THE SYNTHESES OF BIOLOGICALLY ACTIVE 2-(4-HYDROXYBENZYL)-1-CYCLOHEXANONE DERIVATIVES

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The syntheses of various 2-(4-hydroxybenzyl)-1-cyclohexanone derivatives are described in connection with the development of the research of substances with juvenile hormone activity.

The investigation of substances imitating the effect of insect juvenile hormone (juvenoids) represents one of the several possible methods of obtaining nontraditional pesticides[1-7]. Recently, studies have appeared describing a new type of juvenoids with two six-membered – as a rule aromatic – rings in the molecule[7-11]. Franke and coworkers[8] derive this type of substance from one of the possible conformers of Roeller's juvenile hormone (*I*). The structure of the substances described in this paper (their properties are given in Tables I–III) is derived in a similar manner; during their preparation their possible application as biologically active components of juvenogen compounds[12,13] was envisaged. Thus a series of derivatives of 2-(4-hydroxybenzyl)-1-cyclohexanone originated which afforded information concerning the study of the relationships between the structure and the activity in the group of aromatic juvenoids[6,13].

For the synthesis of this type of compounds 2-(4-hydroxybenzyl)-1-cyclohexanone (*II*) served as the key product. For its synthesis we used 2-(4-methoxybenzyl)-1-cyclohexanone (*III*) as the starting compound which was prepared by Stork's reaction[14] of N-(1-cyclohexenyl)pyrrolidine with 4-methoxybenzyl chloride, obtained from 4-methoxybenzyl alcohol. 2-(4-Methoxybenzyl)-1-cyclohexanone (*III*) was reacted with azeotropic hydrobromic acid in acetic anhydride[15] to afford 2-(4-hydroxybenzyl)-1-cyclohexanone (*II*). For the synthesis of compounds *LII–LVII* with juvenoid properties, ketone *II* was converted[16] to 2-(4-hydroxybenzyl)-1-cyclohexanone ethylene acetal (*IV*) or 2-(4-hydroxybenzyl)-1-cyclohexanone hydroxymethylethylene acetal (*V*) on reaction with 1,2-ethanediol or 1,2,3-propanetriol, respectively.

The intermediary products for the construction of the aliphatic side-chains of individual juvenoids were obtained by known methods. Ethyl-(2*E*,*Z*)-4-bromo-3-methyl-2-butenoate (*VI*) was prepared according to Huisman and coworkers[17]. 1-Bromo-4-methyl-2-butene (*VII*) was obtained from 2-methyl-3-buten-2-ol[18]. For the prepara-

tion of 1-bromo-4-methyl-3-pentene (*VIII*) a two-step synthesis was elaborated[19], from cyclopropyl methyl ketone as a starting compound. For the preparation of 1-bro-

TABLE I

Properties of the juvenoid ketones *XIII*—*XXV*

Products (reaction components)	Yield, % (procedure)	IR spectrum cm^{-1}	Formula (Mol.weight)	Calc./Found	
				% C	% H
XIII[a]	57·4[b]	1 152, 1 228, 1 240,	$C_{20}H_{26}O_4$	72·70	7·93
(*II*, *VI*)	(*A*)	1 645, 1 651, 1 714	(330·4)	72·43	8·06
XIV[c]	35·8[b]	1 152, 1 228, 1 240,	$C_{20}H_{26}O_4$	72·70	7·93
(*II*, *VI*)	(*A*)	1 645, 1 651, 1 714	(330·4)	72·95	7·82
XV[d]	86·3	1 005, 1 245, 1 680	$C_{18}H_{24}O_2$	79·37	8·88
(*II*, *VII*)	(*A*)	1 709	(272·4)	79·06	8·55
XVI	13·9[e]	1 086, 1 245, 1 365,	$C_{19}H_{28}O_3$	74·96	9·27
(*XV*)	(*D*)	1 392, 1 712, 2 830	(304·4)	74·87	9·22
XVII	16·7[f]	1 074, 1 229, 1 247,	$C_{20}H_{30}O_3$	75·43	9·50
(*XV*)	(*D*)	1 676, 1 714	(318·4)	75·37	9·42
XVIII	30·0	1 246, 1 712	$C_{18}H_{24}O_3$	74·97	8·39
(*XV*)	(*G*)		(288·4)	75·05	8·34
XIX	74·0	835, 1 247, 1 516,	$C_{19}H_{26}O_2$	79·68	9·15
(*II*, *VIII*)	(*A*)	1 584, 1 614, 1 713	(286·4)	79·61	9·15
XX	39·0[g]	1 247, 1 713	$C_{20}H_{30}O_3$	75·43	9·50
(*XIX*)	(*D*)		(318·4)	75·40	9·52
XXI	41·9[h]	1 075, 1 246, 1 365,	$C_{21}H_{32}O_3$	75·86	9·70
(*XIX*)	(*D*)	1 390, 1 715	(332·5)	75·91	9·68
XXII	72·0	1 088, 1 248, 1 715,	$C_{21}H_{32}O_3$	75·86	9·70
(*II*, *IX*)	(*A*)	2 830	(332·5)	75·90	9·74
XXIII	60·5	1 245, 1 707	$C_{22}H_{34}O_3$	76·26	9·89
(*II*, *X*)	(*A*)		(346·5)	76·28	9·88
XXIV	37·2	1 023, 1 032, 1 060,	$C_{19}H_{26}O_4$	71·67	8·23
(*II*, *XI*)	(*C*)	1 225, 1 248, 1 713	(318·4)	71·72	8·17
XXV	50·0	1 052, 1 065, 1 128,	$C_{20}H_{28}O_4$	72·26	8·49
(*II*, *XII*)	(*B*)	1 247, 1 713	(332·4)	72·26	8·43

[a] B.p. 195°C/130 Pa; [b] products *XIII* and *XIV* were obtained as a mixture of isomers in a single reaction; [c] b.p. 180°C/130 Pa; [d] b.p. 165°C/130 Pa; [e] product *XVI* was obtained in a mixture with *XXXII* and *XXXIII*; [f] product *XVII* was obtained in a mixture with *XXXIV* and *XXXV*; [g] product *XX* was obtained in a mixture with *XL* and *XLI*; [h] product *XXI* was obtained in a mixture with *XLII* and *XLIII*.

