ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. XLVI/XLVII, 3 SECTIO AA 1991/1992

Faculty of Chemistry
Department of Organic Chemistry and Technology

Stanisław DACKA, Zofia ZIMIŃSKA*

Synthesis and Biological Properties of Derivatives of α-(4-Cyclohexylmethoxyphenoxy) Propionic Acid

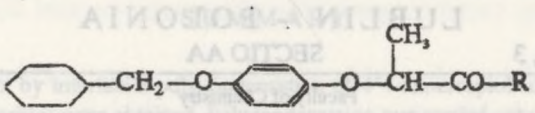
Synteza oraz właściwości biologiczne pochodnych kwasu α-(4-cykloheksylometoksyfenoksy)-propionowego

Lately some reports concerning the synthesis as well as biological activity of derivatives of propionic acid have appeared. These compounds show bactericidal, fungicidal and herbicidal activities. Of these compounds derivatives of aryloxyphenoxypropionic acid reveal good phytocidal activity on monocotyledonous plants [1–5]. For this reason it seems interesting for us to find a method for synthesis of α-(4-cyclohexylmethoxyphenoxy) propionic acid unknown so far and some of its derivatives as well as to determine their biological acivity.

The starting compound was α-(4-hydroxyphenoxy) propionic acid [6] obtained in the reaction of methyl α-bromopropionate and 4-methoxyphenol. This compound with cyclohexylmethyl bromide in the presence of sodium ethylate in the ethanol solution results in α-(4-cyclohexylmethoxyphenoxy) propionic acid (**1**). Phenylphenacyl ester was prepared by heating the compound (**1**) with 4-phenylphenacyl bromide in a weakly alkaline medium. Acid (**1**) was transformed next into acid amides in the reaction of acid chloride with the corresponding amines.

---

* Instytut Przemysłu Organicznego (Warszawa) – Institute of Organic Industry (Warsaw).



1. R=OH
2. R=$OCH_2COC_6H_4C_6H_5$ (4)
3. R=NH_2
4. R=$NHCH_3$
5. R=NHC_2H_5
6. R=$NH(CH_2)_3CH_3$
7. R=$NH(CH_2)_4CH_3$
8. R=$NHCH_2CH_2CH(CH_3)_2$
9. R=$NHCH_2CH(OH)CH_3$
10. R=$NHCH_2C_6H_5$
11. R=NHC6H_5
12. R=NHC6H_4OCH_3 (3)
13. R=NHC6H_4Br (4)
14. R=NHC6H_4CH_3 (4)
15. R=NHCH2C_4H_3O (2)

Tab. 1. Biological activity of derivatives of α-(4-cyclohexylmethoxyphenoxy)propionic acid

Compound No	Dose in ppm for one person or concentration in % causing over 90% of mortality		Blocking concentration [ppm]					% paresis concentration [1000 ppm]
	Housefly	Spider mite %	*Alternaria tenuis*	*Botritis cinerea*	*Rhizoctonia solani*	*Fusarium culmorum*	*Phythophthora cactorum*	*Erysiphe graminis*
1	>25	>0.1	>100	>100	>200	>200	>200	100
2	>25	>0.1	>100	>100	>200	>200	>200	80
3	>25	>0.1	>100	>100	>200	>200	>200	100
4	>25	>0.1	>100	>100	>200	>200	>200	46
5	>0.1%	>0.1	>100	>100	>200	>200	>200	27
6	>0.1%	>0.1	>100	>100	>200	>200	>200	33
7	>0.1%	>0.1	>100	>100	>200	>200	>200	22
8	>0.1%	>0.1	>100	>100	>200	>200	>200	35
9	>0.1%	>0.1	>100	>100	200	200	200	41
10	>0.1%	>0.1	>100	>100	>200	>200	>200	17
11	>25	>0.1	>100	>100	>200	>200	>200	100
12	>0.1%	>0.1	>100	>100	>200	>200	>200	20
13	>0.1%	>0.1	>100	>100	>200	>200	>200	35
14	>0.1%	>0.1	>100	>100	>200	>200	>200	56
15	>0.1%	>0.1	>100	>100	>200	>200	>200	19

The above-mentioned compounds have been tested for insecticidal, spidercidal, fungicidal and phytocidal activities according to the methods worked out for the screening test [7]. Investigations have been carried out with the use of bioindicators: housefly (*Musca domestica*) and spider mite (*Tetranychus uriticea*). In the

experiments 1% and 0.1% dose solutions of the tested compounds were used. After 48h the lethality evaluation of the tested bioindicators was performed. Fungicidal activity for the fungi: *Alternaria tenuis, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum* and *Phytophthora cactorum* was studied in the tests *in vitro* as well as *in vivo* on living plants coated with spores of *Erisiphe graminis*. Phytocidal activity in pre- and post-emergence applications with the use of 10 species of plants as indicators: oat, flax, buckwheat, beet, cucumber, corn, mustard, pea, bean and ryegrass was studied. Concentrations of these compounds were chosen so that the dose would equal to 5 kg/ha.

