Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp. 963-966, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

CARBAMATE SERIES OF JUVENOIDS

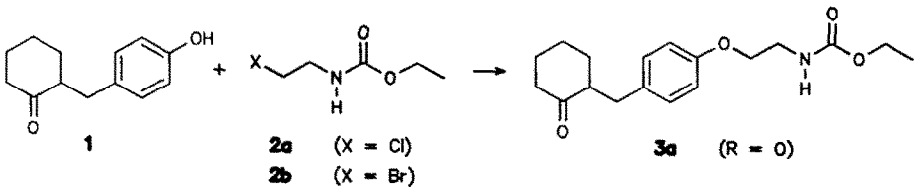
Martin Rejzek, Marie Zarevúcká and Zdeněk Wimmer*

Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Science,
Flemingovo náměstí 2, 166 10 Prague 6, Czechoslovakia

(*Received* 23 *April* 1992)

Abstract: A title series of juvenoids (insect juvenile hormone analogs) has been recently prepared. On the basis of the biological activity observed the compounds have been subjected to a further research. A more convenient method for the synthesis of these compounds has now been described. A changement in the reaction conditions resulted in a substantial augmentation in the yields of the final products.

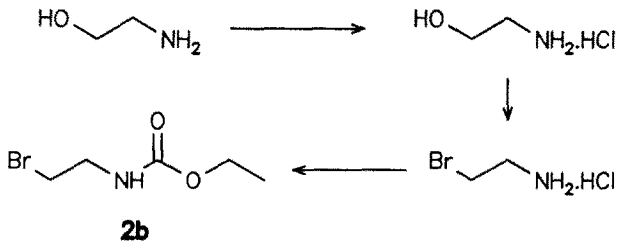
Several years ago, a carbamate series of juvenoids derived from 2-(4-hydroxybenzyl)-1-cyclohexanone (1) has been synthesized.[1] A detailed biological investigation[2,3] resulted recently in a positive finding, on the basis of which the carbamate juvenoids **3a** - **3d** have been envisaged as prospective candidate compounds in an environmentally safe insect pest control (**Table I**). Unfortunately, the former method of the synthesis of juvenoids in question[1] has been found to be non-satisfactory when a larger scale preparation was taken into account. The formation of the ether bond (see **Scheme 1**) by the Kamiya method[4] using ethyl



1 **2a** (X = Cl) **2b** (X = Br) **3a** (R = O)

Scheme 1

N,N-dimethylenecarbamate and both either hydrochloric acid[4] or hydrobromic acid[4,5] in the synthesis of ethyl N-(2-halogenoethyl)carbamates represented the yield lowering step. Moreover, ethylene imine used in the synthesis of ethyl N,N-dimethylenecarbamate is a highly cancerogenic reagent.



2b

Scheme 2

The new procedure (**Scheme 2**) consisted in a treatment of a toluene solution (50 ml) of 2-aminoethanol (4.88 g; 80 mmol) by a conc. hydrochloric acid[6] (7.30 ml) under azeotropic conditions. When 2-aminoethanol hydrochloride was formed, a Dean-Stark water trap was replaced by a reflux condenser, and phosphorus tribromide (8.65 g; 31.9 mmol) was added during a 5 min period at 100°C. The reaction mixture was kept at 100°C for an additional 2 h, then it was cooled to 50°C, and water (20 ml) was added in one portion. The mixture was again cooled to 20°C, stirred for an additional 10 min, then cooled to 0°C, and ethyl chloroformate (9.14 g; 84.5 mmol) was added during a 5 min period. Then 45 % aqueous solution of sodium hydroxide (15 g) was added dropwise to the reaction mixture. Completion of the reaction was indicated by a changement in pH of the water layer of the mixture, which should be maintained at pH = 12 for at least 10 min of stirring. Otherwise an additional amount of 45 % aqueous solution of sodium hydroxide should augment pH of the water layer in the reaction mixture to the desired level (pH = 12). The mixture was then extracted several times with benzene, the collected extracts were washed with saturated brine, and dried over sodium sulphate. Removing of the solvents gave a crude residue, which yielded

Table I : Biological activity of several carbamate juvenoids[2,3]

Compound	ACY[a]	DYS[b]	GAL[c]
3a[d]	0.05	0.008	0.0002
3b[e]	>0.1	0.001	0.0008
3c[f]	>0.1	0.04	0.0008
3d[g]	0.005	0.08	0.0008
Hydroprene[h]	0.04	1.0	0.01

