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SYNTHESIS AND FUNGICIDAL ACTIVITY OF SUBSTITUTED TETRAHYDRO-[3, 4-c]- AND BENZO[h]TETRAHYDROPYRIDO[3,4-c]COUMARINS

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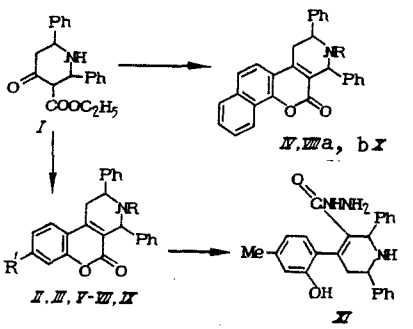
Pyridocoumarins have attracted the attention of investigators in connection with the possibility of using them as organic colors for lasers, luminophores, and fluorescent markers for biological objects [2, 3]. Information about the physiological activity of pyridocoumarins is limited.

With a view to study the fungicidal activity of compounds of this series, we have synthesized substituted 1,2,3,4-tetrahydropyrido[3,4-c]coumarins and 1,2,3,4-tetrahydrobenzo[h]-pyrido[3,4-c]coumarins; the starting compound was 2,6-diphenyl-3-ethoxycarbonylpiperidin-4-one (I). Earlier [4], from this β-ketoester and resorcinol 8-hydroxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c] coumarin (II) was prepared with the Pechmann reaction, which synthesis we repeated in order to record its spectral characteristics and to prepare derivatives through the hydroxy and secondary ammonium groups.

By condensation under the same conditions of β-ketoester I with m-cresol and α-naphthol were prepared in quantitative yields 8-methyl-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c] coumarin (III) and 2,4-diphenyl-1,2,3,4-tetrahydrobenzo[h]pyrido[3,4-c]-coumarin (IV), respectively. Data on these compounds are listed in Table 1. In the IR spectra of compounds II-IV are found an intensive band of the lactone carbonyl and absorption bands of the C=C and NH bonds of the piperidine fragment, and their UV spectra have absorption maxima of the coumarin system in the region 284-367 nm. PMR spectral data also confirm the structures of compounds II-IV (Table 2).



R=H(II—IV,VI), Ac(V,VII,VIIIa), EtCO(VIIIb), Me(IX,X);
R'=OH(II), Me(III,VII,IX), AcO(V,VI)

By reacting compound II with Ac_2O in dry pyridine was prepared 2,4-diphenyl-3-acetyl-8-acetoxy-1,2,3,4-tetrahydropyrido[3,4-c]coumarin (V), which on heating in aqueous pyridine

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TABLE 1. Characteristics of the Prepared Compounds

Compound	mp, °C	IR spectra, ν, cm^{-1}	Empirical formula	Molecular mass	Yield, %
III	173—174	3500, 1738, 1625	$C_{25}H_{21}O_2N$	367	90
IV	228—230	3420, 1723, 1618	$C_{28}H_{21}O_2N$	403	86
V	243—245	1760, 1725, 1643, 1628	$C_{28}H_{23}O_5N$	453	82
VII	196—198	1715, 1644, 1620 пл.	$C_{27}H_{23}O_3N$	409	72
VIIIa	282—284	1715, 1645, 1620	$C_{30}H_{23}O_3N$	445	69
VIIIb	258—261	1722, 1657, 1647, 1620	$C_{31}H_{25}O_3N$	459	64
IX	186—188	1730, 1630	$C_{26}H_{23}O_2N$	381	15—27
X	132—134	1730, 1621	$C_{29}H_{23}O_2N$	417	58
XI	198—201	3470, 3200, 1660, 1622	$C_{28}H_{25}O_3N_3$	415	58

TABLE 2. PMR Spectra of the Prepared Compounds

Compound	Chemical shift, δ, ppm (J, Hz)[a]				
	H-1	H-2	H-4	CH_3CH_2	aromatic protons
II[b]	2,90 and 3,40	4,34	5,30	—	7,25—7,90; 11H; 6,8, 2H
III	2,88 and 3,41	4,19 (8,0)	5,19 (2,5)	2,43	7,12—7,73; 13H
IV	3,20 — 3,70	4,57	5,55	—	7,10—8,60, 16H
V	2,88 — 3,44	5,38	6,86—7,45	2,06 and 2,12	6,86—7,45, 12H; 8,5, 7-H; 7,76, d(8,0 Hz), 9-H
VII	3,13 and 3,63	5,49 (7,0)	6,92	2,49 and 2,13	6,96—7,90 13H
VIII[a]	3,38	5,55 (6,5)	6,95	2,28	7,00—8,00, 15H; 8,65, 7-H
VIII[b]	3,03 — 3,70	5,53 (7,0)	6,98	1,18 and 2,50	7,00—8,00, 15H; 8,65, 7-H
IX	2,88 — 3,44	3,64 (6,0and7,0)	4,48 (2,0)	2,40 and 2,03	7,00—7,60, 13H
X	3,10 — 3,50	3,69	4,54	2,07	7,10—7,90; 15H; 8,40, 7-H
XI[c]	3,0 and 3,40	6,50	4,80 (H-6)	2,48	7,25—8,00, 13H

