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SYNTHESIS AND PESTICIDAL ACTIVITY OF AMINOESTERS OF (+)-α-PINENE

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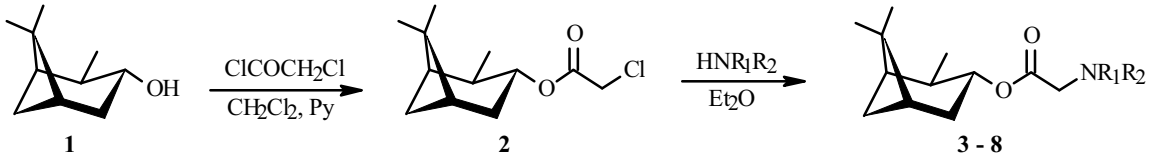
Optically active (–)-(1R,2R,3R) aminoesters of isopinocampheol (2,6,6-trimethylbicyclo[3.1.1]heptan-3-ol) were synthesized from (+)-α-pinene. The antifidant, juvenoidal, growth-regulating, and herbicidal activities of the newly synthesized compounds were studied.

Key words: α-pinene, aminoesters of isopinocampheol, pesticidal activity.

Pinane compounds (2,6,6-trimethylbicyclo[3.1.1]heptane), in particular oxygenated and amino derivatives, are attractive chemicals not only for their unique structure and availability but also for the potential of practical application. The principal raw material for preparing pinane compounds is the dominant component of pine turpentine (*Pinus silvestris* L.), α-pinene, based on which a wide range of compounds with various types of biological activity has been synthesized [1-3].

In continuation of work [4-6] on the synthesis of functionally substituted pinane derivatives and the study of their spectrum of biological activity, we synthesized the previously unreported optically active aminoesters of isopinocampheol.

Isopinocampheol (–)-(1*R*,2*R*,3*R*-pinan-3-ol) (**1**) was prepared by oxidative hydroboration of (+)-α-pinene by the literature method [7]. Then, reaction of secondary terpene alcohol **1** with chloroacetylchloride in CH_2Cl_2 in the presence of pyridine at the boiling point produced the (–)-(1*R*,2*R*,3*R*) monochloroacetate of isopinocampheol (**2**) in quantitative yield. Alkylation with primary (cyclohexylamine) and secondary (dimethylamine, diethylamine, dibutylamine, morpholine, and piperidine) amines by **2** was performed in diethylether solution. Because the Cl atom in **2** is activated by the carbonyl in the α-position, the (–)-(1*R*,2*R*,3*R*) aminoesters **3**-**8** were produced in preparative yields. It is well known that the product yield in alkylation reactions increases with increasing basicity of the amine. The basicity of the amino group increases in the order dimethyl-, diethyl-, and dibutylamine. However, the yield of **5** was slightly less due to steric hindrance of dibutylamine. The better availability of the N atom in piperidine gave a higher yield for **8**. We prepared the corresponding (–)-(1*R*,2*R*,3*R*) hydrochlorides **9**-**14** and (–)-(1*R*,2*R*,3*R*) methyliodides **15**-**19** from the synthesized aminoesters. Table 1 lists the yields and physical chemical constants of the synthesized compounds.



1 **2** **3 - 8**

$R_1R_2 = CH_3$ (**3**); $R_1R_2 = C_2H_5$ (**4**); $R_1R_2 = C_4H_9$ (**5**); $R_1 = H$, $R_2 = C_6H_{11}$ (**6**)
NR_1R_2 = morpholine (**7**); NR_1R_2 = piperidine (**8**)

The structures of **2**-**8** were confirmed by elemental analysis and PMR, IR, and mass spectroscopy.

The PMR spectrum of **2** was characterized by a resonance for the $OCOC\underline{H}_2Cl$ protons as a doublet with integrated intensity 2H at 4.34 ppm. The spectra of **3**-**8** had resonances for the $COC\underline{H}_2NR_1R_2$ protons as a doublet with integrated intensity 2H at 3.32 ppm. Resonances of the pinane protons and substituents on the N atom were characteristic for such compounds [8].

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TABLE 1. Physical Chemical Constants of **2-19**