TABLE II

Properties of the juvenoid alcohols *XXVI—LI*

Products (reaction components)	Yield, % (procedure)	IR spectrum cm^{-1}	Formula (Mol.weight)	Calc./Found	
				% C	% H
XXVI	41·4[a]	974, 1 153, 1 245,	$C_{20}H_{28}O_4$	72·26	8·49
(*XIII*)	(*F*)	1 650, 1 709, 3 620	(332·4)	72·20	8·39
XXVII[b]	44·3[a]	974, 1 153, 1 245,	$C_{20}H_{28}O_4$	72·26	8·49
(*XIII*)	(*F*)	1 650, 1 709, 3 615	(332·4)	72·12	8·36
XXVIII	46·3[c]	974, 1 153, 1 245,	$C_{20}H_{28}O_4$	72·26	8·49
(*XIV*)	(*F*)	1 650, 1 709, 3 620	(332·4)	72·30	8·27
XXIX	49·8[c]	974, 1 153, 1 245,	$C_{20}H_{28}O_4$	72·26	8·49
(*XIV*)	(*F*)	1 650, 1 709, 3 615	(332·4)	72·06	8·18
XXX[d]	38·0[e]	1 005, 3 625	$C_{18}H_{26}O_2$	78·79	9·55
(*XV*)	(*E*)		(274·4)	78·50	9·53
XXXI[f]	38·0[e]	1 005, 3 615	$C_{18}H_{26}O_2$	78·79	9·55
(*XV*)	(*E*)		(274·4)	78·84	9·06
XXXII	36·5	976, 1 070, 1 179,	$C_{19}H_{30}O_3$	74·47	9·87
(*XXX*)	(*D*)	3 620	(306·4)	74·39	9·78
XXXIII	38·0	976, 1 070, 1 179,	$C_{19}H_{30}O_3$	74·47	9·87
(*XXXI*)	(*D*)	3 615	(306·4)	74·50	9·85
XXXIV	35·0	976, 1 070, 1 179,	$C_{20}H_{32}O_3$	74·96	10·06
(*XXX*)	(*D*)	3 620	(320·5)	74·88	9·74
XXXV	35·8	976, 1 070, 1 179,	$C_{20}H_{32}O_3$	74·96	10·06
(*XXXI*)	(*D*)	3 615	(320·5)	74·52	9·98
XXXVI	61·5	833, 976, 1 037,	$C_{18}H_{26}O_3$	74·44	9·03
(*XXX*)	(*G*)	1 243, 3 630	(290·4)	74·36	8·97
XXXVII[g]	66·8	835, 1 036, 1 243,	$C_{18}H_{26}O_3$	74·44	9·03
(*XXXI*)	(*G*)	3 605, 3 625	(290·4)	74·31	9·01
XXXVIII	33·0[h]	975, 1 030, 1 248,	$C_{19}H_{28}O_2$	79·12	9·79
(*XIX*)	(*E*)	1 652, 1 674, 3 620	(288·4)	79·28	9·84
XXXIX[i]	39·2[h]	975, 1 030, 1 248,	$C_{19}H_{28}O_2$	79·12	9·79
(*XIX*)	(*E*)	1 652, 1 674, 3 610	(288·4)	79·19	9·75
XL	35·0	1 248, 3 620	$C_{20}H_{32}O_3$	74·96	10·06
(*XXXVIII*)	(*D*)		(320·5)	75·01	10·02
XLI	33·5	1 248, 3 610	$C_{20}H_{32}O_3$	74·96	10·06
(*XXXIX*)	(*D*)		(320·5)	—	—
XLII	32·6	974, 1 246, 1 367,	$C_{21}H_{34}O_3$	75·40	10·25
(*XXXVIII*)	(*D*)	1 388, 3 620	(334·5)	—	—

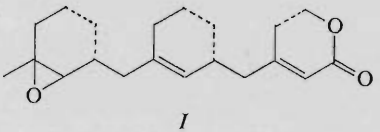
TABLE II
(*Continued*)

Products (reaction components)	Yield, % (procedure)	IR spectrum cm^{-1}	Formula (Mol.weight)	Calc./Found % C	Calc./Found % H
XLIII (*XXXIX*)	34·0 (*D*)	974, 1 246, 1 367, 1 388, 3 610	$C_{21}H_{34}O_3$ (334·5)	75·40 75·44	10·25 10·24
XLIV (*XXII*)	25·0[j] (*E*)	1 246, 3 620	$C_{21}H_{34}O_3$ (334·5)	75·40 —	10·25 —
XLV (*XXII*)	32·7[j] (*E*)	1 246, 3 610	$C_{21}H_{34}O_3$ (334·5)	75·40 75·35	10·25 10·19
XLVI (*XXIII*)	32·7[k] (*E*)	974, 1 029, 3 620	$C_{22}H_{36}O_3$ (348·5)	75·81 75·40	10·41 10·42
XLVII (*XXIII*)	28·5[k] (*E*)	974, 1 029, 3 615	$C_{22}H_{36}O_3$ (348·5)	75·81 75·62	10·41 10·33
XLVIII (*XXIV*)	37·6[l] (*E*)	975, 1 020, 1 123, 1 164, 1 178, 3 620	$C_{19}H_{28}O_4$ (320·4)	71·22 71·14	8·81 8·90
IL (*XXIV*)	45·0[l] (*E*)	1 030, 1 057, 1 121, 1 163, 1 249, 3 615	$C_{19}H_{28}O_4$ (320·4)	71·22 71·09	8·81 8·83
L (*XXV*)	17·4[m] (*E*)	1 052, 1 065, 1 128, 1 250, 3 620	$C_{20}H_{30}O_4$ (334·4)	71·82 71·80	9·04 9·13
LI[n] (*XXV*)	46·5[m] (*E*)	1 052, 1 065, 1 128, 1 250, 3 615	$C_{20}H_{30}O_4$ (334·4)	71·82 71·74	9·04 9·09

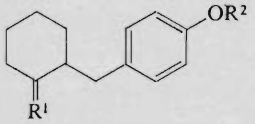
[a] Obtained as a mixture of isomers which were separated by chromatography; [b] m.p. 47—48°C; [c] obtained as a mixture of isomers which were separated chromatographically; [d] b.p. 160°C/130 Pa; [e] obtained as a mixture of isomers which were separated by chromatography; [f] m.p. 71—72°C; [g] m.p. 57—58°C; [h] obtained as a mixture of isomers which were separated chromatographically; [i] m.p. 45—46°C; [j] obtained as a mixture of isomers which were separated chromatographically; [k] obtained as a mixture of isomers which were separated chromatographically; [l] obtained as a mixture of isomers which were separated by chromatography; [m] obtained as a mixture of isomers which were separated by chromatography; [n] m.p. 53—53·5°C.

