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SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTIINFLAMMATORY PROPERTIES OF AMIDES OF SUBSTITUTED TETRAHYDROPYRANACETIC ACIDS

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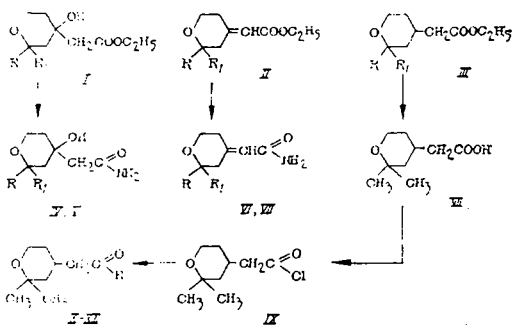
We have previously synthesized [1] saturated and unsaturated tetrahydropyranacetic acids of general formulae I-III.



Amides (IV-VII) were obtained by reaction of (I) or (II) with aqueous ammonia, and amides (X-XIII) were synthesized by hydrolysis of the ester (III), followed by conversion of the acid (VIII) to the acid chloride (IX) and reaction of the latter with ammonia or an amine. The structures of the products were established by their elemental analyses and IR spectra. For example, the amide carbonyl absorbed in all cases at 1650-1670 cm^{-1}, stretching vibrations of the amide NH_2 appeared as two maxima at 3180 and 3380 cm^{-1}, and when a hydroxyl group was present a broad absorption band was seen at 3150-3450 cm^{-1}.

The compounds obtained, like the antiinflammatory flavonoids, contain the tetrahydropyran ring [2]. For this reason, the antiinflammatory and antipyretic properties of (IV-VII) and (X-XII) were studied in carageenin and kaolin models of inflammation [3, 4], and yeast pyrexia [5].

The acute toxicities of the compounds were determined approximately in white mice weighing 16-20 g. Various doses of the drugs were administered intramuscularly, the maximum tolerated doses established, and the behavior of the animals was studied. Each dose of the drug was studied in 4-6 animals. Comparison of the acute toxicities of (IV) and (X-XII) showed that all of them except for (X) and (XII), when administered intraperitoneally in a dose of 500 mg/kg or more, although they did not cause the death of the animals, had a general depressant effect (adynamia).

The antiinflammatory properties of the compounds were studied in rats of both sexes weighing 110-140 g. The drugs were administered intraperitoneally in a dose of 30 mg/kg, and orally in doses of 12.5, 25, 50, and 100 mg/kg. Compounds (V) and (VII), which were water-soluble, were also administered subcutaneously in doses of 10, 25, and 50 mg/kg.

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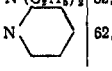
TABLE 1. Effect of Amides (IV-VII) and (X-XII) on Carageenin Edema of the Paw in Rats following intraperitoneal Administration in a Dose of 30 mg/kg

Compound	Maximum tolerated dose, mg/kg	Reduction of edema, % of the control	P
IV	800	23,0	<0,01
V	700	31,8	<0,02
VI	600	54,0	<0,01
VII	600	22,8	>0,05
X	900	28,6	<0,05
XI	250	28,6	<0,05
XII	250	54,0	<0,05

TABLE 2. Effect of Amides (IV), (V), and (XII) on Kaolin Edema of the Paw in Rats following Intraperitoneal Administration

Compound	Dose, mg/kg	Reduction in edema, % of the control			
		3 h	P	24 h	P
IV	30	16,3	<0,05	7,6	<0,05
V	30	25,3	<0,05	12,0	<0,05
XII	30	20,1	<0.05	9,1	<0,05
Indomethacin	3	67.2	=0.01	46,8	=0,01

TABLE 3. Properties of Substituted Tetrahydropyranyl- and Pyranylideneacetamides (X-XIII)

Compound	R	Yield, %	mp or bp, °C (mm)	n_D^{20}	d_4^{20}	Found, %			Molecular formula	Calculated, %		
						C	H	N		C	H	N
X	NH_2	82.0	118—120	—	—	63,55	9,93	7,34	$C_9H_{17}NO_2$	63,15	9,94	7,01
XI	$N(CH_3)_2$	83.4	127 (4)	1,4810	0,9980	67,00	10,00	7,35	$C_9H_{21}NO_2$	66,33	10,55	7,06
XII	$N(C_2H_5)_2$	82.7	133 (3)	1,4758	0,9890	68,55	10,98	6,00	$C_{13}H_{25}NO_2$	69,72	11,01	6,16
XIII		62.0	143—4 (2)	1,5028	1,0440	70,06	10,60	5,66	$C_{14}H_{25}NO_2$	70,26	10,43	5,66

The antipyretic properties of the compounds were studied in rats of both sexes weighing 150-180 g. The drugs were administered intraperitoneally in a dose of 50 mg/kg. Compounds (IV), (X), and (XII) were also studied by intraperitoneal administration in doses of 30 and 100 mg/kg, and (IV) in oral doses of 50 and 100 mg/kg.

In all experiments, each dose was tested in 5-7 rats, and the results were evaluated statistically.

For purposes of comparison, the antiinflammatory drug indomethacin was used as the control, which in a dose of 3 mg/kg, either intraperitoneally or orally, suppressed carageenan edema by 60-70% ($P < 0.01$) (Table 1).

