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Synthesis, structure and properties of 2-dibenzofurylthioisopropylacetic acid and its derivatives

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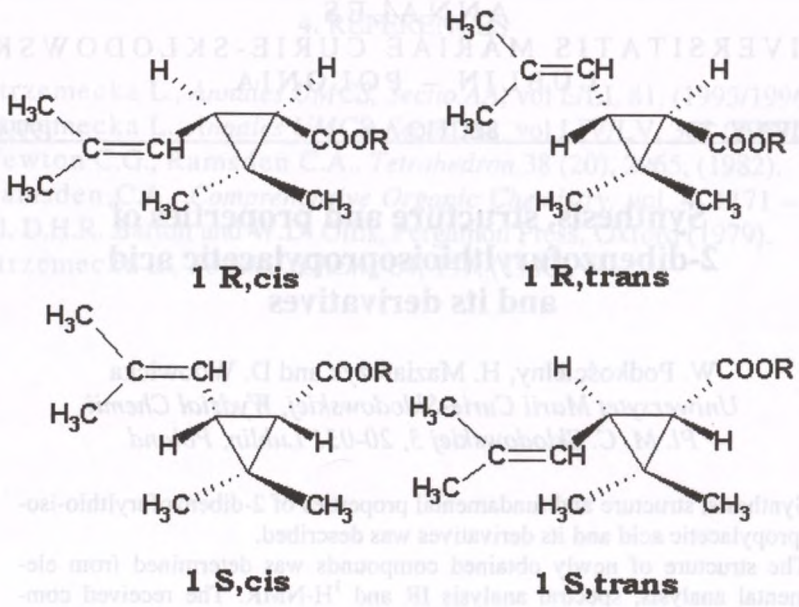
Synthesis, structure and fundamental properties of 2-dibenzofurylthio-iso--propylacetic acid and its derivatives was described.
The structure of newly obtained compounds was determined from elemental analysis, spectral analysis IR and ^{1}H-NMR. The received compounds were investigated at the Institute of Organic Industry in Warsaw in view of their biological activity.

The purpose of the present article, which is a continuation of investigation on finding new compounds exhibiting potential biological activity [1,2], is the synthesis, structure and properties of 2-dibenzofurylthioisopropylacetic acid and some of its derivatives. It is well-known that an essential requirement in effective research on new pesticide compounds is to recognize the dependence between the structure of compounds and their biological activity.

This dependence was unconditionally described by Elliott at co-workers [3] and by O`Brien and Yamamoto [4], on the basis of synthetic pyrethroides. Considering the influence of a three-dimensional group of chiral carbon atom in 1-cyclopropane it was pointed out by the authors, that molecules with 1R configuration show very high biological activity, while those 1S isomers don`t reveal this property completely.

The influence of carbon atom substituent 3-cyclopropane has secondary meaning in comparison with dimethyl group of carbon atom attached in 2-position which plays significant role in high biological activity.

Three-dimensional structures of discussed pyrethroides below.



According to Barteau [5] cyclopropane ring displays little importance in the biological activity of pyrethroides. The influence of this ring as was suggested by authors reduced only the "essential part" of arrangement (O`Brien Yamamodo).The confirmation of the considerations above, not fully justifiable, is a very active insecticide fenvalerate without cyclopropane core, in which carbon atoms are chiral centers responsible for isomerism and, at the same time, for biological activity. Following the information above, we undertook investigations on biological activity of 2-dibenzofurylthioisopropylacetic acid and some of its derivatives containing isopropyl group in their structure. It seems interesting to us to apply compounds containing besides dimethyl group also dibenzofuryl core, the latter taking part in the biological activity of usnic acid [6], as well as, in compounds with discovered cancerigenic activity [7,8].

Newly obtained compounds were investigated at the Institute of Organic Industry in Warsaw in view of their biological activity. The physiological activity of compounds mentioned above was studied against the insects, the *Tetranychus urticae* Koch, some plants and fungi.