The obtained compounds do not reveal any activity either to housefly or spider mite. Fungicidal activity towards *Erysiphe graminis* was observed in most compounds, where compounds (**7**), (**10**), (**12**), and (**15**) were characterized by good activity and the remaining – except for (**1**), (**2**), (**3**) and (**11**) – mean. Compound (**9**) reveals the mean fungicidal activity for the pathogens: *Rhizoctonia solani, Fusarium culmorum* and *Pythophthora cactorum*. The investigated compounds do not reveal phytocidal activity except α-(4-cyclohexylmethoxyphenoxy) propionic acid, the activity of which is mean for the tested plants.

EXPERIMENTAL

IR spectra were recorded in KBr discs with a FT 1725X Perkin Elmer spectrophotometer. ^{1}H NMR spectra were determined using BF 567A Tesla 100 spectrometer with TMS as an internal standard.

1. α-(4-Cyclohexylmethoxyphenoxy) propionic acid

A sample of 56 g (0.3 mole) of α-(4-hydroxyphenoxy) propionic acid and 55 g (0.31 mole) of cyclohexylmethyl bromide was added to the solution of sodium ethylate (prepared from 14.2 g (0.62 mole) of sodium and 250 cm^3 of absolute alcohol) and was refluxed for 5 hours. The precipitate of salt was filtered and crystallized from water (100 cm^3). The salt was dissolved in water and acidified with HCl. The separated acid was filtered and crystallized from benzene-cyclohexane solution (1:2) (300 cm^3). Plates m.p. 129–130°C. Yield 60 g (72%).

Analysis:

For $C_{16}H_{22}O_4$ (278.36) calcd : 69.04% C; 7.94% H;
found : 69.38% C; 8.27% H.

IR [cm^{-1}] 1370, 1450, 1470 δCH_3, CH_2; 2850 $\nu_s CH_2$, CH_3; 2920, 2937 $\nu_{as} CH_2$; 2980 $\nu_{as} CH_3$; 818, 840, 850, 1025, 1035, 1050, 1092, 1140, 1215, 1225 δC_{Ar}—H

(subst. 1.4); 1510, 1627 $\nu C_{Ar}=C_{Ar}$; 943 νOH(COOH); 3430 νOH(COOH); 1290 νC—O(COOH); 1735 νC=O(COOH).

^{1}H NMR [δppm](CDCl$_3$); 0.75 – 2 m 11H(C_6H_{11}); 1.52 d, J=6.6 Hz, 3H(CH_3); 3.70 d J=5.6 Hz, 2H(CH_2O); 4.70 q J=6.6 Hz, 1H(CHO); 6.71 s 4H(OC_6H_4O); 10.75 s 1H(COOH).

2. 4-Phenylphenacyl ester of α-(4-cyclohexylmethoxyphenoxy) propionic acid

4 g (0.014 mole) of acid (**1**) were neutralized with 3% NaOH to *pH* 7.2. To this solution 3.5 g (0.014 mole) of 4-phenylphenacyl bromide in 60 cm^3 of ethanol were added and the mixture was refluxed for 1 h. After cooling the precipitate was filtered and crystallized from methanol. Plates m.p. 106–107°C. Yield 5.5 g (83%).

Analysis:

For $C_{30}H_{32}O_5$ (472.58 calcd: 76.25% C; 6.83% H;
found: 76.52% C; 6.62% H.

IR [cm^{-1}] 1762 νC=O; 1191 νC—O—C.

^{1}H NMR [δppm] ($CDCl_3$) 0.94–1.9 m 11H(C_6H_{11}); 1.74 d J=7 Hz 3H(CH_3—CH); 3.68 d J=6.1 Hz 2H(CH_2O); 4.85 q J=7 Hz 1H(CHO); 5.42 s 2H(CH_2—CO); 6.76–7.99 m 13H (aromatic).

Preparation of N-substituted amides

Method A

6 g (0.021 mole) of acid (**1**) and 25 cm^3 of thionyl chloride were refluxed until the precipitate was almost completely dissolved (1 h). Thionyl chloride was removed under the reduced pressure. 50 cm^3 of 20% aqueous solution of amine were added to the residue. The precipitate was filtered and washed with water.