It will be seen from Table 1 that intraperitoneal administration of (IV–VI) and (X–XII), except for (VII), reduced carageenan edema by 23-54%. On oral administration, only (XII) was active in a dose of 50 mg/kg (24%; $P < 0.05$), the remaining compounds showing no antiinflammatory activity.

The water-soluble compounds (V) and (VII) by subcutaneous administration in all doses increased carageenin edema by 60-80%. These compounds differed from (IV) and (VI) in possessing an ethyl group in the 2-position of the pyran ring instead of methyl.

As these results show, any given compound of those examined had different effects on rat paw edema according to the route of administration (intraperitoneal, oral, or subcutaneous).

For this reason, we studied the antiinflammatory properties of some of the compounds [(IV-V) and (X)] which were examined using the kaolin edema test. It is known [6] that compounds with irritant properties, when administered intraperitoneally, reduce kaolin edema for a short time (3 h), and those with antiinflammatory properties reduce it for a longer period (24-48 h) (Table 2).

It will be seen from Table 2 that (IV-V) and (X) displayed brief activity (3 h), and indomethacin a more prolonged effect (24 h).

These results therefore show that the suppression of carageenan edema following intraperitoneal administration of these compounds is due to their irritant, rather than antiinflammatory properties.

A study of the antipyretic properties showed that only (IV), in a dose of 50 mg/kg by the oral route, reduced the body temperature for a period of 3 h, like indomethacin in a dose of 3 mg/kg, by 0.7 ± 0.1°C ($P < 0.001$).

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a UR-20 instrument (GDR).

2,2-Dimethyl-4-hydroxy-4-tetrahydropyranylacetamide (IV). In a glass ampul were placed 3.78 g (0.02 mole) of 2,2-dimethyl-4-hydroxy-4-ethoxycarbonylmethyltetrahydropyran (I) and 2 g of 25% aqueous ammonia. The ampul was sealed and kept until a homogeneous mass was obtained (approximately 70 h). The water was removed, and the residue distilled in vacuo to give 1.8 g (yield 56.2%) of the amide (IV), bp 180-181°C (3 mm). Found: C 57.54; H 9.42; N 7.05. $C_9H_{17}NO_3$. Calculated, %: C 57.73; H 9.14; N 7.47.

2-Methyl-2-ethyl-4-hydroxy-4-tetrahydropyranylacetamide (V) was obtained similarly. Yield 59.8%, bp 193-194°C (3 mm). Found: C 60.00; H 10.15; N 7.03. $C_{10}H_{19}NO_3$. Calculated, %: C 59.69; H 9.52; N 6.96.

2,2-Dimethyl-4-tetrahydropyranylideneacetamide (VI). This was obtained similarly. Yield 58.4%, mp 137°C. Found: C 57.65; H 9.11; N 8.61. $C_9H_{15}NO_2$. Calculated %: C 57.96; H 8.93; N 8.27.

2-Methyl-2-ethyl-4-tetrahydropyranylideneacetamide (VII) was obtained similarly. Yield 53.2%, bp 165-167°C (2 mm). Found: C 65.72; H 10.00; N 7.82. $C_{10}H_{17}NO_2$. Calculated, %: C 65.56; H 9.35; N 7.64.

2,2-Dimethyl-4-tetrahydropyranylacetic acid (VIII). To 26 g of 20% sodium hydroxide solution was added dropwise with stirring 2.6 g (0.13 mole) of 2,2-dimethyl-4-ethoxycarbonylmethyltetrahydropyran. Following the exothermic reaction, the mixture was stirred for a further 1 h at 30-35°C. Following acidification with hydrochloric acid, extraction with ether, drying over magnesium sulfate, and removal of the ether, the residue was distilled in vacuo, to give 2.07 g (yield 92.5%) of the acid (VIII), bp 128-130°C (3 mm); n_D^{20} 1.4675; d_4^{20} 1.0700. Found, %: C 62.50; H 9.20. $C_9H_{16}O_3$. Calculated, %: C 62.70; H 9.32. According to the literature [7], n_D^{20} 1.4710.

2,2-Dimethyl-4-tetrahydropyranylacetyl Chloride (IX). A mixture of 8.6 g (0.05 mole) of the acid (VIII), 25 ml of benzene, and 7.37 g (0.06 mole) of thionyl chloride was heated for 3 h at 60-65°C, and the benzene was then removed and the residue distilled in vacuo to give 7.6 g (80.0% yield) of the acid chloride (IX), bp 72°C (2 mm); n_4^{20} 1.4745; d_4^{20} 1.0830. Found, %: C 56.57; H 7.95; Cl 18.17. $C_9H_{15}ClO_2$. Calculated %: C 56.68; H 7.87; Cl 18.63.

2,2-Dimethyltetrahydropyranacetamides (X-XIII). To an ethereal solution of 0.03 mole of the acid chloride (IX) was added with ice-water cooling, or in drops, 0.06 mole of the appropriate amine. On the following day, the contents of the flask were treated with potassium carbonate solution, extracted with ether, washed with water, and dried over magnesium sulfate. Following removal of the ether, the residue was distilled in vacuo. The unsubstituted amide was obtained as a crystalline solid. Constants for amides (X-XIII) are given in Table 3.

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