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SYNTHESIS AND PHARMACOLOGICAL STUDY OF N-HETEROCYCLIC PROSTAGLANDIN ANALOGS

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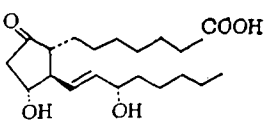
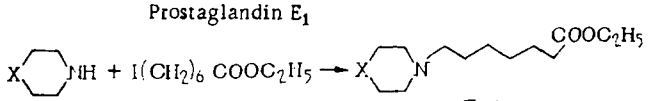
The high and many-sided physiological activity of prostaglandins has attracted the steady attention of biologists and chemists to this class of compounds in recent years [1-3]. Together with the study of natural prostaglandins and the development of methods for their total synthesis, widespread research is being carried out to produce more practicable synthetic analogs of these compounds and to find substances which are more stable, less toxic and have a more selective action on particular systems and functions of the organism than their natural prototypes. The structure of the prostaglandins has mainly been varied by changing the length or character of the side chains and by introducing or eliminating functional groups in the cyclopentane ring. Works relating to the modification of the cyclic part of the prostaglandin molecule, including the synthesis of heterocyclic analogs, have only recently started to appear. The only azaprostaglandins to be described so far are derivatives of indole [4], pyrrolidine [5], pyrazolidine [6], oxazole and thiazole [7]. Prostaglandin analogs in which the cyclopentane ring is replaced by a six-membered nitrogen-containing heterocyclic residue have not been described hitherto.

In order to synthesize piperdine-, morpholine- and piperazine-type prostaglandin analogs IIIa-IIIc, we attached the enanthic acid residue characteristic of natural prostanoids, for example prostaglandin E_1, to the nitrogen atom of the corresponding heterocycles Ia-Ic.



Prostaglandin E_1



Ia,b,c II IIIa,b,c

where a) X = CH_2; b) X = O; c) X = NCH_3

The synthesis was carried out by alkylating the nitrogen-containing heterocycles Ia-Ic with ethyl ω-iodoenanthate in toluene in the presence of potash. Compounds IIIa-IIIc were obtained in yields of 70-75%.

In order to study the effect of the length of the side chain on pharmacological activity, we synthesized the lower homologs of IIIa-IIIc, viz., compounds IIId-IIIf, under the same

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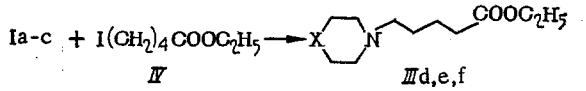
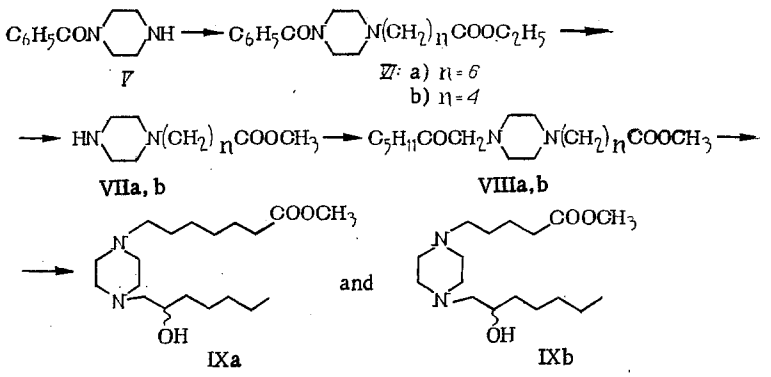
conditions and in approximately the same yields from heterocycles Ia-Ic and ethyl ω-iodovalerate.



Since the piperazine ring contains two nitrogen atoms, we were able to convert this into N-heterocyclic prostaglandin analogs containing both of the chains characteristic of their natural prototypes. The readily available N-benzoylpiperazine (V) was used as the starting materials for these syntheses. By analogy with the reactions described above, N-alkylation of V with ethyl ω-iodoenanthate and ω-iodovalerate gave ethyl ω-(4-benzoyl-1-piperazinyl)-enanthate (VIa) and -valerate (VIb). Acid hydrolysis of VIa and VIb followed by esterification with methanol in the presence of sulfuric acid gave methyl (1-piperazinyl)enanthate (VIIa) and -valerate (VIIb), which were alkylated on the second nitrogen atom by means of 1-chloro-2-heptanone [8] to give keto esters VIIIa and VIIIb, in which the ketone groups were then selectively reduced to alcohol groups by means of sodium borohydride.