3. α-(4-Cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 154—156°C (benzene-cyclohexane (1:1)). Yield 5.5 g (92%)

Analysis:

For $C_{16}H_{23}NO_3$ (277.36) calcd : 5.05% N;
found: 5.05% N.

IR [cm^{-1}] 1600 δN—H; 3185 ν_sN—H; 3390 ν_{as}N—H; 1670 νC=O.

4. N-Methyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 94.5–95.5°C (cyclohexane). Yield 5.3 g (85%).

Analysis:

For $C_{17}H_{25}NO_3$ (2291.39) calcd: 4.81% N;
found: 5.17% N.

IR [cm^{-1}] 1544 δN—H; 3328 νN—H; 1661 νC=O

^1H NMR [δppm] ($CDCl_3$) 0.96–1.9 m 11H(C_6H_{11}); 1.52 d J=6.6 Hz 3H(CH_3—CH); 3.4 d J=7 Hz 3H(CH_3—NH); 3.7 d J=5.6 2H(CH_2O); 4.54 q J=6.6 Hz 1H(CHO); 6.57 1H(NH); 6.81 s 4H(OC_6H_4O).

5. N-Ethyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 85.5—86°C (benzene-hexane (1:5)). Yield 5.6 g (85%).

Analysis:

For $C_{18}H_{27}NO_3$ (305.42) calcd : 4.69% N;
found: 4.55% N.

IR [cm^{-1}] 1539 δN—H; 3325 νN—H; 1654 νC=O.

^1H NMR [δppm]($CDCl_3$) 0.95–1.9 m 11H(C_6H_{11}); 1.12 t J=7 Hz 3H(CH_3CH_2); 1.52 d J=6.6 Hz 3H(CH_3CH); 3.3 q J=7 2H(CH_2N); 3.7 d J=6.1 2H(CH_2O); 4.54 q J=6.6 Hz 1H(CHO); 6.53 1H(NH); 6.81 s 4H(OC_6H_4O).

Method B

6 g (0.021 mole) of acid (**1**) were converted into acid chloride as in method A. The reaction product was heated (1 h) with 0.06 mole of amine in 120 cm^3 of dry benzene. The solvent was removed under the reduced pressure. The precipitate washed with 5% HCl and water.

6. N-Butyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Lumps m.p. 73–73.5°C (hexane). Yield 5.7 g (81%).

Analysis:

For $C_{20}H_{31}NO_3$ (333.47) calcd: 4.20% N;
found: 4.06% N.

IR [cm^{-1}] 1542 δN—H; 3318 νN—H; 1657 νC=O.

^1H NMR [δppm] ($CDCl_3$) 0.88–1.9 m 18H(C_6H_{11}, $CH_2CH_2CH_3$); 1.52 d J=6.6 Hz 3H(CH_3CH); 3.27 q J=6.6 Hz 2H(CH_2—N); 3.69 d J=5.6 Hz 2H(CH_2O); 4.54 q J=6.6 Hz 1H(CHO), 6.53 1H(NH); 6.81 s 4H(OC_6H_4O).

7. N-Pentyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Lumps m.p. 65.5–66.5°C (hexane). Yield 6.3 g (84%).

Analysis:

For $C_{21}H_{33}NO_3$ (347.5) calcd : 4.03% N;
found: 4.07% N.

IR [cm^{-1}] 1542 δN—H; 3321 νN—H; 1657 νC=O.

^{1}H NMR [δppm](CDCl$_3$) 0.79–1.86 m 20H(C$_6$H$_{11}$, CH$_2$CH$_2$CH$_2$CH$_3$); 1.53 d J=7 Hz 3H(CH$_3$—CH); 3.25 q J=6.6 Hz 2H(CH$_2$—N); 3.68 d J=5.6 Hz 2H(CH$_2$O); 4.54 q J=6.6 Hz 1H(CHO); 6.51 1H(NH); 6.81 s 4H(OC$_6$H$_4$O).

8. N-3-Methylbutyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 75–76°C (hexane). Yield 5.9 g (79%).

Analysis:

For C$_{21}$H$_{33}$NO$_3$ (347.5) calcd: 4.03% N;
found: 3.75% N.

IR [cm^{-1}] 1540 δN—H; 3335 νN—H; 1660 νC=O.

^{1}H NMR [δppm](CDCl$_3$) 0.88 d J=6.1 Hz 6H((CH$_3$)$_2$CH); 0.91–1.9 m 11H(C$_6$H$_{11}$); 1.52 d J=6.6 Hz 3H(CH$_3$CH); 3.28 q J=7 Hz 2H(CH$_2$NH); 3.69 d J=6.1 Hz 2H(CH$_2$O); 4.54 q J=6.1 Hz 1H(CHO); 6.49 1H(NH); 6.81 s 4H(OC$_6$H$_4$O).