[a]Solvent: $CDCl_3$ (compounds VIII-X), $(CD_3)_2CO$ (III), DMSO-d_6 (II, IV, VII, XI), pyridine-d_5 (V).
[b]The proton of the hydroxyl group resonates at 10.5 ppm as a singlet.
[c]Other protons: 10.6 pp, OH-2'; 3.80 ppm, NH_2; 9.30 ppm, -NH—N.

yielded the N-deacetylated analog VI, which was described earlier in [4]. Likewise, from compound V were prepared in high yields N-acyl derivatives VII and VIIIa, b by reaction of tetrahydropyridocoumarins III and IV with acetic or propionic anhydride in dry pyridine.

N-Methylation of compound III was carried out under various conditions. In practically the same yield (22-27%), 3,8-diemthyl-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c]coumarin (IX) was prepared by treating compound III with dimethyl sulfate in the presence of sodium hydroxide and also under conditions of phase transfer catalysis by reaction of compound III with dimethyl sulfate in benzene and 15% NaOH in the presence of Bu_4NI. N-methyl derivative IX was prepared in low yield by methylation of compound III according to Leuckart's method by reacting it with formaldehyde and formic acid.

3-Methyl-2,4-diphenyl-1,2,3,4-tetrahydrobenzo[h]pyrido-[3,4-c]coumarin (X) was synthesized in 58% yield by methylation of compound IV with methyl iodide in the presence of potassium carbonate.

We also carried out the opening of the α-pyrone ring of tetrahydropyridocoumarin III by reaction with hydrazone hydrate in alcohol. In that case we isolated in 58% yield the hydrazide of 2,6-diphenyl-4-(4-methyl-2-hydroxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid (XI).

Scheme 1

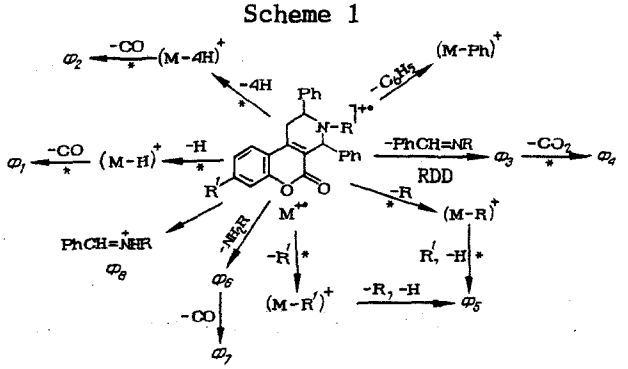

TABLE 3. Characteristic Ions and Their Relative Intensities in the Mass Spectra of Compounds II-VIIIa and IX

Compound	Value of m/z*															
	M^+	$(M-H)^+$	$(M-4H)^+$	$(M-R)^+$	$(M-R^1)^+$	$(M-Ph)^+$	Φ_1	Φ_2	Φ_3	Φ_4	Φ_5	Φ_6	Φ_7	Φ_8	$C_6H_5^+$	$C_7H_7^+$
II	369	368	365	—	352	292	340	337	264	220	—	—	—	106	77	91
	(31)	(15)	(25)		(2)	(84)	(5)	(8)	(50)	(15)				(15)	(18)	(7)
III	367	366	363	—	352	290	338	335	262	218	—	—	—	106	77	91
	(100)	(20)	(22)		(8)	(92)	(7)	(9)	(48)	(14)				(18)	(20)	(5)
IV	403	402	399	—	—	326	374	371	298	254	—	—	—	106	77	91
	(23)	(6)	(100)			(23)	(23)	(47)	(18)	(6)				(17)	(20)	(33)
V	453	—	—	410	394	376	—	—	306	262	350	394	366	148	77	91
	(67)			(19)	(22)	(12)			(9)	(6)	(100)	(22)	(5)	(4)	(9)	(11)
VII	409	—	—	366	—	332	—	—	262	218	—	350	322	148	77	91
	(40)	—	—	(37)		(5)			(7)	(7)		(100)	(15)	(7)	(11)	(12)
VIIIa	445	—	—	—	402	368	—	—	298	254	—	386	358	148	77	91
	(57)				(41)	(13)			(7)	(7)		(100)	(25)	(9)	(18)	(19)
IX	381	380	377	—	366	304	352	349	262	218	—	—	—	120	77	91
	(24)	(3)	(10)		(4)	(100)	(11)	(9)	(13)	(7)				(20)	(7)	(9)

*In parentheses the relative intensity (in %).