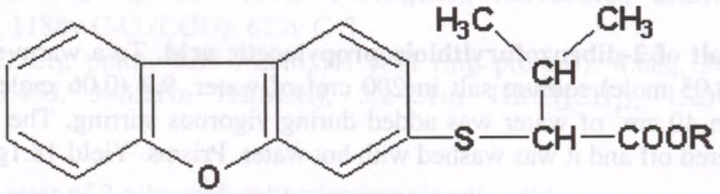
The studies of the insecticide activity were carried out in the laboratory, using some bioindiicators like *Musca domestica* and *Tetranychus urticae* Koch. In the investigations, a sample of 0.1% aceton solution of investigated compounds in the case of *Tetranychus urticae* Koch, and 25μg for *Musca domestica* was used. After 48 hours the mortality test of the bioindicators was carried out. The fungicidal activity was studied in vitro, using the fungi *Alternalia tenuis, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum* on the living plants cov-

ered with the spores of *Erysiphe graminis*. The phytocidal reaction of the compounds was studied before germination and after germination on 10 selected indicative plants, using the concentration corresponding to a dose of 5 kg/hectare. The investigated compounds did not show any insecticide activity, neither the *Musca domestica* and *Tetranychus urticae* Koch. However, 2-dibenzofurylisopropylacetic acid and its ethyl and isopropyl derivatives turned out to have a weak *Erysiphe graminis* reaction, whereas methyl ester only reveal a limited reaction of this insecticide.

As starting material, 2-dibenzofurylthio-iso-propyl acid was used, which was obtained according to the procedure given by Gilman and co-workers [9] in sulfonation reaction dibenzofuran in tetrachloromethane at 25 °C. Natrium salt of this acid was then converted into 2-dibenzofuransulphonylchloride in reaction with $POCl_3$ at 165-180 °C. Next, 2-dibenzofuransulfonylchloride (m.p. 140 °C) was undergoing reduction according to the method given by Ghosal and Dutta [10] by means of zinc dust in dilute (1:3) H_2SO_4. 2-Dibenzofuranthiol obtained in this way was the starting material for preparing 2-dibenzofurylthioisopropyl-acetic acid and its derivatives.

EXPERIMENTAL

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



1. R = H
2. R = CH_3
3. R = C_2H_5
4. R = $CH(CH_3)_2$
5. R = $CH_2C_6H_4NO_2$
6. R = $CH_2COC_6H_5$
7. R = $CH_2COC_6H_4Br$

1. 2-Dibenzofurylthioisopropylacetic acid

Sodium salt of 2-dibenzofurylthioisopropylacetic acid. To a solution of 20 g (0.1 mole) of 2-mercaptodibenzofuran in 110 cm^3 of 10% NaOH, 19 g (0.105 mole) of α-bromoisovaleric acid in 100 cm^3 of water alkalized with solid Na_2CO_3 was added, and the resulting mixture was refluxed for 10 min. The precipitate was isolated and after washing with hot water it was dried. Plates. Yield 30.6 g (95%).

A solution 30.6g (0.094 mole) of sodium salt of 2-dibenzofurylthioisopropylacetic acid in 100 cm^3 of water was acidified with dilute (1:1) hydrochloric acid. The oily residue solidified soon. The precipitate of this acid was crystallized from glacial acetic acid. Needles, m.p. 114-115 °C. Yield 24.5g (87%).

Analysis:
For $C_{17}H_{16}O_3S$ (300.36) - calcd: 67.97% C ; 5.37% H;
found: 67.65% C ; 5.15% H.

IR (cm^{-1}): 3066ν C_{Ar}-H; 866.815δ C_{Ar}-H (subst, 1,2,4); 750δ C_{Ar}-H (subst. 1,2); 1627, 1589, 1443ν C_{Ar}=C_{Ar};1245ν =C_{Ar}-O; 2963$\nu_{as}CH_3$; 2873ν_s CH_3 1465$\delta_{as}CH_3$;1388$\delta_s CH_3$; 1688ν C=O(COOH); 1421, 1296ν C-O and δ OH(COOH); 934δ OH; 625ν C-S.

