PREPARATION OF CARBAMATE DERIVATIVES OF 2-(4-HYDROXYBENZYL)-1-CYCLOHEXANONE WITH A JUVENOID ACTIVITY

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Dedicated to the memory of Professor Luigi Canonica, the director of the Institute of Organic Chemistry, Milano, Italy.

The synthesis of four carbamate derivatives of 2-(4-hydroxybenzyl)-1-cyclohexanone displaying a juvenilizing effect in insects is described. The substances prepared have a greater stability and activity than their carba-analogues prepared earlier.

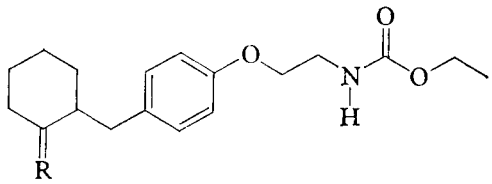
In an effort to improve the chemical and biological properties of juvenoids synthetized earlier[1] we modified a part of their molecule. While preserving the dicyclic system of the molecule, which proved very suitable from the biological point of view, but also from that of further possibilities of transforming these compounds to juvenogen complex compounds[2,3], we introduced the carbamate group into the aliphatic moiety of the molecule. We preserved the length of this side chain in all the analogues synthetized, and modified only the functional group of the cyclohexanone ring.

The key intermediate for the synthesis of derivatives *I*–*III* was 2-(4-hydroxybenzyl)-1-cyclohexanone (*IV*) (ref.[1]).

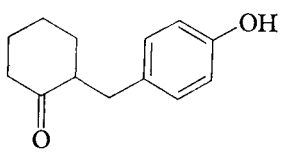
For the synthesis of ethyl N-(2-chloroethyl)carbamate (*V*) we started from ethyl chloroformate, the reaction of which with 40% aqueous methylamine solution[4] gave ethyl N-methylcarbamate. Nitrosation of the latter compound gave ethyl N-nitroso-N-methylcarbamate[5] which on reaction with ethyleneimine[5] afforded ethyl N,N-dimethylenecarbamate. On opening the three-membered ring of ethyl N,N-dimethylenecarbamate with dilute hydrochloric acid[5], derivative *V* was obtained.

The final products *I* or *II* were synthetized on reaction of compound *IV* or its derivative *VI* (ref.[1]) with carbamate *V* in dimethyl sulfoxide in the presence of sodium hydroxide[6]. The same synthesis when carried out in dimethylformamide in the presence of potassium carbonate gave substantially lower yields of products *I* or *II*, or it did not take place at all[6]. Corresponding hydroxy derivative *III* was prepared on reduction of compound *I* with sodium borohydride. Chromatography on silica gel gave racemic forms of both geometric isomers *IIIa* and *IIIb* in a pure state.

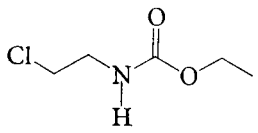
Preliminary biological tests indicate a high activity of the synthetized juvenoids in comparison with the commercial preparation Methoprene. The results of the biological tests on some species of agricultural or social pests (for example the aphids *Acyrtosiphon pisum*, termites of the *Rhinotermididae* family *etc.*) will be published later.



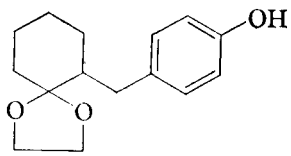
I, R = =O
II, R = —OCH_2CH_2O—
III a, R = —OH_{ax}, —H_{eq}
III b, R = —OH_{eq}, —H_{ax}



IV



V



VI

EXPERIMENTAL

Column chromatographies were carried out on silica gel Silpearl (Kavalier, Votice). The reaction course and the purity of the compounds were checked by 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 instrument (Carl Zeiss, Jena). The mass spectra were measured on an AEI MS-902 spectrometer, the ^{1}H NMR spectra were measured in deuteriochloroform on a Varian XL-200 (200 MHz) instrument, using tetramethylsilane as internal reference. The chemical shift values are given in ppm (δ-scale) and the coupling constants in Hz. Elemental analyses were carried out in the analytical laboratory of our Institute. The melting points were determined on a Kofler block and they are not corrected.

2-(4-(2-(Ethoxycarbamato)ethoxy)benzyl)-1-cyclohexanone (*I*)