The synthesized N-heterocyclic prostaglandin analogs (IXa, IXb) differ from their natural prototypes not only in the much greater ease of synthesis, but also in the absence of complicated stereochemical problems associated with prostaglandins. These problems, which are due to the presence of chiral centers in the cyclopentane ring of natural prostanoids, disappear on passing to N-heterocyclic analogs with side chains attached to nitrogen. The facile inversion of the substituents attached to the nitrogen atoms leads to the formation of the energetically more favorable chair forms of the piperazine rings, in which the bulkiest substituents are in the equatorial position.

EXPERIMENTAL

Pharmacology

In our pharmacological study of compounds IIIa-IIIf, VIa, VIb, VIIIa, VIIIb, IXa, and IXb, we determined their effect on smooth muscle tonus and arterial pressure in narcotized rats. In addition, we studied their effect on the spasmogenic and hypotensive effects of prostaglandin E_2 (PGE_2) and bradykinin.

In tests on isolated rat uterus and sections of guinea pig ileum, all the compounds studied caused an increase in smooth muscle tonus at concentrations of 10^{-6}-10^{-5} g/ml; this increase was similar to the spasmogenic reaction induced by PGE_2 at a concentration of 10^{-9} g/ml. As in the case of PGE_2, the spasmogenic action of the test compounds was short-lived (30-60 sec), after which the smooth muscle tonus dropped to its initial level.

When administered intravenously to rats at a dose of 0.5-1 mg/kg, the test compounds decreased the arterial pressure by 10-40 mm Hg for between 30 sec and 2 min. A more pronounced hypotensive effect was displayed by VIIIa, VIIIb, IXa and IXb, which have both of the side chains characteristic of prostaglandins. Compared with PGE_2, the reduction in arterial pressure induced by these compounds developed more slowly and returned to the initial level after a longer time.

TABLE 1. ω-Heteryl-Substituted Enanthate and Valerate Esters

Compound	Boiling point, deg (mm)	Found, %			Empirical formula	Calculated, %			Hydrochloride			
		C	H	N		C	H	N	melting point, deg	found, % Cl	empirical formula	calculated, % Cl
IIIa	120—2 (0,8)	69,4	11,2	5,9	$C_{14}H_{27}NO_2$	69,6	11,3	5,8	126—8	12,8	$C_{14}H_{27}NO_2 \cdot HCl$	12,8
IIIb	130—4 (0,8)	64,1	10,5	5,8	$C_{13}H_{25}NO_3$	64,2	10,3	5,8	118—20	12,4	$C_{13}H_{25}NO_3 \cdot HCl$	12,7
IIIc	112—5 (0,8)	65,9	10,7	10,6	$C_{14}H_{28}N_2O_2$	65,6	11,0	10,9	245—6	21,9	$C_{14}H_{28}N_2O_2 \cdot 2HCl$	21,5
IIId	98—100 (0,5)	67,4	10,7	6,6	$C_{13}H_{23}NO_2$	67,6	10,8	6,6	164—5	13,9	$C_{12}H_{23}NO_2 \cdot HCl$	14,2
IIIe	123—5 (0,5)	61,3	9,6	6,7	$C_{11}H_{21}NO_2$	61,4	9,8	6,5	124—5	14,3	$C_{11}H_{21}NO_2 \cdot HCl$	14,1
IIIf	110—2 (0,4)	62,8	10,7	12,7	$C_{12}H_{24}N_2O_2$	63,1	10,6	12,3	240—1	23,4	$C_{12}H_{24}N_2O_2 \cdot 2HCl$	23,5
VIa	235—6 (0,5)	69,2	8,7	8,3	$C_{20}H_{30}N_2O_3$	69,3	8,7	8,1	207—8	9,1	$C_{20}H_{30}N_2O_3 \cdot HCl$	9,3
VIb	205—6 (0,2)	68,3	8,4	8,5	$C_{18}H_{26}N_2O_3$	67,9	8,2	8,8	189—190	10,2	$C_{18}H_{26}N_2O_3 \cdot HCl$	10,0
VIIa	140—2 (2)	62,9	10,5	11,9	$C_{12}H_{24}N_2O_2$	63,1	10,6	12,3	—	—	—	
VIIb	160—2 (5)	60,1	9,7	14,1	$C_{10}H_{24}N_2O_2$	59,9	10,1	14,0	—	—	—	—
VIIIa	180—1 (0,6)	66,9	10,7	8,3	$C_{19}H_{36}N_2O_3$	67,0	10,6	8,3	204—5	16,9	$C_{19}H_{36}N_2O_3 \cdot 2HCl$	17,1
VIIIb	160—3 (0,5)	65,7	10,2	9,1	$C_{17}H_{32}N_2O_3$	65,3	10,3	9,0	195—6	18,5	$C_{17}H_{32}N_2O_3 \cdot 2HCl$	18,4
IXa	180—2 (0,8)	66,5	10,8	7,8	$C_{19}H_{38}N_2O_3$	66,6	11,2	8,2	206—7	16,8	$C_{19}H_{38}N_2O_3 \cdot 2HCl$	17,1
IXb	150—5 (0,4)	64,2	10,5	8,7	$C_{17}H_{34}N_2O_3$	64,9	10,9	8,9	186—8	18,7	$C_{17}H_{34}N_2O_3 \cdot 2HCl$	18,3