^{1}H-NMR ($CDCl_3$ ppm): 9.81s 1H(OH); 8.08-7.27m 7H (ring protons); 3.36d, J=8.9 Hz 1H(SCH); 2.16-2.07m 1H(C<u>H</u>CH_3); 1.19d,J=6.6Hz 3H(CH_3); 1.06d, J=6.6Hz 3H (CH_3).

Silver salt of 2-dibenzofurylthioisopropylacetic acid. To a warm solution of 16.1g (0.05 mole) sodium salt in 200 cm^3 of water, 9.2 (0.06 mole) of silver nitrate in 40 cm^3 of water was added during vigorous stirring. The precipitate was filtered off and it was washed with hot water. Prisms. Yield 18.1g (89%).

2. Methyl ester of 2-dibenzofurylthioisopropylacetic acid

a) A sample of 4.5g (0.015 mole) of 2-dibenzofurylthioisopropylacetic acid suspended in 15 cm^3 of dry diethyl ether was treated with etheral solution of diazomethane until the mixture became permanently colored. Then, the resulting solution was filtered and, after removing the solvent, the oily residue solidified at 0 °C, and it was crystallized from methanol. Prisms, m.p. 39.5-40.5 °C. Yield 4.1g (87%).
b) A sample of 2g (0.005 mole) of silver salt of acid (1) was suspended in 25 cm^3 of benzene and 3.55g (0.025 mole) of methyl iodide was added gradually, and the mixture was refluxed for 4 h. The solution was filtered and, af-

ter removing the solvent, the oily residue after solidification was crystallized from methanol. Prisms, m.p. 40-41 °C. Yield 1g (64%).

Analysis

For $C_{18}H_{18}O_3S$ (314.39) - calcd: 68.76% C ; 5.08% H;
found: 68.76% C ; 5.17% H

IR (cm^{-1}): 2965 $\nu_{as}CH_3$; 2874$\nu_s CH_3$; 1465$\delta_{as}CH_3$; 1388δ_s CH_3 1722ν C=0.1199ν C-O (COO); 624ν C-S.

^{1}H-NMR ($CDCl_3$,ppm): 8.09-7.27m 7H (CH_2 ring protons); 3.61s 3H (OCH_3); 3.44d, J=9 Hz 1H(SCH); 2.33-1.97m 1H (C<u>H</u>CH_3); 1.20d, J=6.6Hz 3H (CH_3);1.04d, J=6.6 Hz 3H(CH_3).

3. Ethyl ester of 2-dibenzofurylthioisopropylacetic acid

A sample of 5 g (0.0125 mole) of silver salt of acid (1) was suspended in 40 cm^3 of benzene and 7.48g (0.048 mole) of ethyl iodide was added and the mixture was refluxed for 4 h. The solution was filtered and, after removing the solvent, the oily residue solidified at –5 °C, and it was crystallized from ethanol. Prisms, m.p. 52-53 °C. Yield 2.4g (59%).

Analysis

For $C_{19}H_{20}O_3S$ (328.41) - calcd: 69.48% C ; 6.14% H;
found: 69.61% C ; 5.83% H.

IR (cm^{-1}): 2964$\nu_{as}CH_3$; 2872$\nu_s CH_3$; 1467$\delta_{as}CH_3$; 1387δsCH$_3$; 2928$\nu_{as}CH_2$; 1726ν C=O, 1188ν C-O (COO); 623ν C-S.

^{1}H-NMR ($CDCl_3$, ppm): 8.09-7.28m 7H (CH ring protons); 4.08q, J=7.5Hz 2H(CH_2); 3.43d, J=8.9Hz 1H(SCH); 2.2-2.1m 1H(C<u>H</u>CH_3); 1.23-1.02m 9H(CH_3).

