NITROGEN DERIVATIVES OF PINENES POSSESSING THE PROPERTIES OF PLANT RETARDANTS

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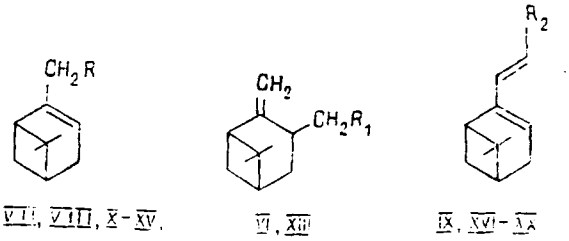
New nitrogen derivatives possessing the activity of plant growth regulators have been synthesized from the readily available natural terpenoids α- and β-pinenes.

Among quaternary ammonium salts possessing a high retardant activity, compounds are known which contain as substituents at the quaternary nitrogen terpenoid residues such as those of limonene [1], α- and β-ionones [2], labdane [3], α-pinene [5], etc. They are all active both on monocotyledonous and dicotyledonous plants. The further search for new highly effective ammonium derivatives of the isoprene series and an investigation of the dependence of the activity on their structure with the aim of revealing the most promising substances therefore appeared of interest.

We have synthesized the new ammonium salts (I-IX) starting from readily available terpenes – the pinenes – and have studied their growth-inhibiting properties in various biotests.



I-V, VII, VIII, X-XV. VI, XIII. IX, XVI-XX.

I. $R=-\overset{+}{N}(CH_3)_3\cdot Br^-$; II. $R=-\overset{+}{N}(C_2H_5)_3\cdot Br^-$; III. $R=-\overset{+}{N}H(CH_3)_2\cdot Br^-$;

IV. $R=-\overset{+}{N}(CH_3)_2CH_2$  Br^-; V. $R=C_5H_{10}\overset{+}{N}(CH_2CH=CH_2)\cdot Br^-$;

VI. $R_1=-\overset{+}{N}(CH_3)_2\cdot I^-$; VII. $R=-CH_2\overset{+}{N}(CH_3)_3\cdot I^-$;

VIII. $R=-CH_2(CH_3)\overset{+}{N}C_5H_{10}\cdot I^-$; IX. $R_2=-CH_2\overset{+}{N}(CH_3)_3\cdot I^-$;

X. R=OH; XI. R=Br; XII. $R=C_5H_{10}N-$; XIII. $R=-CH_2N(CH_3)_2$;

XIV. $R=-CH_2N(CH_3)_2$; XV. $R=C_5H_{10}NCH_2-$; XVI. $R_2=-COCH_3$; XVII. $R_2=-COOH$;

XVIII. $R_2=-CH_2OH$; XIX. $R_2=-CH_2Br$; XX. $R_2=-CH_2N(CH_3)_2$.

As the starting material in the synthesis of salts (I-V) we used myrtenyl bromide (XI), obtained by the bromination of myrtenol with phosphorus tribromide. Its interaction with a twofold amount of the corresponding amines in ethanol at room temperature gave the salts (I-III). In the synthesis of (IV), the reaction was performed in a sealed tube with an excess of dimethylamine at 100°C. Compound (V) was formed by the action of allyl bromide in acetone on the amine (XII), obtained, in its turn, from myrtenyl bromide and piperidine. Compounds (VI)-(VIII) were synthesized by the aminoalkylation of α- and β-pinenes by a modified Mannich reaction [4] to give the corresponding amines (XIII-XV) and the subsequent action of methyl iodide on them.

The ammonium salt (IX) was obtained in several stages from the ketone (XVI), which has been described previously [5]. By oxidation with sodium hypochlorite it was converted into

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TABLE 1. Action of the Compounds Tested on the Length of Plant Shoots, % on Control