When we investigated the interaction of the test compounds with PGE_2 and bradykinin, we found that at concentrations of 10^{-7}, 10^{-6} or 10^{-5} g/ml they all increase the spasmogenic reactions of rat uterus and sections of guinea pig ileum induced by PGE_2 (10^{-8} g/ml) and bradykinin (10^{-8}-10^{-7} g/ml). Depending on the concentration used, the test compounds increase the reactions of the smooth muscle organs by 20-60%, the most active in these experiments being VIIIa, VIIIb, IXa, and IXb. Compounds VIIIa, VIIIb, IXa and IXb reinforce the hypotensive effect of PGE_2 and bradykinin in rats at doses of 0.5-1 mg/kg, whereas compounds IIIa-IIIf have no appreciable influence on the effects of PGE_2 and bradykinin at these doses. The duration of the effect of VIIIa, VIIIb, IXa, and IXb was 40 min.

Thus, the test compounds increase smooth muscle tonus and reinforce reactions induced by PGE_2 and bradykinin. These properties are most pronounced in the case of compounds VIIIa, VIIIb, IXa, and IXb, which contain both of the chains characteristic of prostaglandin molecules. The test compounds are considerably less active than the natural prostaglandins (PGE_2 and $PGE_{2\alpha}$).

Chemistry

Alkylation of Nitrogen-Containing Heterocycles Ia-Ic with Ethyl ω-Iodoenanthate (II) and ω-Iodovalerate (IV). Equimolar amounts (0.01 mole each) of I and II were boiled for 7 h in the presence of 2.8 g (0.02 mole) potash and 50 ml toluene. The reaction mixture was cooled to 15° with ice. The basic reaction products were extracted from the toluene solution with 18% hydrochloric acid. The hydrochloric acid solution was separated, washed with toluene, made alkaline with 50% potash solution, and extracted with chloroform. After removing the solvent, the residue was distilled under vacuum. Compounds IIIa-IIIf were obtained in yields of 70-75%. The constants and elementary analyses of IIIa-IIIf are given in Table 1.

Alkylation of N-Benzoylpiperazine (V) with Ethyl ω-Iodoenanthate (II) and ω-Iodovalerate (IV). Equimolar amounts (0.01 mole each) of V and II were boiled in 25 ml toluene with 3 g (0.03 mole) of triethylamine for 5 h. The cooled reaction mixture was treated with 20 ml of 50% aqueous potash solution. The toluene layer was separated, washed with water (10 ml), dried with magnesium sulfate, the toluene distilled off, and the residue distilled under vacuum. The yields of VIa and VIb were 75-78%. The constants and elementary analyses of VIa and VIb are given in Table 1.