Compound	Yield, %	bp, mm Hg; mp, °C	$[\alpha]_D^{20}$, deg	n_D^{20}	Emp. formula	M^+
2	88.3	119-120 (4)	−19.0	1.4820	$C_{12}H_{19}ClO_2$	230.7
3	87.6	103-105 (3)	−17.1	1.4735	$C_{14}H_{25}NO_2$	239.3
4	84.3	119-120 (3)	−17.4	1.4720	$C_{16}H_{29}NO_2$	267.4
5	73.7	155-157 (3)	−24.2	1.4672	$C_{20}H_{27}NO_2$	313.4
6	84.9	157-159 (2)	−24.3	1.4780	$C_{18}H_{31}NO_2$	293.4
7	86.9	150 (3)	−10.6	1.4880	$C_{16}H_{27}NO_3$	281.3
8	87.2	144-145 (3)	−12.4	1.4870	$C_{17}H_{29}NO_2$	279.4
9	86.8	213-214	−15.0	-	$C_{14}H_{26}NO_2Cl$	275.8
10	87.5	232-234	-	-	$C_{16}H_{30}NO_2Cl$	303.8
11	81.2	274-275	-	-	$C_{20}H_{38}NO_2Cl$	359.9
12	87.5	211-212	-	-	$C_{18}H_{32}NO_2Cl$	329.9
13	88.4	181-182	+0.9	-	$C_{16}H_{28}NO_3Cl$	317.8
14	90.3	216-218	−15.0	-	$C_{17}H_{30}NO_2Cl$	315.8
15	76.0	200-201	−8.3	-	$C_{15}H_{28}NO_2J$	381.2
16	77.8	156-157.5	−10.7	-	$C_{17}H_{32}NO_2J$	409.3
17	73.9	137-138.5	−12.5	-	$C_{21}H_{40}NO_2J$	465.4
18	77.8	170-172.5	−9.4	-	$C_{17}H_{30}NO_3J$	423.3
19	80.0	189-191	−10.8	-	$C_{18}H_{32}NO_2J$	421.3

$[M]^+$ values of all compounds agree with those calculated.

TABLE 2. Antifidant Activity of **2-19** for Yellow Mealworm Beetles

Compound	Isopinocampheol derivative	Protection degree, %	Compound	Isopinocampheol derivative	Protection degree, %
2	Monochloroacetate	20	**11**	Dibutylaminoacetate hydrochloride	40
3	Dimethylaminoacetate	40	**12**	Cyclohexylaminoacetate hydrochloride	20
4	Diethylaminoacetate	80	**13**	*N*-morpholineacetate hydrochloride	40
5	Dibutylaminoacetate	25	**14**	*N*-piperidineacetate hydrochloride	85
6	Cyclohexylaminoacetate	15	**15**	Dimethylaminoacetate methyliodide	35
7	*N*-morpholineacetate	35	**16**	Diethylaminoacetate methyliodide	83
8	*N*-piperidineacetate	30	**17**	Dibutylaminoacetate methyliodide	30
9	Dimethylaminoacetate hydrochloride	45	**18**	*N*-morpholineacetate methyliodide	30
10	Diethylaminoacetate hydrochloride	40	**19**	*N*-piperidineacetate methyliodide	20

The IR spectrum of **2** contained an absorption band for the carbonyl near 1745 cm^{-1} and for C–O–C near 1260 cm^{-1}. The C–Cl vibrations appeared at 830 cm^{-1}. The IR spectra of **3-19** showed absorption bands in the range 1750-1735 cm^{-1} due to C=O stretching vibrations. The C–O–C stretching vibrations appeared in the range 1260-1230 cm^{-1}; of R_3N, at 1260-1275 cm^{-1}. Compounds **6** and **12** contained a band at 3350 cm^{-1} that was characterized as N–H stretching vibrations.

Mass spectra of **3-8** exhibited peaks for molecular ions, the intensity of which reached 10% of the maximum, and peaks for decomposition products from electron impact via loss of amino groups: **3**, *m*/*z* 44; **4**, 72; **5**, 128; **6**, 97; **7**, 86; **8**, 84. All compounds gave ionic fragments with *m*/*z* 137, pinyl; 44, O–C–O; and 58, $OCOCH_2$.

The antifidant activity of the isopinocampheol aminoesters and their salts were studied relative to the yellow mealworm beetle *Tenebrio molitor* by the literature method [5]. All tested compounds had more or less antifidant activity. Table 2 lists the results.

Aminoester **4**, which contains an *N*-diethylamino group, and its methyliodide **16** in addition to the hydrochloride **14** exhibited distinct antifidant activity, the degree of bean-leaf protection for which was above 80%. The solution concentrations PK_{50} for which the leaf protection was 50% were determined for the active compounds. It was 0.24%, 0.18, and 0.15 for **4**, **14**,

and **16**, respectively. It should be noted for comparison that PK_{50} of brestan, triphenyltin acetate (standard), for yellow mealworm beetle was 0.1%. Thus, although the activity of the studied compounds was lower or equal to that of the standard brestan, the terpenoids and their derivatives are less toxic for warm-blooded animals than the tin-containing preparation and less polluting of the environment because they are easily biodegraded.

The growth-regulating activity of **2-19** was studied using the literature method [9] in cell culture of sugar beet and chlorella alga. The test results showed that **2**, **5**, **8**, **9**, **15**, and **16** had distinct growth-regulating activity relative to chlorella. Compound **16** acted as a retardant under hothouse conditions; **7**, as a plant growth inhibitor. This indicates that searching this series of compounds for herbicides and photosynthesis inhibitors is promising.

The herbicidal activity of **2-19** was studied using the literature method [10] under hothouse conditions on biotests of oats, soy, and mustard. Compounds **2**, **9**, **14**, **16**, **17**, and **19** suppressed development of the test plants by 20-80%. The herbicidal activity of the prepared compounds was evident only if they were applied to vegetative plants. This is probably explained by the difficulty of penetrating through the sprouts rather than through the vegetative organs of the plants.