Compound	Garden peppergrass			Tomato			Wheat			Barley		
	Concentration, mg/liter											
	10	25	50	10	25	50	100	200	400	100	200	400
I	100,0	97,2	91,4	100,0	96,2	94,6	91,8	72,0	51,3	76,7	54,2	46,8
II	70,1	59,6	48,1	81,4	70,3	59,2	93,6	80,9	57,5	68,5	53,0	42,5
III	96,5	87,9	71,3	98,7	91,3	80,6	95,3	81,1	74,8	95,7	85,7	63,3
IV	47,6	27,0	18,9	48,1	39,7	33,7	76,4	62,8	51,3	81,8	73,7	65,4
V	79,7	49,1	42,6	88,8	73,8	68,7	96,3	85,0	63,5	79,9	60,7	51,2
VI	82,5	71,5	54,4	78,5	68,2	56,2	85,8	69,8	61,8	72,4	66,0	56,5
VII	80,2	69,7	45,7	70,1	60,7	57,9	48,0	37,1	28,5	58,5	47,5	41,8
VIII	45,1	26,5	16,9	45,9	41,4	33,5	52,0	41,5	28,0	64,5	51,3	45,1
IX	38,0	26,5	16,9	48,6	39,2	35,9	53,2	44,7	35,5	73,6	59,3	35,0
XXX	84,9	80,5	71,1	87,9	67,2	61,6	83,8	76,6	74,0	75,2	63,0	53,6
control (water)	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0	100,0

the acid (XVII), which by reduction with lithium tetrahydroaluminate to the alcohol (XVIII) and subsequent bromination, was converted into the bromide (XIX). The interaction of the latter with dimethylamine and methyl iodide gave the salt (IX).

The structures of all the compounds obtained were confirmed by elementary analysis and by their IR and PMR spectra.

The retardant properties of salts (I-IX) were studied by the method of biological testing on shoots of garden peppergrass, tomato, wheat, and barley in comparison with the well-known standard chlorocholine chloride (XXX). As can be seen from Table 1, the majority of the substances exhibited pronounced growth-inhibiting properties and retarded the growth of the plants mentioned more strongly than the standard. From them we must single out compounds (VIII) and (IX), which were considerably more active than (XXX) in all the tests. Some salts exhibited a selective action in relation to different plant species. Thus, for example, substance (IV) was most active on garden peppergrass and tomatoes while (VII) was most active on wheat and barley. Substances (II), (V), and (VI) also possessed a considerable activity. In the concentrations tested, none of the compounds obtained exhibited a phytotoxic action on the plants. Furthermore, the shoots acquired a compact form with the thickening of the stems and an intensive green coloration of the leaves. The facts presented characterized the quaternary ammonium salts of the pinene series that were synthesized as active retardants of interest for further detailed study.

EXPERIMENTAL

IR spectra were recorded on Specord-75 instrument in paraffin oil, and PMR spectra on a Tesla-467 instrument (60 MHz, TMS, in $CDCl_3$). The results of the elementary analysis of all the compounds corresponded to the calculated figures.

Myrtenyl Bromide (XI). Over 40 min, a solution of 6.0 g of PBr_3 in 10 ml of ether was added to a mixture of 6.5 g of myrtenol, 2.3 ml of pyridine, and 45 ml of dry ether cooled to −15°C, and the mixture was left in the temperature interval of 0 to −5°C for 20 min. Then it was diluted with 50 ml of ether and 30 ml of water. The ethereal layer was washed three times with 50-ml portions of 3% NaOH solution and with water and was dried over $CaCl_2$ and evaporated. This gave 7.5 g of crude myrtenyl bromide in the form of a yellow oil which was used without purification in the subsequent stages.

Compounds (I-IV). To 2.1 g of myrtenyl bromide in 12 ml of dry ether was added 2 g of triethylamine, and the mixture was left at room temperature for 16 h and was then heated at 70°C for 1 h and, after cooling, the precipitate of triethylamine hydrochloride was filtered off. The filtrate was evaporated and the residue was recrystallized from a mixture of ethanol and ether. This gave 1.8 g (58% yield) of white crystals of [(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl]triethylammonium bromide (II) with mp 153-156°C. IR spectrum, ν_{max} (cm^{-1}): 790, 1630 (CH=C), 1025, 1170. $C_{16}H_{30}BrN$. The following compounds were obtained similarly, using trimethylamine or dimethylamine, respectively, in place of triethylamine: [(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl]trimethylammonium bromide (I) (55% yield), mp 227-228°C; IR spectrum, ν_{max} (cm^{-1}): 750, 832, 1635 (CH=C), $C_{13}H_{24}BrN$; and

[(6,6-dimethylbicyclo[3.3.1]hept-2-en-2-yl)]dimethylammonium bromide (III) (45% yield), mp 173-177°C; IR spectrum, ν_{max} (cm^{-1}): 800, 1645 (CH=C), 1088, 1145; $C_{22}H_{36}BrN$.