4. Isopropyl ester of 2-bibenzofurylthioisopropylacetic acid

A sample of 3.2g (0.01 mole) of sodium salt of acid (1) was suspended in 50 cm^3 of ethanol and 3.4g (0.02 mole) of isopropyl iodide was added dropwise, and the mixture was refluxed for 4 h. The solution was filtered and, after removing the solvent, the oily residue solidified and it was crystallized from methanol. Plates, m.p. 50-51.5 °C. Yield 1.8g (53%).

Analysis

For $C_{20}H_{22}O_3S$ (342.44)- calcd: 70.14% C ; 6.47% H;
found: 69.87% C ; 6.36% H.

IR (cm^{-1}): 2960$\nu_{as}CH_3$; 2869$\nu_s CH_3$; 1467$\delta_{as}CH_3$; 1382δs CH_3; 1720ν C=O, 1189νC-O(COO); 623νC-S.

^{1}H-NMR ($CDCl_3$, ppm): 8.1-7.28m 7H(ring protons); 5.15-4.7m 1H(OCH); 3.42d, J=9Hz 1H(SCH); 2.33-1.98m 1H(C<u>H</u>CH_3); 1.23-1.03m 12H(CH_3)

5. p-Nitrobenzyl ester of 2-dibenzofurylthioisopropylacetic acid

a) To a sample of 4.07g (0.01 mole) of silver salt of acid(1) suspended in 60 cm^3 of benzene, 2.2g (0.01 mole) of p-nitrobenzyl bromide was added gradually, and the mixture was refluxed for 4h. The solution was filtered and, after removing the solvent, the oily residue solidified at -5 °C, and it was crystallized from ethanol. Prisms, m.p. 84-86 °C. Yield 3.9g (89%).
b) To a sample of 2.3g (0.007 mole) of sodium salt of acid (1) suspended in 15 cm^3 of water, 1.65g (0.0076 mole) of p-nitrobenzyl bromide dissolved in 45cm^3 of ethanol was added and the mixture was refluxed for 4.5h. The solution was filtered and, after cooling, the precipitate was isolated and crystallized from ethanol. Prisms, m.p. 84-86 °C. Yield 2.2g (72%)

Analysis
For $C_{24}H_{21}NO_5S$ (435.48) -calcd: 3.2% N,
found: 3.24%N

IR (cm^{-1}): 2964$\nu_{as}CH_3$; 2873ν_sCH_3; 1467$\delta_{as}CH_2$ and CH_3; 1371δ_sCH_3; 2935$\nu_{as}CH_2$; 1724ν C=O; 1189ν C-O(COO); 1521$\nu_{as}NO_2$; 1346ν_sNO_2; 822δ C_{Ar}-H (subst.1, 4); 625νC-S.
^{1}H-NMR ($CDCl_3$,ppm): 7.99-7.21m 11H(rings' protons);5.07d ,^{2}J=4.7H_z 2H(CH_2)) 3.55d, J=8.9Hz ;1H(SCH); 2.26-2.17; m 1H(C<u>H</u>CH_3);1.24d, J=7Hz 3H(CH_3);1.07d, J=7Hz 3H(CH_3).

6. Phenacyl ester of 2-dibezofurylthioisopropylacetic acid

A sample of 4.07 g (0.01 mole) of silver salt of acid (1) was suspended in 50 cm^3 of benzene and 1.99 g (0.01 mole) of phenacyl bromide was added gradually and the mixture was refluxed for 4 h. The resulting solution was filtered and after removing the solvent, the oily residue solidified, and it was crystallized from ethanol. Needles, m.p. 82-83.5 °C. Yield 3.15 g (75%)

Analysis
For $C_{25}H_{22}O_4S$ (418.49)- calcd:71.75%C ; 5.30%
found: 71.78%C ;5.45% H.

