PROSTANOIDS. PART LXX. SYNTHESIS AND STUDY OF ANTIINFLAMMATORY AND ANTIULCEROGENIC ACTIVITY OF 2-(3-HYDROXY-1*E*-OCTENYL)PHENYLACETIC ACID METHYL ESTER

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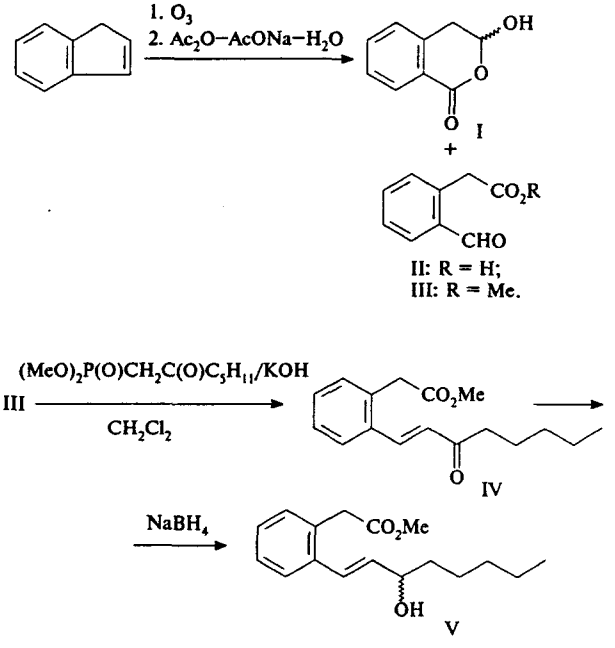
Good results in the prophylaxis of ulcerogenic activity of nonsteroidal antiinflammatory drugs were obtained with prostaglandin preparations. The therapeutic effect of these drugs includes suppressed secretion of acid products, accelerated healing of ulcers, and cytoprotective action [1, 2].

The nonsteroidal antiinflammatory drugs most frequently used (salicylates, ibuprofen, voltaren. naproxen, ketoprofen, indomethacin, flurbiprofen, etc.) can be considered derivatives of arylcarboxylic acids [3]. In this context, we have synthesized a series of new nonsteroidal antiinflammatory drugs with the structure combining prostanoid elements and arylcarboxylic acid fragments.

The syntheses proceeded from indene whose structure offers the possibility of using the method of selective oxidation for the cleavage of double bonds in the cyclopentene fragments to provide for a single-stage yield of key products – 1,2-disubstituted benzenes containing various functional groups.

Indene is ozonated in a cyclohexene solution in the presence of acetic acid, followed by the hydrolytic cleavage of the ozonide with an $Ac_2O-AcONa-H_2O$ mixture on heating [4]. This leads to a mixture of isocoumarin (I) and aldehydic acid (II) with a 1 : 1 ratio and a total yield of 60 %. The individual aldehydic acid II is isolated by crystallization. The subsequent treatment with MeOH in the presence of *p*-toluenesulfonic acid (TSA) leads to an aldehydic ester (III).

The planned structure of α-pentanorbenzoprostanoid (compound V) was obtained by olefination [5, 6] of aldehydic ester III with dimethyl-2-oxoheptylphosphonate [7], followed by reduction of the resulting enone (IV) with sodium borohydride.



EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer using thin-layer samples. The ^1H NMR spectra were recorded on a Tesla BS-480 spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. The mass spectra were obtained with an MX-1306 spectrometer operated at an electron impact energy of 70 eV and an ionization chamber temperature of 30 – 50°C. TLC patterns were obtained on commercial chromatographic Silufol plates; the spots were visualized by wetting the plates with a solution of anisaldehyde and sulfuric acid in ethanol followed by heating to 120 – 150°C.

2-Formylphenylacetic acid (II) and 3-hydroxy-3,4-dihydroisocoumarin (I). A solution of 23.0 g of indene in a

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, OH); found (%): C, 66.52; H, 5.01; for calcd. (%): C, 65.85; H, 4.88.

phenylacetic acid methyl ester (III). A solu- aldehydic acid II and 1.0 g TSA in 100 ml of H was allowed to stand at room temperature for ixture was added 100 ml of saturated aqueous , and the reaction product was extracted with × 40 ml). The extracts were combined, washed vith saturated $NaHCO_3$ and NaCl solutions, SO_4, filtered, and evaporated to obtain 10.2 g pound III in the form of a light-yellow oil; the urified by chromatography on a silica gel col- ith a hexane – ethyl acetate mixture (7 : 3). IR ompound III (ν_{max}, cm^{-1}): 1720, 2820 (CHO);); ^1H NMR spectrum (δ, ppm): 3.70 (s, 3H, 7 (s, 2H, CH_2CO_2), 7.30 – 7.33 (m, 4H, C_6H_4), CHO); mass spectrum (m/z): 178 (M^+), 150 5 ($M–CH_3OH$), 118 ($M–CH_3OH–CO$), 91 $CO_2CH_3^+$); found (%): C, 66.65; H, 5.54; for l. calcd. (%): C, 67.42; H, 5.62.