Compounds **2-19** were tested as juvenoids by topical administration of test liquids on six-hour pupae of yellow mealworm beetle. No noticeable activity was noted.

The toxicity of **2-19** for root-knot nematode larvae in a laboratory *in vitro* experiment with concentrations of 0.5-2.0% for the tested compounds did not exceed 40%.

The results for the pesticidal activity of the isopinocampheol aminoesters showed that **3** had moderate activity whereas **4** exhibited high pesticidal activity, especially for its methyliodide **16**. The activity of the compounds decreased with a further increase of the molecular weight of the amino group. The only exception was piperidine derivative **8** and its hydrochloride **14**. The results can be used further for directed synthesis of biorational pesticides of the terpenoid series.

EXPERIMENTAL

IR spectra in a thin layer between KBr were recorded on a UR-20 spectrophotometer in the range 400-3800 cm^{-1}. PMR spectra in $CDCl_3$ with internal standard TMS were recorded on a WM-360 spectrometer. Mass spectra were recorded in a Varian MAT-311 instrument with cathode emission 1000 mA, ionizing electron energy 70 eV, vaporizer temperature 150-200°C, and ion-source temperature 200°C. Specific rotations in ethanol at room (20-25°C) temperature were measured on a Jasko J-20 polarimeter. Melting points were determined on a Kofler microheating stage. GC analysis was performed on a Vyrukhrom instrument with a FID, 2000 × 3 mm column, Chromaton N-AW-DMCS solid support, Reoplex-400 stationary phase, 100°C, and carrier gas (N_2) at 50 mL/min.

Isopinocampheol (1) was prepared by oxidative hydroboration by the literature method [7]; α-pinene (n_D^{20} 1.4655, $[\alpha]_D^{20}$ +30.9°), isolated from pine turpentine by fractionational distillation (60 theor. plates). The resulting secondary alcohol (**1**) had mp 56-57°C, $[\alpha]_D^{20}$ –21.8° (*c* 1%, benzene); lit. [7] mp 55-57°C, $[\alpha]_D^{20}$ –32.8° (*c* 10, benzene).

Isopinocampheol Monochloroacetate (2). A solution of **1** (15.4 g, 0.1 mol) in CH_2Cl_2 (50 mL) and pyridine (7.9 mL) was stirred vigorously, treated dropwise with a solution of monochloroacetic acid chloride (11.3 g, 0.1 mol) in CH_2Cl_2 (25 mL), heated to 40°C, and refluxed for 2-5 h with constant stirring. When the reaction was finished the mixture was diluted with water (100 mL). The organic layer was separated, washed twice with water, and passed over a column of Al_2O_3 with elution by CH_2Cl_2. Solvent was distilled off. Vacuum distillation produced isopinocampheol chloroacetate (20.3 g, 88.3%). IR spectrum (ν, cm^{-1}): 2960, 2875 (C–H), 1745 (C=O), 1475, 1420, 1370, 1320, 1260 (C–O–C), 1190, 1155, 1006, 980, 830 (C–Cl). Mass spectrum (*m*/*z*): 230 (10%) $[M]^+$, 137, 121, 107, 93 (100), 78, 67, 58, 56, 49, 44, 35. PMR spectrum (δ, ppm): 1.06 (d, CH_3 on C-2), 1.11 [s, $(CH_3)_2C$ on C-6], 1.2 (m, H-7e), 1.34 (m, H-4a), 1.38 (m, H-4e), 1.46 (m, H-2a), 1.64 (m, H-1), 1.65 (m, H-5, H-7a), 4.34 (d, $COC\underline{H}_2Cl$), 4.69 (m, H-3a).

Isopinocampheol Aminoacetates 3-8 (general method). Equimolar amounts of isopinocampheol monochloroacetate (**2**) and the appropriate amine (dimethyl-, diethyl-, dibutyl-, cyclohexylamine, morpholine, and piperidine) were refluxed in diethylether for 2-5 h. The reaction mixture was treated with KOH solution (5%). The product was extracted with ether. The ether extracts were washed with water and dried over calcined $CaCl_2$. Ether was distilled off. The residue was vacuum distilled.

Isopinocampheol Aminoacetate Hydrochlorides 9-14 (general method). Dry HCl was passed through an ether solution of **3-8**. The resulting precipitate was separated by filtration, washed on the filter with solvent, dried in air, and recrystallized from CH_2Cl_2 if needed.

Isopinocampheol Aminoacetate Methyliodides 15-19 (general method). A solution of **3-8** in benzene and a 1.5-fold excess of methyliodide was heated on a boiling water bath for 5-6 h and left overnight. The resulting precipitate of the aminoester (**3-8**) methyliodide was filtered on a Schott filter, washed with a small amount of benzene, pressed, and dried in air or in a drying cabinet at 40-50°C.

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