In the preparation of di[(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl]dimethylammonium bromide (IV), the reaction was performed at 100°C in a sealed tube for 6 h, using a fivefold excess of dimethylamine. After the mixture had cooled, the solvent was evaporated off and a fourfold amount of water and a 5% solution of NaOH to pH 9-10 were added and the product was extracted three times with ether and then with chloroform. The chloroform layer was washed with a small amount of water, dried over Na_2SO_4, and evaporated. The residue obtained was recrystallized from a mixture of ethanol and ether. This gave the white crystalline substance (IV) (yield 42%), mp 200-202°C. IR spectrum, ν_{max} (cm^{-1}): 825, 1648 (CH=C), $C_{22}H_{36}BrN$.

The Salt (V). The reaction of myrtenyl bromide with piperidine was carried out under the conditions for the preparation of (I-III). The mixture after the reaction was evaporated, the residue was diluted with a fourfold amount of water, and the neutral part was extracted with ether. The aqueous residue was made alkaline with 10% NaOH solution to pH 10-12, and the product was extracted with ether. The ethereal solution was washed with water and dried over Na_2SO_4 and was carefully evaporated in vacuum to eliminate the excess of piperdine. The residue – a yellow oil – consisted of N-[(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl]piperidine (XII) (yield 68%). IR spectrum, ν_{max}^{film} (cm^{-1}): 800, 1640 (CH=C), 1068, 1115; $C_{15}H_{25}N$. A solution of 0.5 g of the amine (XII) in 2 ml of acetone was treated with 0.5 g of allyl bromide and the mixture was left at room temperature for 24 h. The resulting solution was evaporated and the residue was triturated in ether. This gave 0.58 g (75% yield) of the amorphous noncrystallizing N-allyl-N-[(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl]piperidinium bromide (V). IR spectrum, ν_{max} (cm^{-1}): 810, 955, 1635 (double bonds), 1070; $C_{18}H_{30}BrN$.

The Amines (XIII-XV). A mixture of 1.2 g of dimethylamine hydrochloride, 0.44 g of paraformaldehyde, and 5 ml of propanol was treated with 2 g of α-pinene and was heated under reflux for 8 h. The reaction mixture was evaporated in vacuum, 10 ml of water was added to the residue, and the α-pinene that had not reacted was extracted with ether. The residual aqueous solution was treated with 5 ml of saturated K_2CO_3 solution, and the product was extracted with ether. After further treatment of the ethereal solution, 0.6 g of an amine fraction was obtained. Its chromatography on alumina in benzene gave 0.42 (22% yield) of the amine (XIII) in the form of a viscous liquid. IR spectrum, ν_{max}^{film} (cm^{-1}): 895, 1638, 3065 ($C=CH_2$), 2730 ($N(CH_3)_2$); $C_{13}H_{23}N$.

The liquid amine (XIV) was isolated with a yield of 57% by the same procedure, with the replacement of α-pinene by β-pinene, as the result of heating the reaction mixture for 2 h and chromatography of the product. IR spectrum, ν_{max}^{film} (cm^{-1}): 800, 1640 (CH=C), 2765 ($N(CH_3)_2$); $C_{13}H_{23}N$. The liquid amine (XV) was obtained with a yield of 45% in the same way, using β-pinene and, in place of dimethylamine hydrochloride, piperidine hydrochloride. IR spectrum, ν_{max}^{film} (cm^{-1}): 810, 1635 (CH=C); $C_{16}H_{27}N$.

The Salts (VI-VIII). A solution of 0.3 g of the amine (XIII) in 1.5 ml of acetone was treated with 0.45 g of CH_3I, and the mixture was left at room temperature for 16 h. Then it was evaporated and the residue was crystallized from acetone. This gave 0.32 g (62% yield) of [(6,6-dimethyl-2-methylenebicyclo[3.1.1]hept-3-yl)methyl]trimethylammonium iodide (VI), mp 212-214°C. IR spectrum, ν_{max} (cm^{-1}): 895, 1630, 3060 ($C=CH_2$). $C_{14}H_{26}IN$ in the same way, from (XIV) and (XV) were obtained, respectively, [(2,6,6-dimethylbicyclo[3.1.1]-hept-2-en-2-yl)ethyl]trimethylammonium iodide (VII) (63% yield, mp 179-182°C, IR spectrum, ν_{max}^{KBr} (cm^{-1}): 855, 1640 (CH=C), 1045; $C_{14}H_{26}IN$ and N-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl]-N-methylpiperidinium iodide (VIII) (55% yield, mp 176-179°C, IR spectrum, ν_{max} (cm^{-1}): 840, 1630 (CH=C), $C_{17}H_{30}IN$).