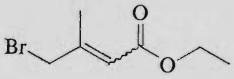
mo-5-methoxy-5-methylhexane (*IX*) the route was selected starting from 6-methyl--5-hepten-2-one. This ketone was first converted to 6-methoxy-6-methyl-2-heptanone on reaction with methanol in acid medium[20], which was then submitted to Lieben's methylation cleavage with alkali hypobromite[21,22] under formation of 5-methoxy--5-methyl-1-hexanoic acid. Its methyl ester was further reduced to 5-methoxy-5-methyl-1-hexanol, which was converted to 1-bromo-5-methoxy-5-methylhexane (*IX*)

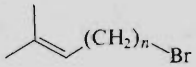
using a frequently used method for the preparation of alkyl halides[23]. 6-Methyl--5-hepten-2-one also served as a starting compound for the synthesis of 2-bromo--6-methoxy-6-methylheptane (*X*). Its preparation consisted in the reduction of its 6-methoxy derivative to 6-methoxy-6-methyl-2-heptanol which was converted[23]



I



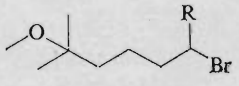


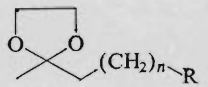


II; $R^1 = =O$, $R^2 = H$
III; $R^1 = =O$, $R^2 = CH_3$
IV; $R^1 = -OCH_2-OCH_2$, $R^2 = H$
V; $R^1 = -OCH_2-OCH(CH_2OH)$, $R^2 = H$

VI

VII; n = 1
VIII; n = 2





IX; R = H
X; R = CH_3

XI; n = 1, R = OTs
XII; n = 2, R = Cl

to the required 2-bromo-6-methoxy-6-methylheptane (*X*). A further derivative used for the synthesis of the aliphatic side chain of some juvenoid compounds was 3,3-ethylenedioxybutyl 4-toluenesulfonate (*XI*). For its synthesis ethyl aceto acetate served as a starting compound which was converted by the known Salmi method[24] to ethyl--3,3-ethylenedioxybutanoate. This ester was reduced to 2-(2-hydroxyethyl)-2-methyl--1,3-dioxolane which afforded[25] the required 3,3-ethylenedioxybutyl 4-toluenesulfonate (*XI*).

The last of the alkyl halides used, 5-chloro-2-pentanone ethylene acetal (*XII*), is commercially available.

The terminal steps of the syntheses of juvenoid substances could be summed up into seven general procedures. For the preparation of juvenoids *XIII*–*XV*, *XIX*, *XXII* to *XXV*, *LII*, *LIV*, *LVI* and *LVII* from phenolic derivatives *II*, *IV* or *V* and the corres-

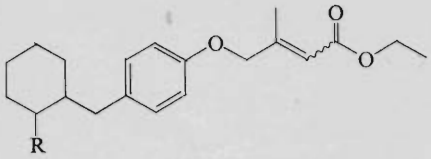
ponding alkenyl or alkyl halides or alkyl 4-toluenesulfonates three similar procedures were used, in dependence on the functional group of the alkenyl or alkyl intermediate. For the preparation of juvenoids *XIII–XV*, *XIX*, *XXII*, *XXIII*, *LII* and *LIV* from bromoalkenes or bromoalkanes the procedure described by Canonica and co-workers[26] was found convenient. It consisted in the reaction of phenolic derivatives *II*, *IV* or *V* with bromoalkenes or bromoalkanes in 2-butanone in the presence of anhydrous potassium carbonate (procedure *A*). However, this procedure was unsuitable when chloroalkanes or alkyl 4-toluenesulfonates were used. In the first case it had to be replaced by the procedure described by Shekhter and Tsizin[27], consisting in the reaction of the sodium salt of the phenolic derivative *II* or *IV* (formed on reaction of derivative *II* or *IV* with powdered sodium hydroxide) with chloroalkane (procedure *B*). In the second case an analogous procedure[28] was used on application of a stronger base (sodium hydride) in an inert atmosphere (procedure *C*). For the preparation of some juvenoids Hejno's modification[29] of the solvomercuration reaction[30] was used (*XVI*, *XVII*, *XX*, *XXI*, *XXXII–XXXV*, *XL–XLIII*, *LIII*, *LV*). More complex mixtures were obtained during the preparation of juvenoids *XVI*, *XVII*, *XX* and *XXI* in consequence of the reduction of the keto group to an alco-

TABLE III
Properties of the juvenoid acetals *LII–LVII*

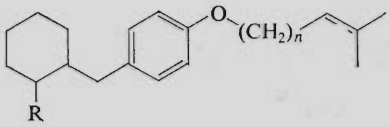
Products (reaction components)	Yield, % (procedure)	IR spectrum cm^{-1}	Formula (Mol.weight)	Calc./Found	
				% C	% H
LII	73·2	1 019, 1 089, 1 239,	$C_{20}H_{28}O_3$	75·91	8·92
(*IV*, *VII*)	(*A*)	1 680	(316·4)	75·52	9·05
LIII	35·5	1 019, 1 089, 1 157,	$C_{22}H_{34}O_4$	72·89	9·45
(*LII*)	(*D*)	1 239	(362·5)	72·84	9·36
LIV	58·5	1 008, 1 252, 1 384,	$C_{21}H_{30}O_4$	72·80	8·73
(*V*, *VII*)	(*A*)	1 676, 3 605, 3 630	(346·5)	72·78	8·76
LV	53·5	1 030, 1 247, 1 384,	$C_{23}H_{36}O_5$	70·37	9·24
(*LIV*)	(*D*)	1 392, 3 605, 3 630	(392·5)	70·70	9·08
LVI	40·0	1 019, 1 057, 1 089,	$C_{21}H_{30}O_5$	69·58	8·34
(*IV*, *XI*)	(*C*)	1 158, 1 248	(362·5)	69·51	8·35
LVII[a]	75·0	1 055, 1 168, 1245,	$C_{22}H_{32}O_5$	70·18	8·57
(*IV*, *XII*)	(*B*)	1 516, 1 584, 1 613	(376·5)	70·21	8·57

[a] M.p. 57–59°C.