Ground sodium hydroxide (0·5 g, 12·5 mmol) was added to a solution of *IV* (2 g, 9·8 mmol) in dimethyl sulfoxide (40 ml) and the mixture was stirred at 100°C for 2 h. The oily compound *V* (2 g, 13·2 mmol) was added dropwise and the stirring and heating were continued for another 4 h. After cooling the mixture was diluted with water (40 ml) and extracted with ether. The extract was dried over sodium sulfate, the solvent evaporated and the residue purified by column chromatography on silica gel. Yield, 3·0 g (50%) of compound *I*. ^{1}H NMR spectrum (ppm): 1·21 (t, J = = 7·1, 3 H), 1·50–2·35 (m, 8 H), 2·36 (dd, J = 8·8 and 13·4, 1 H), 2·52 (m, 1 H), 3·15 (dd, J = 4·5 and 13·4, 1 H), 3·48 (q, J = 7·1, 1 H), 3·56 (q, J = 5·4, 1 H), 4·00 (AB system, 2 H), 4·12 (bq, J = 7·1, 2 H), 5·11 (bs, 1 H), 6·80 (m, J = 8·7, 2 H), 7·07 (m, J = 8·7, 2 H). IR spectrum (cm^{-1}): 3 455, 1 711, 1 612, 1 583, 1 518, 1 250. Mass spectrum, *m/z*: 319 (M^+), 273, 230, 204, 116 (base peak), 107, 88. For $C_{18}H_{25}NO_4$ (319·4) calculated: 67·68% C, 7·89% H, 4·39% N; found: 67·70% C, 7·90% H, 4·35% N.

2-(4-(2-(Ethoxycarbamato)ethoxy)benzyl)-1-cyclohexanone Ethylene Acetal (*II*)

Compound *II* was prepared analogously from *VI* (1·36 g, 5·5 mmol) in 23% yield (0·45 g), m.p. 63–64°C. ^{1}H NMR spectrum (ppm): 1·20–1·73 (m, 8 H), 1·24 (t, J = 7·1, 3 H), 1·78 (m, 1 H), 2·20 (dd, J = 11·0 and 13·2, 1 H), 2·99 (dd, J = 3·1 and 13·2, 1 H), 3·56 (q, J = 5·4, 2 H), 4·00 (m, 6 H), 4·12 (q, J = 7·1, 2 H), 5·12 (bs, 1 H), 6·80 (m, J = 8·8, 2 H), 7·07 (m, J = 8·8, 2 H). IR spectrum (cm^{-1}): 3 455, 1 720, 1 521, 1 250, 1 158, 1 101, 1 088, 1 056, 927. Mass spectrum, *m/z*: 363 (M^+), 320, 317, 274, 248, 141, 116 (base peak), 107, 99, 88. For $C_{20}H_{29}NO_5$ (363·4) calculated: 66·10% C, 8·04% H, 3·85% N; found: 66·06% C, 8·10% H, 3·84% N.

2-(4-(2-(Ethoxycarbamato)ethoxy)benzyl)-1-cyclohexanol (*III*)

Sodium borohydride (0·7 g, 18·48 mmol) was added in one portion under stirring to a cooled (0°C) solution of *I* (1·4 g, 4·38 mmol) in methanol (40 ml). After 45 min methanol was evaporated, the residue diluted with a saturated sodium chloride solution (25 ml), extracted with ether and the extract dried over Na_2SO_4. The residue was separated by column chromatography on silica gel, affording both racemic geometrical isomers *IIIa* (0·6 g, 43%) and *IIIb* (0·6 g, 43%). *cis*-Isomer *IIIa*: ^{1}H NMR spectrum (ppm): 1·24 (t, J = 7·2, 3 H), 1·26–1·83 (m, 9 H), 2·47 (dd, J = 7·5 and 13·5, 1 H), 2·66 (dd, J = 7·3 and 13·5, 1 H), 3·56 (q, J = 5·4, 2 H), 3·78 (dt, J = 4·3, 2·5, and 2·5, 1 H), 4·00 (AB system, 2 H), 4·12 (q, J = 7·2, 2 H), 5·21 (bs, 1 H), 6·80 (m, J = 8·7, 2 H), 7·10 (m, J = 8·7, 2 H). IR spectrum (cm^{-1}): 3 630, 3 465, 1 729, 1 516, 1 246, 979. Mass spectrum, *m/z*: 321 (M^+), 275, 258, 257, 232, 206, 188, 116 (base peak), 107, 88. For $C_{18}H_{27}NO_4$ (321·4) calculated: 67·26% C, 8·47% H, 4·36% N; found: 67·20% C, 8·49% H, 4·32% N. *trans*-Isomer *IIIb*: ^{1}H NMR spectrum (ppm): 1·25 (t, J = 7·1, 3 H), 1·29–1·62 (m, 9 H), 2·33 (dd, J = 9·0 and 13·5, 1 H), 3·08 (dd, J = 4·0 and 13·5, 1 H), 3·28 (dt, J = 4·4, 9·5, and 9·5, 1 H), 3·57 (q, J = 5·4, 2 H), 4·01 (AB system, 2 H), 4·13 (q, J = 7·1, 2 H), 5·12 (bs, 1 H), 6·81 (m, J = 8·7, 2 H), 7·09 (m, J = 8·7, 2 H). IR spectrum (cm^{-1}): 3 625, 3 465, 1 726, 1 513, 1 243, 1 069, 1 052. Mass spectrum, *m/z*: 321 (M^+), 275, 258, 257, 232, 206, 188, 116 (base peak), 107, 88. For $C_{18}H_{27}NO_4$ (321·4) calculated: 67·26% C, 8·47% H, 4·36% N; found: 67·29% C, 8·48% H, 4·41% N.

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