9. N-2-Propanolo α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 85–86°C (hexane). Yield 6.2 g (86%).

Analysis:

For C$_{19}$H$_{29}$NO$_4$ (335.44) calcd: 4.17% N;
found: 4.03% N.

IR [cm^{-1}] 1547 δN—H; 3334 νN—H and OH; 1660 νC=O.

^{1}H NMR [δppm] (CDCl$_3$) 0.94–2.15 m 14H(C$_6$H$_{11}$, CH$_3$CHOH); 1.53 d J=6.6 Hz 3H(CH$_3$CHO); 2.98–3.2 m 2H(CH$_2$NH); 3.69 d J=5.6 Hz 2H(CH$_2$O); 3.86 1H(OH); 4.56 q J=7 Hz 1H(CHO); 6.91 s 4H(OC$_6$H$_4$O); 7.00 1H(NH).

10. N-Benzyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 91–91.5°C (hexane). Yield 6.5 g (82%).

Analysis:

For C$_{23}$H$_{29}$NO$_3$ (367.5) calcd: 3.91% N;
found: 3.47% N.

IR [cm^{-1}] 1535 δN—H; 3340 νN—H; 1657 νC=O.

^{1}H NMR [δppm] (CDCl$_3$) 0.95–1.9 m 11H(C$_6$H$_{11}$); 1.56 d J=6.6 Hz 3H(CH$_3$CH); 3.69 J=6.1 Hz 2H(CH$_2$O); 4.46 d J=5.6 Hz 2H(CH$_2$N); 4.62 q J=6.6 Hz 1H(CHO); 6.8 s 4H(OC$_6$H$_4$O); 6.88–7.32 m 6H(C$_6$H$_5$, NH).

11. N-Phenyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 109.5–110°C (ethanol). Yield 6.7 g (88%).

Analysis:

For C$_{22}$H$_{27}$NO$_3$ (353.47) calcd: 3.96% N;
found: 4.20% N.

IR [cm^{-1}] 1530 δN—H; 3308 νN—H; 1663 νC=O.

12. N-3-Methoxyphenyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Plates m.p. 87.5–88.5°C (hexane). Yield 7.2 g (87%).
Analysis:
For $C_{23}H_{29}NO_4$ (383.49) calcd: 3.65% N;
found: 3.52% N.
IR [cm^{-1}] 1527 δN—H; 3295 νN—H; 1661 νC=O.
^1H NMR δppm ($CDCl_3$) 0.93–1.87 m 11H(C_6H_{11}); 1.59 d J=6.6 Hz 3H(CH_3CH); 3.67 d J=6.1 Hz 2H(CH_2O); 3.76 s 3H(CH_3O); 4.63 q J=6.6 Hz 1H(CHO); 6.6–7.35 m 8H(7H aromatic, NH); 8.31 s 1H(aromatic).

13. N-4-Bromophenyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 113–114°C (hexene). Yield 7.8 g (84%).
Analysis:
For $C_{22}H_{26}BrNO_3$ (432.36) calcd: 3.24% N;
found: 3.40% N.
IR [cm^{-1}] 1524 δN—H; 3304 νN—H; 1672 νC=O
^1H NMR [δppm] ($CDCl_3$) 1.05–1.88 m 11H(C_6H_{11}); 1.6 d J=7 Hz 3H(CH_3CH); 3.69 d J=5.6 Hz 2H(CH_2O); 4.51 q J=6.6 Hz 1H(CHO); 6.29 1H(NH); 6.86 s 4H(OC_6H_4O); 7.44 s 4H(C_6H_4Br)

14. N-4-Methylphenyl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles m.p. 90–91°C (heptane). Yield 6.8 g (85%).
Analysis:
For $C_{23}H_{29}NO_3$ (367.49) calcd: 3.81% N;
found: 3.70% N.
IR [cm^{-1}] 1526 δN—H; 3305 νN—H; 1660 νC=O.

15. N-2-Furfuryl α-(4-cyclohexylmethoxyphenoxy) propionamide

Needles 83.5–84°C (hextane). Yield 6.5 g (84%).
Analysis:
For $C_{21}H_{27}NO_4$ (357.45) calcd:3.77% N;
found:3.91% N.
IR [cm^{-1}] 1546 δN—H; 3295 νN—H; 1665 νC=O.
^1H NMR [δppm] ($CDCl_3$) 0.94–1.9 m 11H(C_6H_{11}); 1.53 d J=7 Hz 3H(CH_3CH); 3.68 d J=5.6 Hz 2H(CH_2O); 4.45 d J=5.6 Hz 2H(CH_2N); 4.59 q J=6.6 Hz 1H(CHO); 6.1–6.3 m 3H(NH, 2H positions 3 and 4 in furane); 6.8 s 4H(OC6H4O); 7.3 d 1H(position 5 in furane).