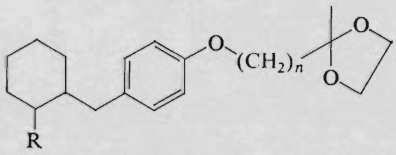
holic one during the decomposition of the reaction mixture with sodium borohydride. The mixture contained in addition to juvenoid ketones *XVI*, *XVII*, *XX*, and *XXI* also *cis-trans* isomers of corresponding juvenoid alcohols *XXXII*–*XXXV*,



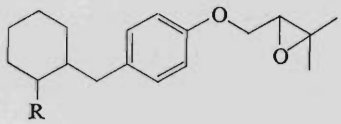
XIII; (*E*)-isomer, R = =O
XIV; (*Z*)-isomer, R = =O
XXVI[a], *XXVII*[b]; (*E*)-isomers, R = OH
XXVIII[a], *XXIX*[b]; (*Z*)-isomers, R = OH



XV; n = 1, R = =O
XIX; n = 2, R = =O
XXX[a], *XXXI*[b]; n = 1, R = OH
XXXVIII[a], *XXXIX*[b]; n = 2, R = OH
LII; n = 1, R = —OCH$_2$—OCH$_2$—
LIV; n = 1, R = —OCH$_2$—OCH(—CH$_2$OH)—



XXIV; n = 2, R = =O
XXV; n = 3, R = =O
XLVIII[a], *IL*[b]; n = 2, R = OH
L[a], *LI*[b]; n = 3, R = OH
LVI; n = 2, R = —OCH$_2$—OCH$_2$—
LVII; n = 3, R = —OCH$_2$—OCH$_2$—

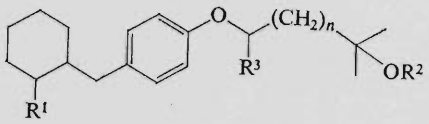


XVIII; R = =O
XXXVI[a], *XXXVII*[b]; R = OH

XL–*XL III*(procedure *D*). For the preparation of the majority of juvenoid alcohols *XXX*, *XXXI*, *XXXVIII*, *XXXIX*, *XLIV*–*LI* from juvenoid ketones *XV*, *XIX*, *XXII*–*XXV* reduction with lithium aluminum hydride in ether was employed (procedure *E*). Only in the case of keto esters *XIII* and *XIV* reduction with sodium borohydride in methanol to hydroxy esters *XXVI*–*XXIX* had to be used (procedure *F*). The juvenoids *XVIII*, *XXXVI* and *XXXVII* with an oxirane ring in the molecule

were prepared from corresponding olefins *XV*, *XXX*, and *XXXI* on reaction with perphthalic acid[31] (procedure *G*).

We also tried to determine the relative configuration of 1,2-substituents on the cyclohexane ring in the molecules of juvenoid alcohols *XXVI*–*LI*. In this we based our considerations on the ^{1}H-NMR and IR spectral data of *cis*- and *trans*-2-benzyl -1-cyclohexanols published by some authors[32–34] and on the results of the measure-



	n	R^1	R^2	R^3
XVI:	1	=O	CH_3	H
XVII:	1	=O	C_2H_5	H
XX:	2	=O	CH_3	H
XXI:	2	=O	C_2H_5	H
XXII:	3	=O	CH_3	H
XXIII:	3	=O	CH_3	CH_3
XXXII[a], *XXXIII*[b]:	1	OH	CH_3	H
XXXIV[a], *XXXV*[b]:	1	OH	C_2H_5	H
XL[a], *XLI*[b]:	2	OH	CH_3	H
XLII[a], *XLIII*[b]:	2	OH	C_2H_5	H
XLIV[a], *XLV*[b]:	3	OH	CH_3	H
XLVI[a], *XLVII*[b]:	3	OH	CH_3	CH_3
LIII:	1	—OCH | —OCH	C_2H_5	H
LV:	1	—OCH | —OCH—CH_2OH	C_2H_5	H

[a] *cis*-Isomer of the corresponding alcohol, [b] *trans*-isomer of the corresponding alcohol.

ments of the ^{1}H-NMR and IR spectra of our juvenoid alcohols *XXVI*–*XXIX*. Granger and coworkers[32] studied the ^{1}H-NMR spectra of both isomers of 2-benzyl--1-cyclohexanol, measured in deuteriochloroform and the ^{1}H-NMR spectra measured after addition of tris(dipivalomethanato)europium, and they could differentiate the isomers. The bulky benzyl substituent always assumes the equatorial position on the cyclohexanol ring, while the hydroxyl group can assume the axial position as well. In accordance with this Sehgal and coworkers[33] measured the values for the axial and the equatorial hydroxyl group. The results of these spectral studies[32–34], as well as our own measurements are summarized in Table IV and they were applied to other isomeric pairs of juvenoid alcohols (*XXX*–*LI*) as well. From the data

it follows unambiguously that in these alcohols *XXVI–LI* the *para*-substituted benzyl group also assumes only the equatorial position on the cyclohexanol ring, and that the *cis-trans* isomerism is in fact determined according to the configuration of the hydroxyl group, because – in agreement with the measurements of the ^{1}H-NMR and the IR spectra – the hydroxyl group assumes in all *cis*-isomers of the alcohols the axial configuration, and in all *trans*-isomers the equatorial position.

EXPERIMENTAL

Column chromatographies were carried out on silica gel (Herrmann, Koen-Ehrenfeld) or on neutral alumina (Woelm, Eschwege, activity III according to Brockmann). The reaction course and the purity of the substances were checked either by analytical thin-layer chromatography on silica gel (Kieselgel G nach Stahl, type 60, Merck, Darmstadt) or by gas chromatography on a Perkin–Elmer F-11 instrument with a FID detector. The IR spectra were measured in tetrachloromethane or chloroform on a UR-20 (Carl Zeiss, Jena) spectrophotometer. The ^{1}H-NMR spectra were measured on a Varian HA-100 (100 MHz) or Tesla BS-467 (60 MHz) instrument in deuteriochloroform, using tetramethylsilane as an internal reference. The mass spectra were measured on an AEI MS-902 spectrometer.