IR (cm^{-1}); 2930 $\nu_{as}CH_2$; 2870ν_s CH_2 and CH_3; 1465δ CH_2 and CH_3; 1728ν C=O,COO)1196νC-O(COO); 1702ν C=O(COC_6H_5); 748δ C-H (subst 1).
^{1}H-NMR ($CDCl_3$, ppm): 8.21-7.32 m 12H(rings protons); 5.29 d,^{2}J=3.3Hz 2H(CH_2); 3.60 d, J=8.9 Hz 1H(SCH); 2.43-2.08 m 1H (C<u>H</u>CH_3);1.26d, J=7Hz 3H(CH_3); 1.18d, J=7Hz 3H(CH_3)

7. p-Bromophenacyl ester of 2-dibenzofurylthioisopropylacetic acid

A sample of 4.07 g (0.01 mole) of silver salt of acid (1) was suspended in 50 cm^3 of benzene and 2.78g (0.01 mole) of p-bromophenacyl bromide was added gradually and the mixture was refluxed for 4h. The solution was filtered and, after removing the solvent, the oily residue solidified, and it was crystallized from ethanol. Prisms, m.p. 112-113 °C Yield 4.4g (88%).

Analysis

For $C_{25}H_{21}BrO_4S$ (497.40) - calcd: 60.36%C ; 4.25%H;
found: 60.22%C ; 4.01%H.

IR (cm^{-1}): 2964 $\nu_{as}CH_3$; 2871ν_s CH_3; 1466 δ_{as} CH_3 and CH_2; 1388 δ_s CH_3; 2939ν_{as} CH_2; 1726ν C=O (COO); 1197ν C-O (COO); 1703ν C=O (COC_6H_5); 831δ C-H (subst. 1.4)

^{1}H-NMR ($CDCl_3$, ppm): 8.17-7.30m 11H (rings' protons); 5.21d, ^{2}J=3Hz 2H(CH_2); 3.58 d, J=8.4 Hz 1H (SCH); 2.41-2.07m 1H ($C\underline{H}CH_3$); 1.26d, J=6.6Hz 3H(CH_3); 1.17d, J=6.6 Hz 3H (CH_3)

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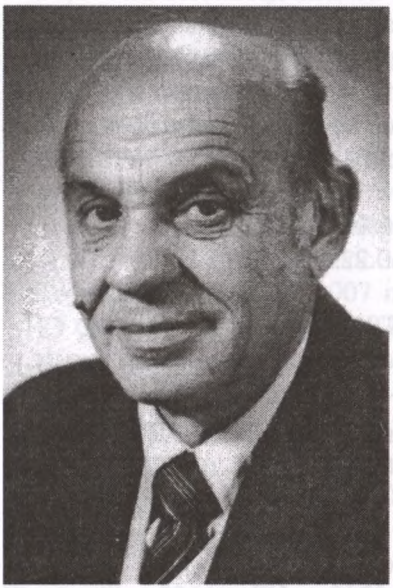

Wawrzyniec Podkościelny. Assistant Professor. M. Sc. 1955; Ph.D. 1964, Habilitation 1994. Postdoc: University of Wisconsin, McArdle Laboratory for Cancer Research, USA (1966–1967), Vice-Director of the Institute of Chemistry, UMCS (1970–1978); (1981–1984). Director of Institute of Chemistry (1988–1989), Head of the Department of Organic Synthesis (1970–1976), Head of Department of Organic Chemistry and Technology (1979–). Research areas: Organic chemistry

-polymer chemistry, chemistry of compounds of potential bilogical activity.

-Synthesis, structure and properties of polymers containing sulfur in the main chain, particularly of polythioesters, polisulfonates, thioetherglicydyl resins and recently non-segmented and segmented polyurethanes.

-Synthesis, structure and properties of new compounds of potential biological activity.

-Synthesis, structure and properties of monomers, oligomers and polymers as well as UV cured compositions for optical fibre coatings.

Results of the investigations from these various areas were presented in over 100 scientific national and foreign journals, 60 patents and 50 communications. In 1958 he became member of Polish Chemical Society and, up to now he promoted 8 doctoral dissertations and over 200 M. Sc. degrees.