REFERENCES

[1] White S. R.: *Pest. środ.*, **49** (1977).
[2] Kenneth H. A.: *Chem. pesticid.*, **265** (1982).
[3] Carter Ch. G., Lee D. L.: US Pat. No. 4613 357 (1986).
[4] Fujinawa Shoji, Hashiba Isao, Suzuki Kenji: Jap. Pat. No. 61 158 947 (1986).
[5] Rehn K., Nester J. H.: Ger Pat. 3240 805 (1984).
[6] Lewis R. H., Housley R. J., Richards C. H., Nicholson S. J., Baker W. M., Adams S. St.: GB Pat. 916 242 (1959).
[7] Bakuniak E., Bakuniak J.: *Pestycydy*, **12**, 4 (1978).

STRESZCZENIE

W ostatnich latach opublikowano wiele artykułów nt. syntezy oraz aktywności biologicznej pochodnych kwasu propionowego. Takie pochodne wykazują właściwości grzybobójcze, bakteriobójcze, jak również chwastobójcze. Na przykład pochodne kwasu aryloksyfenoksypropionowego wykazują silne działanie fitocydalne na rośliny jednoliścienne [1–5]. W związku z tym wydało się celowe opracowanie metody syntezy dotychczas nieznanego kwasu α-(4-cykloheksylometoksyfenoksy)-propionowego i niektórych jego pochodnych, a także zbadanie ich biologicznej aktywności.

Substratem w przeprowadzonych doświadczeniach był kwas α-(4-hydroksyfenoksy)-propionowy [6] otrzymany w reakcji α-bromopropionianu metylu z 4-metoksyfenolem. Kwas α-(4-hydroksyfenoksy)-propionowy tworzył z bromkiem cykloheksylometylowym w etanolu w obecności etanolanu sodowego kwas α-(4-cykloheksylometoksyfenoksy)-propionowy (**1**). Ester 4-fenylofenacylowy otrzymano przez ogrzewanie kwasu (**1**) z bromkiem 4-fenylofenacylowym w środowisku słabo alkalicznym. Kwas karboksylowy (**1**) przeprowadzono w pochodne amidowe przez działanie na chlorek kwasowy (otrzymany przez ogrzewanie kwasu (**1**) z chlorkiem tionylu) odpowiednimi aminami.

Wymienione związki zostały poddane badaniu, które miało wyjaśnić, czy wykazują aktywność owado- i przędziorkobójczą, grzybobójczą i fitocydalną (metodami opracowanymi dla *screening* testu) [7]. Badania przeprowadzono używając bioindykatorów: muchy domowej (*Musca domestica*) i przędziorka chmielowca (*Tetranychus urticea*). W doświadczeniach stosowano 1% i 0,1% dawkę roztworu badanego związku. Po upływie 48 h przeprowadzono ocenę śmiertelności badanych bioindykatorów. Aktywność grzybobójczą badano w testach *in vitro* dla grzybów *Alternaria tenuis, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum* i *Phytophthora cactorum* oraz *in vivo* na żywych roślinach pokrytych zarodnikami mączniaka właściwego (*Erysiphe graminis*). Działanie fitocydalne zbadano przedwschodowo i powschodowo z użyciem 10 gatunków roślin wskaźnikowych, takich jak owies, len, gryka, burak, ogórek, kukurydza, gorczyca, groch, fasola i rajgras, przy czym stężenia związków były tak dobrane, aby dawka wynosiła 5 kg/ha.

Badane związki nie były aktywne ani w stosunku do muchy domowej, ani do przędziorka. Niewielką aktywność grzybobójczą wobec *Erysiphe graminis* wykazała większość połączeń: związki (**7**), (**10**), (**12**) i (**15**) wykazują działanie silne, a pozostałe – z wyjątkiem (**1**), (**2**), (**3**) i (**11**) – aktywność przeciętną. Związek (**9**) wykazuje przeciętną aktywność grzybobójczą wobec takich patogenów, jak *Rhizoctonia solani, Fusarium culmorum* i *Phytophthora cactorum*. Badane związki nie wykazują aktywności fitocydalnej (z wyjątkiem kwasu α-(4-cykloheksylometoksyfenoksy)-propionowego, który wykazuje przeciętną aktywność wobec roślin testowanych).