TABLE 4. Pesticidal Activity of Compounds III-V and VII-XI

Test subject	Pesticidal activity of the compounds*							
	III	IV	V	VII	VIIIa	IX	X	XI
Xanthomonas malvacearum	0	9	0	18	9	0	9	0
Fusarium maniliforme	20	18	2	10	6	22	14	16
Rhizoctonia solanis	13	30	0	0	2	15	0	0
Powdery mildew of cucumber	38	68	46	52	0	0	8	30
Phytophthora infection of tomatoes	83	83	0	83	0	0	0	0
Gray mold of beans	0	32	0	11	21	0	0	0

*Reported are the percentages of growth reduction of bacteria and the mycelium of the fungus or mold in comparison with the control.

We have studied the mass spectra of tetrahydropyrido-coumarins II-V and VII-IX. These spectra contain peaks of the molecular ions M^+ of high and medium intensities (Table 3). Their dissociative ionization is pictured in Scheme 1. The appearance of peaks of the ions $(M-H)^+$, $(M-2H)^+$, $(M-4H)^+$, and $(M-3H)^+$ in the mass spectra of compounds II-IV and IX is caused by dehydrogenation of the piperidine ring. On fragmentation of all the compounds investigated a retrodiene decomposition of that ring takes place, which leads to formation of fragment ϕ_3 and rearranged ion ϕ_8. The appearance of the characteristic fragments $(M-C_6H_5)^+$ is caused by the presence of phenyl radicals at the α-position of the piperidine ring. The formation of the ions $(M-R)^+$ and $(M-R^1)^+$, and also of fragment ϕ_5, is caused by the presence of substituents at the nitrogen atom and the phenylene ring. A special feature of the dissociative ionization of N-acyl derivatives V, VII, and VIII is the unusual loss of the particle RNH_2 from their ions M^+, which leads to formation of rearranged fragment ϕ_6. The formation of ions ϕ_1, ϕ_2, ϕ_4, and ϕ_7 is connected with loss of the particles CO and CO_2 from the coumarin fragment. The presence of the metastable transitions in the mass spectra confirms the genetic link of the formed ions.

The pesticidal activities of the prepared compounds (Table 4) were determined as described in [1]. Weak bactericidal activity is shown by compounds VII (18%), and IV, VIII, and X (9%); the other compounds were not toxic to that test subject.

The fungicidal activity was studied with some subjects in vitro and in vivo. In the case of Fusarium moniliforme a weak (from 18 to 22%), but the largest, activity is shown by

compounds IV, III, and IX. An insignificant action displayed all the studied compounds with regard to Rhizoctonia solanis, and also with regard to gray mold of beans. With respect to these last two subjects a noticeable effect was given only by benzopyridocoumarin IV (30 and 32%, respectively).

Compounds VIII-X are inactive against powdery mildew of cucumber, but compound V has medium acitivity (46%). The same compounds, and also pyridocoumarin V and arylpiperideine XI are inert with regard to phytophthora infection of tomatoes. In experiments in vivo with powdery mildew of cucumber and phytophthora infection of tomatoes high activity (from 38 to 83%) is shown by 8-methyl substituted pyridocoumarins III and VII, and also by benzopyridocoumarin IV.

In all the cases the fungicidal activity of tetrahydrobenzopyridocoumarin IV is considerably higher than the activity of the compounds of the series of tetrahydropyridocoumarins. It is also necessary to note that substituting the secondary amino group in the most toxic compound IV for an N-acetyl group (conversion to compound VIII) or for an N-methyl group (compound X) leads to a considerable lowering or complete loss of fungicidal action on green plants. The fungicidal activity is also considerably lowered on acetylation of the secondary amino group of compounds II and III (conversion to compounds V and VII).

EXPERIMENTAL

PMR spectra were recorded on a Bruker WP-80 spectrometer in $CDCl_3$. Mass spectra were taken on an LKB-2091 spectrometer at an ionization potential of 70 eV. IR spectra were recorded on a UR-20 spectrometer from KBr disks and TLC was carried out on Silufol plates.

