petroleum–ether mixture (2 : 1) the corresponding keto ester has been obtained (Table I). In a similar manner ester-urethane *II* (Table I) was also prepared from DL-tert-butoxycarbonyl-β--aminobutyric acid (*III*) and 5-methoxycarbonyl-4-methyl-4-pentenoic acid (*IV*). A pure product was obtained from the reaction mixture by column chromatography on a 100-fold amount of alumina, using light petroleum–ether mixture (3 : 1) for elution.

tert-Butyl Hydrogen β-Methylglutarate (*IX*)

To a solution of β-methylglutaric anhydride[17] (12·50 g) in benzene (150 ml) potassium tert-butoxide (10·80) was added gradually under vigorous stirring and the mixture was allowed to react at room temperature and under stirring for 5 h. After addition of water and extraction with ether the aqueous fraction was acidified with sulfuric acid and the half-ester extracted with ether. After evaporation of the solvent the residue was purified by column chromatography on a hundred-fold amount of silica gel. Elution with light petroleum–ether 1 : 1, evaporation of the solvents and drying in a vacuum (oil pump) gave a product of n_D^{22} 1·4343 and characteristic frequencies in the IR spectrum: 1154, 1294, 1368, 1392, 1710, 1728, 2400–3400 cm^{-1}. For $C_{10}H_{18}O_4$ (202·2) calculated: 59·38% C, 8·97% H; found: 59·66% C, 8·55% H.

tert-Butyl Hydrogen β-Ethylglutarate (*X*)

In a similar manner half-ester *X* was prepared from β-ethylglutaric anhydride[18] (13·45 g) and potassium tert-butoxide (10·80 g), n_D^{23} 1·4351, IR spectrum: 1155, 1370, 1392, 1710, 1728, 2400, 3400 cm^{-1}. For $C_{11}H_{20}O_4$ (216·3) calculated: 61·09% C, 9·33% H; found: 61·29% C, 9·02% H.

Wadsworth-Emmons Reaction

A solution of a corresponding diethyl phosphonoacetic acid derivative (*XVI*, *XIX*, *XX*; 3·20 mmol) in Dimethyl Cellosolve (1 ml) was added dropwise at 0°C and under stirring to a suspension of sodium hydride (3·00 mmol) in Dimethyl Cellosolve (10 ml) under nitrogen. The obtained mixture was stirred under nitrogen at 0°C for another 30 min and then at room temperature for 1 h. A solution of 1-(tert-butoxycarbonyl)-2-methylheptane-6-one (*XIV*; 3·00 mmol) in Di-

methyl Cellosolve (1 ml) was then added to it and the mixture was stirred at room temperature for 30 min and at 50°C for 2 h. The mixture was poured into a threefold amount of water, salted out with sodium chloride and extracted with ether. After evaporation of the solvent the residue was chromatographed on a hundredfold amount of silica gel. The pure product (Table I) was obtained on elution with light petroleum–ether mixture (3 : 1 for diesters *V* and *VI*, 1 : 1 for ester-amides *VII*— *VIII*) and vacuum distillation.

Elemental analyses were carried out in our laboratories by Mrs E. Sýkorová, V. Pejchalová, V. Rusová and Mr V. Štěrba. The infrared spectra were measured on a Zeiss UR 10 apparatus. We thank Dr J. Smolíková for help in their interpretation. The purity of the substances was controlled by gas chromatography on a Perkin Elmer F 11 gas chromatograph with FID. The columns were filled with the silicone elastomer E 301 and the analyses were carried out by Dr V. Lukeš and Mrs S. Holubová. The mass spectra were measured on a MS 902 mass spectrometer. We are grateful to Dr L. Dolejš and Dr K. Ubik for their interpretation. Our thanks are also due to Dr K. Poduška for kindly supplying DL-*tert-butoxycarbonyl*-β-*aminobutyric acid.*

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