2-(4-Methoxybenzyl)-1-cyclohexanone (*III*)

A solution of 4-methoxybenzyl chloride (9·1 g, 58 mmol) in dioxane (15 ml) was added dropwise to a solution of N-(1-cyclohexenyl)pyrrolidine[14] (13·6 g, 90 mmol) in dioxane (35 ml) and the mixture was refluxed for 5 h. Water was added (15 ml) and the refluxing was continued for 45 min. After evaporation of dioxane under reduced pressure the residue was diluted with water and the organic layer was extracted with ether. The extract was washed with 5% hydrochloric acid,

TABLE IV

Comparison of some signals of the ^{1}H-NMR spectra and the IR bands of the model 2-benzyl-1-cyclohexanol with those of juvenoid alcohols *XXVI–XXIX*

Compound	Configuration[a]	^{1}H-NMR, $CDCl_3$, ppm				IR, cm^{-1}	
		H_{ax}	H_{eq}	OH_{ax}	OH_{eq}	OH_{ax}	OH_{eq}
2-Benzyl-1-cyclohexanol	*cis*	–	3·84[b]	4·19[c,d]	–	3 632[e]	–
	trans	3·30[b]	–	–	4·50[c,d]	–	3 627[e]
XXVI, XXVIII	*cis*	–	3·77	1·48	–	3 620	–
XXVII, XXIX	*trans*	3·20	–	–	1·68	–	3 615

[a] Configuration of 1,2-substituents on the cyclohexane ring; [b] Granger and coworkers[32]; [c] measured in dimethyl sulfoxide; [d] Sehgal and coworkers[33]; [e] Moreau and coworkers[34].

5% sodium carbonate solution and water until neutral. After drying over sodium sulfate, filtration and evaporation the residue was distilled, affording 6·63 g (52·5%) of product *III*, b.p. 185°C/200 Pa. Bec and Huet[15] give b.p. 150°C/130 Pa. ^{1}H-NMR spectrum (ppm): 1·50—2·60 (m), 3·16 (m, 1 H), 3·73 (s, 3 H), 6·78 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5); IR spectrum (cm^{-1}): 1 250, 1 694, 1 710, 2 840; Mass spectrum: m/z = 218 ($M^{\pm}$). For $C_{14}H_{18}O_2$ (218·3) calculated: 77·03% C, 8·31% H; found: 77·11% C, 8·29% H.

2-(4-Hydroxybenzyl)-1-cyclohexanone (*II*)

The title compound was prepared by cleavage of the ethereal bond[15] in *III* (5·1 g, 23·4 mmol) using azeotropic hydrobromic acid (12 g) in acetic anhydride (12 g). Yield, 2·6 g (55%) of ketone *II*, m.p. 96—97°C, which was in agreement with the literature data[15]. ^{1}H-NMR spectrum (ppm): 1·20—2·65 (m), 3·14 (m, 1 H), 5·83 (broad, 1 H), 6·74 (d, 2 H, 8·5), 6·97 (d, 2 H, 8·5); IR spectrum (cm^{-1}): 1 258, 1 706, 1 795, 3 605; Mass spectrum: m/z = 204 ($M^{\pm}$), 175, 107 (base peak), 94. For $C_{13}H_{16}O_2$ (204·3) calculated: 76·44% C, 7·90% H; found 77·18% C, 8·11% H.

2-(4-Hydroxybenzyl)-1-cyclohexanone Ethylene Acetal (*IV*)

2-(4-Hydroxybenzyl)-1-cyclohexanone ethylene acetal was obtained on acetalization[16] of *II* (2 g, 9·8 mmol) with 1,2-ethanediol (2 ml), under simultaneous elimination of water by azeotropic distillation. Yield 2·2 g (90·5%), m.p. 86—88°C. ^{1}H-NMR spectrum (ppm): 1·50—3·15 (m), 3·95 (s, 4 H), 6·68 (d, 2 H, 8·5), 7·00 (d, 2 H, 8·5); IR spectrum (cm^{-1}): 3 400, 3 612; Mass spectrum: m/z = 248 ($M^{\pm}$). For $C_{15}H_{20}O_3$ (248·3) calculated: 72·55% C, 8·12% H; found: 72·69% C, 8·12% H.

2-(4-Hydroxybenzyl)-1-cyclohexanone Hydroxymethylethylene Acetal (*V*)

The title compound was obtained analogously[16] from *II* (2 g, 9·8 mmol) and 1,2,3-propanetriol (2·5 ml) in a 55% (1·5 g) yield. M.p. 94—97°C ^{1}H-NMR spectrum (ppm): 1·20—3·20 (m), 3·63 (s, 1 H), 3·70 (s, 2 H), 4·13 (d, 2 H, 4·0), 6·72 (d, 2 H, 8·5), 6·98 (d, 2 H, 8·5); IR spectrum (cm^{-1}): 1 052, 1 090, 1 100, 1 156, 1 172, 1 257, 3 600; Mass spectrum: m/z = 278 ($M^{\pm}$). For $C_{16}H_{22}O_4$ (278·3) calculated: 69·04% C, 7·97% H; found: 69·11% C, 8·01% H.

Preparation of Compounds *XIII—XV*, *XIX*, *XXII*, *XXIII*, *LII* and *LIV*, Procedure *A*

A solution of compound *II*, *IV* or *V* (10 mmol) and of corresponding bromo derivative *VI—X* (ref.[17—23]) (15 mmol) in 2-butanone (25 ml) was refluxed at 100—110°C for 2·5—5 h in the presence of anhydrous potassium carbonate (40 mmol). After cooling the mixture was diluted with water, the organic layer was extracted with ether and dried over Na_2SO_4. Chromatography on a fifty to hundred-fold amount of silica gel gave pure products the properties of which are given in Tables I and III.

Preparations of Compounds *XXV* and *LVII*, Procedure *B*

Powdered sodium hydroxide (2·5 mmol) was added to a solution of compound *II* or *IV* (2·45 mmol) in dimethyl sulfoxide (10 ml) and the mixture was heated at 100°C under stirring for 2 h. Corresponding chloro derivative *XII* was then added *in substantia* (4·14 mmol) and the mixture was heated at 100—110°C for 2 h. After cooling it was diluted with water, the organic layer was extracted with ether and the extract dried over Na_2SO_4. Chromatography on a fifty-fold amount of silica gel afforded pure products the properties of which are given in Tables I and III.