2,4-Diphenyl-8-methyl-1,2,3,4-tetrahydropyrido[3,4-c]-coumarin (III). A thoroughly stirred mixture of 6.5 g (20 mmole) of piperidone I, 2.1 g (20 mmole) of m-cresol, and 10 ml of conc. H_2SO_4 was stored for 24 h and then poured out on ice. The precipitate was washed with water and dried. Yield 6.6 g of compound III, beige crystals. R_f 0.9 (acetone–benzene 2:1).

2,4-Diphenyl-1,2,3,4-tetrahydrobenzol[h]pyrido[3,4-c]coumarin (IV). The reaction was carried out in much the same way with 6.5 g (20 mmole) of piperidone I, 2.9 g (20 mmole) of α-naphthol, and 10 ml of sulfuric acid. Compound IV was obtained as yellow crystals. R_f 0.56 (acetone–benzene 1:5). In the same way was prepared the known 8-hydroxy-2,4-diphenyltetrahydropyridocoumarin II, mp 249-250°C [4]. IR spectrum, ν_{max}, cm^{-1}: 3240, 3050, 1738. R_f 0.6 (acetone–benzene 1:1).

3-Acetyl-8-acetoxy (V),-8-Acetoxy (VI),-8-Methyl-3-acetyl (VII)-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c]coumarins and 3-Acetyl (VIIIa),- 3-Propionyl (VIIIb)-2,4-diphenyl-1,2,3,4-tetrahydrobenzo[h]pyrido[3,4-c]coumarins. A solution of 1.8 g (4.9 mmole) of compound II and 2 ml of Ac_2O in 2 ml of dry pyridine was stored for 1 day, poured out on ice, and diluted with water. The precipitate was washed with water, dried, and crystallized from acetone. Yield 1.8 g of compound V as colorless crystals.

One gram (2.2 mmole) of compound V was refluxed in 3 ml of aqueous pyridine. Yield 0.82 g (90%) of compound VI, colorless crystals, mp 304-307°C [4]. IR spectrum, ν_{max}, cm^{-1}: 3460, 3100, 1640, 1742.

In the form of colorless crystals were obtained N-acyl derivatives VII and VIIIa, b from compounds III and IV, respectively, by treating the latter with acetic or propionic anhydride in dry pyridine.

3,8-Dimethyl-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c]-coumarin (IX). A. In a mixture of 20 ml of water and 65 ml of alcohol are dissolved with heating 3 g (8.1 mmole) of compound III and 6.1 g of NaOH. The mixture is cooled to 5°C and 15 ml of Me_2SO_4 is added gradually. The mixture is heated for 5 min and then the alcohol is distilled off. From the residue is extracted with ether 0.85 g (27%) of N-methyl derivative IX as pale yellow crystals (after crystallization from ethyl acetate). R_f 0.75 (ether–hexane 2:1).

B. To a solution of 0.73 g (1.97 mmole) of compound III in 40 ml of benzene is added 0.46 g (2 mmole) of Bu_4NI, 15 ml of 15% NaOH, and 0.8 ml (8 mmole) of Me_2SO_4. The mixture is kept at 50-55°C for 2 h. The benzene layer is separated off, extracted with NaCl solution

and water and dried over $MgSO_4$. The residue obtained after evaporation of the benzene is chromatographed over a silica gel column with the eluent ether–hexane 2:1. Yield 0.17 g (22%) of compound IX.

C. A mixture of 2 g (5.4 mmole) of compound II, 7 ml of 37% formaldehyde, and 0.8 ml of formic acid is kept at 100°C for 11 h. A soda solution is added until the pH is 8 and then the mixture is extracted with ether. Yield 0.3 g (15%) of compound IX.

3-Methyl-2,4-diphenyl-1,2,3,4-tetrahydrobenzo[h]pyrido[3,4-c]-coumarin (X). The reaction is carried out with 1 g (2.48 mmole) of compound IV, 5 ml of MeI, 1 g of water-free potassium carbonate, and 5 ml of alcohol. The mixture is refluxed for 15 h. The alcohol is evaporated and the residue is treated with an aqueous ammonia solution. The precipitate is washed with water and dried. Yield 0.6 g of compound X, which was crystallized from alcohol.

Hydrazide of 2,6-Diphenyl-4-(2-hydroxy-4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (XI). To a solution of 2 g (5.4 mmole) of compound II in 15 ml of ethanol is gradually added with stirring and refluxing 1 ml of hydrazine hydrate. The mixture is refluxed for 2 h, cooled, and 5 ml of acetone is added. The precipitate is washed with acetone and dried. Yield 1.5 g of hydrazide XI as colorless crystals.

Characteristics of the prepared compounds are listed in Table 1. Found and calculated values of elemental analyses match.

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