[a] *Acyrthosiphon pisum*, IC 50 values (percent of the active ingredient), [b] *Dysdercus cingulatus*, ED 50 values (ug per g), [c] *Galleria mellonella*, ED 50 values (ug per g), [d] R = O, [e] R = H, OH (*cis* isomer), [f] R = H, OH (*trans* isomer), [g] R = $O(CH_2)_2O$, [h] a Zoecon (Palo Alto, CA) juvenoid[7] (ethyl 3,7,11-trimethyl-2,4-dodecadienoate) as a reference compound.

ethyl N-(2-bromoethyl)carbamate[8] (**2b**) in an amount of 13.8 g (88 %); b.p. 115-117°C / 2 kPa (Kamiya[4] gave b.p. 87-89°C / 0.8 kPa). Ethyl N-(2-bromoethyl)carbamate (**2b**) has been used in a final synthesis of the carbamate juvenoids (**Scheme 1**). This step has also been modified in comparison with the originally used method.[1] The improvement consisted in a treatment of a solution of 2-(4-hydroxybenzyl)-1-cyclohexanone (**1**; 2.0 g; 9.8 mmol) in DMFA (40 ml) by sodium hydride (a 50 % dispersion in a mineral oil; 0.52 g; 9.8 mmol) under vigorous stirring at room temperature. The reaction proceeded for 60 min, and then the mixture was heated up to 100°C. A solution of ethyl N-(2-bromoethyl)carbamate (**2b**; 2.5 g; 12.7 mmol) in DMFA (10 ml) was added dropwise into the reaction mixture under vigorous stirring. After 0.5 h of heating[9] at 100°C the mixture was cooled to 0°C, poured into a mixture of ice and 5 % hydrochloric acid (1 : 1; 100 ml), and extracted by ether. After drying over sodium sulphate, and removing of the solvent, the crude residue was purified by column chromatography on silica gel yielding 2.5 g (80 %) of the carbamate compound[10] **3a**.

In comparison with the original method, the augmentation of the yield of the final product from 50 % (published formerly[1]) up to at least 80 % during the key pathway step shown in **Scheme 1** has been demonstrated and proved.

References and Notes:

1. Wimmer, Z.; Streinz, L.; Romaňuk, M. *Coll. Czech. Chem. Commun.* **1985**, *50*, 2453-2456.
2. Wimmer, Z.; Romaňuk, M.; Kuldová, J.; Hrdý, I.; Sehnal, F. *Insect Chemical Ecology*; Hrdý, I., Ed.; Academia / SPB Acad. Publ.; Prague / The Hague, 1991; pp. 453-456.
3. Kuldová, J.; Wimmer, Z.; Hrdý, I. *Insect Chemical Ecology*; Hrdý, I., Ed.; Academia / SPB Acad. Publ.; Prague / The Hague, 1991; pp. 461-466.
4. Kamiya, S. *Chem. Pharm. Bull.* **1972**, *20*, 2497-2500.
5. Vimmer, Z. *unpublished results.*
6. Using hydrobromic acid in this step resulted in a depression of the yield of ethyl N-(2-bromoethyl)carbamate, which did not exceed 50 %.
7. Henrick, C.A.; Willy, W.E.; Staal, G.B. *J. Agric. Food Chem.* **1976**, *24*, 207-218.
8. Spectral data: **2b**: ^{1}H NMR ($CDCl_3$) δ (ppm): 5.10 (broad s, 1H); 4.13 (q, 7.1 Hz, 2H); 3.62 (m, 2H); 3.51 (q, 7.1 Hz, 2H); 1.25 (t, 7.1 Hz, 3H).
9. Extending of the reaction time resulted in a yield depression due to a saponification of the ester moiety in an alcalic media. The exact reaction time, however, should be monitored by an analytical method (TLC, HPLC etc.). Using ethyl N-(2-chloroethyl)carbamate (**2a**) in this step proved a lower reaction rate due to a more significant participation of the ester moiety saponification in the overall process.
10. Spectral data: **3a**: ^{1}H NMR ($CDCl_3$) δ (ppm): 7.07 (m, 2H); 6.80 (m, 2H); 5.11 (broad s, 1H); 4.12 (q, 7.1 Hz, 2H); 4.00 (AB system, 2H); 3.56 (q, 5.4 Hz, 1H), 3.48 (q, 7.1 Hz, 1H); 3.15 (dd, 4.5, 13.4 Hz, 1H); 2.52 (m, 1H); 2.36 (dd, 8.8, 13.4 Hz); 2.35 - 1.50 (m, 8H), 1.21 (t, 7.1 Hz, 3H).