1E-octenyl)phenylacetic acid methyl ester ure of 2.0 g aldehydic ester III, 2.7 g of di- heptylphosphonate, and 0.5 g KOH in 5 ml of I_2Cl_2 was stirred for 2 h at room temperature in sphere. Then the mixture was neutralized with tion (pH 6 – 7) and extracted with CH_2Cl_2 (2 × rganic extracts were combined, washed with ous NaCl solution, dried over $MgSO_4$, filtered, d. The residue was purified by chromatography l column eluted with an ethyl acetate – hexane) to obtain 1.9 g (60%) of enone IV; IR spec- m^{-1}): 990, 1615, 1660, 1690 (HC=CH–C=O); e); ^1H NMR spectrum (δ, ppm): 0.92 (t, 3H,), 1.10 – 1.75 (m, 6H, CH_2), 2.65 (t, 2H,

ctive Effect of Compound V for the Stomach Mucous Mem- Induced by Indomethacin or Cinchophen

npound	Drug dose, mg / kg	Average number of damaged areas	Inhibition of ulceration, %	p	ED_{50}, mg / kg
= 40)	1	8.3 ± 1.3	13.2	< 0.05	
	5	6.4 ± 1.3	43.1	< 0.05	12
	10	5.0 ± 2.1	49.3	< 0.02,	
	30	2.8 ± 0.9	65.9	< 0.001	
ıtrol = 7)		9.3 ± 0.8	–	–	
= 42)	1	8.2 ± 1.4	15.5	< 0.05	
	5	5.8 ± 1.1	35.1	< 0.05	8
	10	4.0 ± 1.1	57.9	< 0.01	
	30	3.2 ± 0.4	66.3	< 0.001	
ntrol = 7)		9.5 ± 1.3	–	–	

CH_2=CO, J 8 Hz), 3.68 (s, 3H, CO_2CH_3), 3.77 (s, 2H, CH_2CO_2), 7.17 – 7.58 (m, 4H, C_6H_4), 8.72, 6.65 (2d, 1H, HC=CH–C=O, J 16 Hz); found (%): C, 73.96; H, 8.10; for $C_{17}H_{22}O_3$ anal. calcd. (%): C, 74.45; H, 8.03.

2-(3-Hydroxy-1E-octenyl)phenylacetic acid methyl ester (V). To a suspension of 0.5 g $NaBH_4$ in 10 ml of absolute MeOH was added dropwise with stirring at – 20... – 30°C a solution of 1.5 g of enole IV in 10 ml MeOH, after which the mixture was kept at this temperature for 1 h. Then the reaction mixture was acidified with 3 N HCl solution to pH 5 and heated to room temperature. Methanol was evaporated and the residue was extracted with $CHCl_3$ (4 × 20 ml). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on a silica gel column eluted with an ethyl acetate – hexane mixture (1 : 1) to obtain 1.3 g (90%) of compound V; IR spectrum (ν_{max}, cm^{-1}): 980 (HC=CH-*trans*); 1730 (CO_2Me), 3440 (OH); ^1H NMR spectrum (δ, ppm): 0.98 (t, 3H, CH_3, J 4.5 Hz), 1.19 – 1.70 (m, 8H, CH_2), 2.40 (s, 1H, OH), 3.68 (s, 3H, CO_2CH_3), 3.70 (s, 2H, CH_2C=O), 4.28 (m, 1H, CHO), 6.09 (dd, 1H, J 6 Hz, J 16 Hz, HC=(CH), 6.83 (d, 1H, J 16 Hz), HC=CH), 7.17 – 7.58 (m, 4H, C_6H_4); found (%): C, 73.29; H, 8.58; for $C_{17}H_{24}O_3$ anal. calcd. (%): C, 73.91; H, 8.69.

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity of compound V was studied on a group of 42 white mongrel mice with an acute inflammation model induced by injecting 0.05 ml of a 3% formalin solution into a hind paw aponeurosis. The drug to be tested was introduced subcutaneously at a dose of 0.1, 0.5, 1, 10, 25, or 30 μg / kg 1 h before and 1 and 2 h after the induction of inflammation.

The antiinflammatory effect of compound V was also studied on a group of 30 white mongrel mice with a model of inflammation induced by injecting 0.05 ml of a 1% carrageenan solution into a hind paw aponeurosis. Compound 5 was injected subcutaneously at a dose of 5, 10, or 25 μg / kg 1 h before and 1 and 2 h after carrageenan. One hour after the last drug introduction, the test animals were killed by chloroform. The inflammed paws were cut and weighed. In both experimental models studied, the antiinflammatory activity was evaluated as percentage inhibition of the edema growth. The reference compound was voltaren administered perorally at a dose of 8 mg / kg corresponding to ED_{50} [9].

The antiulcerogenic activity of compound V was studied on a group of 82 mice with a model of mucous membrane damage induced by indomethacin (200 mg / kg, i.p.) or by cinchophen (300 mg / kg, p.o.). Compound 5 was administered perorally at a dose of 1, 5, 10, or 30 mg / kg 30 min before the induction of gastric ulcers. The antiulcer activity was evaluated by a decrease in the amount of damage in the mucous membrane.

It was established that compound V introduced at a dose of 0.1 – 1 μg / kg exhibited a pronounced antiinflammatory effect markedly exceeding that of voltaren (Table 1). At a higher dose level (10 – 30 μg / kg), the protective effect of compound V on the formalin edema model was not reliably reproduced.

As for the model of the mucous membrane damage in the stomach induced by indomethacin or cinchophen, compound V showed a dose-dependent antiulcerogenic effect, also markedly exceeding the action of voltaren (Table 2).

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