Preparation of Compounds *XXIV* and *LVI*, Procedure *C*

A solution of compound *II* or *IV* (10 mmol) in toluene (30 ml) was added to a stirred suspension of sodium hydride (10 mmol) in toluene (30 ml) and the mixture was refluxed for 30 min. Tosylate *XI* (ref.[24,25]) was then added *in substantia* (11·5 mmol) and the mixture was refluxed for 7 h. After decomposition with water the mixture was extracted with benzene, the extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a 20-fold amount of alumina. Pure products were obtained the properties of which are given in Tables I and III.

Preparation of Compounds *XVI*, *XVII*, *XX*, *XXI*, *XXXII—XXXV*, *XL—XLIII*, *LIII* and *LV*, Procedure *D*

A solution of compound *XV*, *XIX*, *XXX*, *XXXI*, *XXXVIII*, *XXXIX*, *LII* or *LIV* (4·58 mmol) in corresponding absolute alcohol (6 ml) was added dropwise to a stirred solution of mercuric trifluoro acetate[30] (4·7 mmol) in corresponding absolute alcohol (12 ml). The addition was carried out over 10 min and the mixture was kept at 17—18°C. The stirring continued for 0·25 to 0·5 h at the same temperature. The mixture was cooled to 2—3°C and a 3M-solution of potassium hydroxide in corresponding absolute alcohol (6 ml) was added dropwise, followed by a solution of sodium borohydride (3·5 mmol) in 3M-alcoholic potassium hydroxide solution (6 ml). After further stirring at 2—3°C for one hour the precipitated mercury was filtered off and the filtrate concentrated by evaporation of alcohol under reduced pressure. A saturated sodium chloride solution (30 ml) was added to the residue, the organic material was extracted with ether and the extract dried over Na_2SO_4. Chromatography of the mixture on a 50-fold amount of silica gel gave corresponding alkoxylated products the properties of which are given in Tables I—III.

Preparation of Compounds *XXX*, *XXXI*, *XXXVIII*, *XXXIX*, *XLIV—LI*, Procedure *E*

Ketones *XV*, *XIX*, *XXII—XXV* (10 mmol) were reduced with lithium aluminum hydride (25 mmol) in ether (50 ml). The mixture was worked up as described earlier[35]. The mixture of *cis*/*trans* isomers of the juvenoid alcohols obtained was separated by column chromatography on a 100-fold amount of silica gel. The *cis*- and the *trans*-isomers of alcohols *XXX*, *XXXI*, *XXXVIII*, *XXXIX*, *XLIV—LI* were obtained in pure form. Their properties are given in Table II.

Preparation of Compounds *XXVI—XXIX*, Procedure *F*

Sodium borohydride (15 mmol) was added in portions, under stirring and cooling at 0°C, to a solution of ketone *XIII* or *XIV* (4·25 mmol) in methanol (75 ml) and stirring was continued for 1·5 h. Methanol was evaporated under reduced pressure and saturated sodium chloride solution (75 ml) was added to the residue. The organic material was extracted with ether and the extract dried over sodium sulfate. Chromatographic separation gave pure *cis*- and *trans*-isomers of alcohols *XXVI—XXIX* the properties of which are given in Table II.

Preparation of Compounds *XVIII*, *XXXVI* and *XXXVII*, Procedure *G*

A solution of compound *XV*, *XXX* or *XXXI* (5 mmol) in ether (20 ml) was added dropwise and under cooling at 0°C to a solution of perphthalic acid in ether (20 ml, concentration about 100 mg/l ml) and the mixture was allowed to stand in an ice-box for 6—8 h. Ether was evaporated and the residue purified by chromatography on a 30 to 40-fold amount of silica gel. The properties of the products are given in Tables I and II.

Characterization of Compounds *XIII*—*LVII* by Mass Spectra and ^{1}H-NMR Spectra