Oxidation of (XVI). Slowly, 22 ml of a freshly prepared solution of NaOCl (obtained by passing chlorine through a solution of 20 g of NaOH in 55 ml of water with cooling to 0°C until the gain in weight was 11.0 g) was added to 6 g of the ketone (XVI) cooled to 0°C. The mixture was then heated at 40-50°C for 1 h, after which 10 ml of ethanol was carefully added to it and, at 0°C, it was neutralized with a solution of phosphoric acid, and then the product was extracted with chloroform. After the usual working up of the chloroform extract, 6 g (96% yield) was obtained of 3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl) acrylic acid (XVII) in the form of a crystallizing oil with mp 80-82°C. IR spectrum, ν_{max} (cm^{-1}): 785, 975, 1615 (double bonds), 1685 (COOH). PMR spectrum (δ, ppm); 0.75, 1.32

(6H, $2CH_3$); 5.72 (1H, d, J = 15.0 Hz, CH=CH); 6.08 (1H, m, CH=C); 7.60 (1H, d, J = 15.0 Hz, CH=CH). $C_{12}H_{16}O_2$.

The Alcohol (XVIII). A solution of 3.0 g of the acid (XVII) in 40 ml of ether was treated with 5 g of $LiAlH_4$, and the mixture was left at room temperature for 24 h. After the usual working up, 2.57 g (91.6% yield) of pure, according to TLC, 3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl) allyl alcohol (XIV) was obtained in the form of a viscous colorless oil unstable on storage. PMR spectrum (δ, ppm): 0.76, 1.30 (6H, s, $2CH_3$), 4.08 (2H, d, J = 5.5 Hz, CH_2OH); 5.50 (2H, m, 2CH=C); 6.32 (1H, d, J = 15.0 Hz, CH=CH), $C_{12}H_{18}O$.

Bromination of the Alcohol (XVIII). With cooling (0-2°C), a solution of 1.56 g of PBr_3 in 1.5 ml of ether was added in a current of nitrogen to a solution of 2 g of the alcohol (XVIII) in 35 ml of dry ether and 0.15 ml of dry pyridine. The reaction mixture was stirred at the same temperature for 1 h and at room temperature for 1.5 h. Then it was filtered and 25 ml of ether was added, and the ethereal solution was washed three times with 15-ml portions of saturated ammonium chloride solution and three 20-ml portions of water. After drying over $CaCl_2$ and evaporation of the solvent, 2.5 g of the crude bromide (XIX) was isolated, and this was converted directly, without purification and analysis, into the amine (XX).

The Amine (XX). A cold solution of 1.5 g of dimethylamine in 10 ml of ether was added to a cold (0-5°C) solution of the bromide (XIX) obtained in 3 ml of ether, and the mixture was left for 1 h at room temperature. The solution so obtained was evaporated to dryness, and the residue was dissolved in 5 ml of water, the resulting solution was acidified with 10% HCl to pH 4-5, and the neutral fraction was eliminated by extraction with ether. The aqueous layer was alkalinized with 10% NaOH to pH 12, and the product was extracted with ether. Working up of the extract led to 1.65 g of the amine, which was purified by chromatography on Al_2O_3 in hexane. This gave 1.2 g of pure [3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)allyl]dimethylamine (XX) in the form of an oil. IR spectrum ν_{max}^{film} (cm^{-1}); 780, 840, 960, 1648 (double bonds), 2765 ($N(CH_3)_2$). $C_{14}H_{23}N$.

The Salt (IX). A solution of 1 g of the amine (XX) in 5 ml of dry acetone was treated with 1.1 g of CH_3I and the mixture was left at room temperature for 3 h and in the refrigerator for 1 h. The crystals that had deposited were filtered off, giving 1.2 g (71% yield) of [3-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)allyl]trimethylammonium iodide (IX), mp 160-163°C. IR spectrum, ν_{max} (cm^{-1}): 960, 1630 (CH=CH). $C_{15}H_{26}IN$.

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