The structures of the compounds from Tables I—III were also characterized by mass and ^{1}H-NMR spectra. However, since high-resolution mass spectra were not measured, but the structures were checked only, the results of mass spectrometry are not published here, since other data are amply sufficient for characterization. The interpretation of the ^{1}H-NMR spectra (ppm) is presented here. The ^{1}H-NMR spectra for isomeric pairs of compounds are presented in summary. The signals which are not common for both isomers are indicated by the number of the isomer to which they belong. *XIII* and *XIV*: 1·28 (t, 3 H, 7·0), 1·70—2·70 (m), 2·02 (s, 3 H, *XIV*), 2·20 (s, 3 H, *XIII*), 3·15 (m, 1 H), 4·17 (q, 2 H, 7·0), 4·47 (d, 2 H, 1·0, *XIII*), 5·18 (s, 2 H, *XIV*), 5·82 (s, 1 H, *XIV*), 6·05 (s, 1 H, *XIII*), 7·30 (d, 2 H, 8·5), 7·58 (d, 2 H, 8·5). *XV*: 1·20—2·68 (m), 1·78 (d, 6 H, 5·5), 3·16 (m, 1 H), 4·48 (d, 2 H, 6·0), 5·50 (m, 1 H), 6·84 (d, 2 H, 8·5), 7·08 (d, 2 H, 8·5). *XVI*: 1·20 (s, 2 H), 1·30—2·60 (m), 3·06 (m, 1 H), 3·15 (s, 3 H), 4·02 (t, 2 H, 7·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XVII*: 1·12 (t, 3 H, 7·0), 1·20 (s, 6 H), 1·50—2·60 (m), 3·06 (m, 1 H),, 3·38 (q, 2 H, 7·0), 4·02 (t, 2 H, 7·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XVIII*: 1·10—2·20 (m), 1·35 (d, 6 H, 2·0), 3·11 (m, 2 H), 4·06 (d, 2 H, 5·5), 6·84 (d, 2 H, 8·5), 7·12 (d, 2 H, 8·5). *XIX*: 1·50—2·80 (m), 1·64 (d, 6 H, 5·5), 3·87 (t, 2 H, 7·0), 4·70 (s, 1 H), 6·75 (d, 2 H, 8·5), 7·03 (d, 2 H, 8·5). *XX*: 1·12 (s, 6 H), 1·20—2·00 (m), 3·14 (s, 3 H), 3·90 (t, 2 H, 6·0), 6·78 (d, 2 H, 8·5), 7·09 (d, 2 H, 8·5). *XXI*: 1·12 (t, 3 H, 7·0), 1·13 (s, 6 H), 1·30—1·90 (m), 3·34 (q, 2 H, 7·0), 3·90 (t, 2 H, 7·0), 6·75 (d, 2 H, 8·5), 7·03 (d, 2 H, 8·5). *XXII*: 1·12 (s, 6 H), 1·50—2·65 (m), 3·16 (s, 3 H), 3·16 (m, 1 H), 3·93 (t, 2 H, 6·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XXIII*: 1·12 (s, 6 H), 1·27 (s, 3 H), 1·30—2·65 (m), 3·13 (s, 3 H), 4·32 (m, 1 H), 6·81 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XXIV*: 1·20 to 2·60 (m), 1·40 (s, 3 H), 3·09 (m, 0·5 H), 3·26 (m, 0·5 H), 3·96 (s, 4 H), 4·08 (t, 2 H, 7·0), 6·81 (d, 2 H, 8·5), 7·10 (d, 2 H, 8·5). *XXV*: 1·10—2·65 (m), 1·33 (s, 3 H), 3·15 (m, 1 H), 3·93 (s, 4 H), 3·93 (t, 2 H, 6·0), 6·78 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XXVI*—*XXIX*: 1·27 (t, 3 H, 7·0), 1·48 (s, 1 H, *XXVI*, *XXVIII*), 1·50—2·60 (m), 1·68 (s, 1 H, *XXVII*, *XXIX*), 2·00 (s, 3 H, *XXVIII*, *XXIX*), 2·17 (s, 3 H, *XXVI*, *XXVII*), 3·20 (m, 1 H, *XXVII*, *XXIX*), 3·77 (m, 1 H, *XXVI*, *XXVIII*), 4·17 (q, 2 H, 7·0), 4·46 (s, 2 H, *XXVI*, *XXVII*), 5·17 (d, 2 H, 1·0, *XXVIII*, *XXIX*), 5·82 (m, 1 H, *XXVIII*, *XXIX*), 6·07 (m, 1 H, *XXVI*, *XXVII*), 6·90 (d, 2 H, 8·5), 7·06 (d, 2 H, 8·5). *XXX* and *XXXI*: 1·26—1·95 (m), 1·77 (d, 6 H, 5·5), 2·29 (d, 0·5 H, 14·0, *XXXI*), 2·38 (d, 0·5 H, 14·0, *XXXI*), 2·57 (t, 1 H, 7·0, *XXX*), 3·15 (m, 1 H, *XXXI*), 3·81 (m, 1 H, *XXX*), 4·49 (d, 2 H, 7·0), 5·49 (s, 1 H), 6·81 (d, 2 H, 8·5), 7·08 (d, 2 H, 8·5). *XXXII* and *XXXIII*: 1·10—2·20 (m), 1·21 (s, 6 H), 2·93 (m, 1 H, *XXXIII*), 3·15 (s, 3 H), 3·78 (m, 1 H, *XXXII*), 4·03 (t, 2 H, 7·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XXXIV* and *XXXV*: 1·13 (t, 3 H, 7·0), 1·20—2·20 (m), 1·21 (s, 6 H), 2·93 (m, 1 H, *XXXV*), 3·39 (q, 2 H, 7·0), 3·78 (m, 1 H, *XXXIV*), 4·03 (t, 2 H, 7·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *XXXVI* and *XXXVII*: 1·15—2·00 (m), 1·32 (s, 3 H), 1·37 (s, 3 H), 3·10 (t, 1 H, 5·0), 3·22 (broad, 1 H, *XXXVII*), 3·75 (broad, 1 H, *XXXVI*), 4·06 (d, 2 H, 5·0), 6·83 (d, 2 H, 8·5), 7·10 (d, 2 H, 8·5). *XXXVIII* and *XXXIX*: 1·30—1·80 (m), 1·64 (d, 6 H, 5·5), 3·85 (t, 2 H, 7·0), 4·70 (s, 1 H), 6·75 (d, 2 H, 8·5), 7·06 (d, 2 H, 8·5). *XL* and *XLI*: 1·10—2·00 (m), 1·12 (s, 6 H), 2·28 (broad, 1 H, *XLI*), 3·14 (s, 3 H), 3·90 (t, 2 H, 6·0), 3·90 (m, 1 H, *XLI*), 6·78 (d, 2 H, 8·5), 7·09 (d, 2 H, 8·5). *XLII* and *XLIII*: 1·10—2·00 (m), 1·13 (t, 3 H, 7·0), 1·15 (s, 6 H), 3·36 (q, 2 H, 7·0), 3·92 (t, 2 H, 7·0), 6·77 (d, 2 H, 8·5), 7·08 (d, 2 H, 8·5). *XLIV* and *XLV*: 1·12 (s, 6 H), 1·30—1·80 (m), 2·33 (broad, 1 H, *XLV*), 2·55 (broad, 1 H, *XLIV*), 2·93 (m, 1 H, *XLV*), 3·15 (s, 3H), 3·83 (m, 1 H, *XLIV*), 3·92 (t, 2 H, 6·0), 6·79 (d, 2 H, 8·5), 7·10 (d, 2 H, 8·5). *XLVI* and *XLVII*: 1·12 (s, 6 H), 1·20—1·80 (m), 1·27 (d, 3 H, 6·0), 1·52 (s, 1 H, *XLVI*), 1·62 (s, 1 H, *XLVII*), 3·13 (s, 3 H), 4·30 (m, 1 H), 6·78 (d, 2 H, 8·5), 7·08 (d, 2 H, 8·5). *XLVIII* and *IL*: 1·20 to 2·20 (m), 1·40 (s, 3 H), 1·54 (broad, 1 H, *XLVIII*), 1·64 (broad, 1 H, *IL*), 3·96 (s, 4 H), 4·10 (t, 2 H, 7·0), 6·81 (d, 2 H, 8·5), 7·09 (d, 2 H, 8·5). *L* and *LI*: 1·20—2·00 (m), 1·33 (s, 3 H), 1·50 (broad, 1 H, *L*), 1·60 (broad, 1 H, *LI*), 3·93 (s, 4 H), 3·95 (t, 2 H, 6·0), 6·80 (d, 2 H, 8·5), 7·10 (d, 2 H, 8·5). *LII*: 1·50—3·15 (m), 1·74 (d, 6 H, 3·0), 3·96 (s, 4 H), 4·45 (d, 2 H, 7·0), 5·49 (m, 1 H), 6·78

(d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *LIII*: 1·12 (t, 3 H, 7·0), 1·20 (s, 6 H), 1·50—2·45 (m), 3·38 (q, 2 H, 7·0), 3·97 (s, 4 H), 4·02 (t, 2 H, 7·0), 6·80 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *LIV*: 1·20—2·30 (m), 1·73 (d, 6 H, 3·0), 3·57 (s, 1 H), 3·72 (s, 2 H), 4·12 (s, 2 H), 4·45 (d, 2 H, 7·0), 5·48 (s, 1 H), 6·78 (d, 2 H, 8·5), 7·07 (d, 2 H, 8·5). *LV* 1·00—2·10 (m), 1·20 (t, 3 H, 7·0), 1·21 (s, 6 H), 3·39 (q, 2 H, 7·0), 3·46 (s, 1 H), 3·72 (s, 2 H), 4·03 (t, 2 H, 7·0), 6·82 (d, 2 H, 8·5), 7·08 (d, 2 H, 8·5). *LVI*: 1·15—1·85 (m), 1·40 (s, 3 H), 2·89 (m, 0·5 H), 3·09 (m, 0·5 H), 3·96 (s, 4 H), 4·00 (s, 4 H), 4·08 (t, 2 H, 7·0), 6·81 (d, 2 H, 8·5), 7·10 (d, 2 H, 8·5). *LVII*: 1·10—2·00 (m), 1·37 (s, 3 H), 3·95 (s, 4 H), 4·00 (s, 4 H), 6·77 (d, 2 H, 8·5), 7·04 (d, 2 H, 8·5).

Biological Activity of the Substances Prepared

The final products *XIII—LVII*, described in this paper, possess biological properties similar to those of the native juvenile hormone[6,13]. Their effects on some species of aphids will be described in greater detail elsewhere.

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REFERENCES

1. Menn J. J., Beroza M. (Eds): *Insect Juvenile Hormones, Chemistry and Action.* Academic Press, New York 1972.
2. Sláma K., Romaňuk M., Šorm F.: *Insect Hormones and Bioanalogues.* Springer, Wien 1974.
3. Gilbert L. I. (Ed.): *The Juvenile Hormones.* Plenum Press, New York 1976.
4. Sláma K.: Annu. Rev. Biochem. *40*, 1079 (1971).
5. Romaňuk M.: Arch. Zool. Exp. Gén. *112*, 553 (1971).
6. Romaňuk M. in the book: *Regulation of Insect Development and Behaviour* (F. Sehnal, A. Zabza, J. J. Menn, B. Cymborowski Eds), p. 247. Wroclaw 1981.
7. Romaňuk M.: Nova Acta Leopold. Suppl. *7*, 445 (1976).
8. Franke A., Mattern G., Traber W.: Helv. Chim. Acta *58*, 268 (1975).
9. Franke A., Mattern G., Traber W.: Helv. Chim. Acta *58*, 278 (1975).
10. Franke A., Mattern G., Traber W.: Helv. Chim. Acta *58*, 283 (1975).
11. Franke A., Mattern G., Traber W.: Helv. Chim. Acta *58*, 293 (1975).
12. Sláma K., Romaňuk M.: Insect Biochem. *6*, 579 (1976).
13. Sláma K., Wimmer Z., Romaňuk M.: Hoppe-Seyler's Z. Physiol. Chem. *359*, 1407 (1978).
14. Stork G., Brizzolara A., Landesman H., Szumszkovicz J., Terrell R.: J. Amer. Chem. Soc. *85*, 207 (1963).
15. Bec J.-M., Huet J.: Bull. Soc. Chim. Fr. *1972*, 1627.
16. Peterson Q. R., Sowers E. E.: J. Org. Chem. *29*, 1627 (1964).
17. Huisman H. D., Smit A., Vromen S., Fisscher L. G. M.: Rec. Trav. Chim. Pays-Bas *71*, 899 (1952).
18. Krimer M. Z., Lavrinenko E. S., Shamshurin A. A.: Zh. Org. Khim. *9*, 485 (1973).
19. Julia M., Julia S., Guégan R.: Bull. Soc. Chim. Fr. *1960*, 1072.
20. Surmatis J. D., Ofner A.: J. Org. Chem. *28*, 2735 (1963).
21. Levine R., Stephens J. R.: J. Amer. Chem. Soc. *72*, 1642 (1950).

22. Farrah M. W.: J. Org. Chem. *22*, 1708 (1957).
23. Smith L. H.: Org. Syn., Coll. Vol. *3*, 793 (1955).
24. Salmi E. J.: Ber. Deut. Chem. Ges. *71B*, 1803 (1938).
25. Mori K., Tamada S.: Tetrahedron *35*, 1279 (1979).
26. Canonica L., Fiecchi A., Adobbati M.: Rend. Ist. Lombardo Sci., Pt. I, Classe Sci. Mat. Nat. *87*, 257 (1954); Chem. Abstr. *50*, 6376f (1956).
27. Shekhter O. V., Tsizin Yu. S.: Zh. Org. Khim. *13*, 993 (1977).
28. Wheatley W. B., Fitzgibbon W. E., Cheney L. C., Binkley S. B.: J. Amer. Chem. Soc. *72*, 1655 (1950).
29. Hejno K., Šorm F.: This Journal *41*, 151 (1976).
30. Brown H. C., Min-Hon Rei: J. Amer. Chem. Soc. *91*, 5646 (1969).
31. Fieser L. F., Goto T.: J. Amer. Chem. Soc. *82*, 1693 (1960).
32. Granger P., Claudon M. M., Guinet J. F.: Tetrahedron Lett. *1971*, 4167.
33. Sehgal R. K., Koenigsberger R. U., Howard T. J.: Tetrahedron Lett. *1974*, 4173.
34. Moreau M., Quagliaro R., Longeray R., Dreux J.: Bull. Soc. Chim. Fr. *1969*, 1362.
35. Mićović V. M., Mihailović M. J.: J. Org. Chem. *18*, 1190 (1953).

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