Methyl ω-(1-Piperazinyl)enanthate (VIIa). A solution of 3.5 g (0.01 mole) of ethyl ω-(4-benzoyl-1-piperazinyl)enanthate in 35 ml of 10% hydrochloric acid was boiled for 4 h. The precipitated benzoic acid (about 1.2 g) was filtered off. The aqueous filtrate was evaporated to dryness under vacuum and dried by azeotropic distillation with benzene. The residue was treated with 30 ml methanol and 5 ml concentrated sulfuric acid, boiled for 6 h, cooled to 20°, and neutralized with excess 50% aqueous potash. The product was extracted with chloroform, the extract dried with magnesium sulfate, the chloroform removed under vacuum, and the residue distilled under vacuum to give 1.26 g (55%) of VIIa. Analogously, 0.98 g (49%) of VIIb was obtained from 3.18 g (0.01 mole) of VIb. The constants and elementary analyses of VIIa and VIIb are given in Table 1.

Methyl ω-[4-(2-Oxoheptyl)-1-piperazinyl]enanthate (VIIIa). A solution of 2.28 g (0.01 mole) VIIa, 1.5 g (0.011 mole) 1-chloro-2-heptanone and 3 g (0.03 mole) triethylamine in 50 ml benzene was boiled for 10 h. The cooled reaction mixture was treated with 10 ml of 50% aqueous potash solution. The aqueous layer was extracted with benzene, the extract was dried with magnesium sulfate, the benzene was evaporated off *in vacuo*, and the residue was fractionally distilled under vacuum, to give 2.15 g (63%) of VIIIa. Analogously, 2.1 g (67%) of VIIIb was obtained from 2 g (0.01 mole) of VIIb. The constants and elementary analyses of VIIIa and VIIIb are given in Table 1.

Methyl ω-[4-(2-Hydroxyheptyl)-1-piperazinyl]enanthate (IXa). A solution of 1.7 g (0.005 mole) of VIIIa in 40 ml methanol was cooled to 0° and treated with a cooled (0°) solution of 5.1 g (0.134 mole) sodium borohydride in 80 ml methanol. The mixture was stirred at room temperature for 1 h, cooled to 0°, again treated with a solution of 5.1 g (0.134 mole) sodium borohydride in 80 ml methanol, stirred at 0° for 20 min and at room temperature for 40 min, and evaporated to dryness with benzene. The benzene was evaporated off and the residue distilled under vacuum to give 1.3 g (75%) of IXa.

Analogously, 1.2 g (77%) of IXb was obtained from 1.56 g (0.005 mole) of VIIIb. The constants and elementary analyses of IXa and IXb are given in Table 1.

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EFFECT OF THE NEW ANTIHISTAMINIC AGENT PHENCAROL ON EMBRYOGENESIS IN WHITE RATS

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A number of quinuclidine derivatives have been synthesized and studied at the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry. One of these, viz., quinuclidyl-3-diphenylcarbinol hydrochloride, is not inferior to diprazin (pipolphen) and is superior to diphenylhydramine in its antihistamine activity [1]. Under the name phencarol, this compound was recommended in 1975 by the Pharmacological Committee of the USSR Ministry of Public Health for use as an antihistaminic agent in medical practice.

We have studied the ability of phencarol to pass through the placental barrier and its effect on intrauterine development when administered to pregnant female white rats.

EXPERIMENTAL

The experiment was performed on nonlineal white rats. Females weighing 180-200 g were mated with males in a ratio of two females per male. The first day of pregnancy was taken to be the day on which spermatozoa were detected in vaginal smears. The compound was administered in the form of a suspension in starch gel by means of a stomach probe. This was done at different times during pregnancy. Control animals received the corresponding volume of gel.

To investigate the ability of phencarol to pass through the placental barrier, we administered the compound labeled with tritium in the quinuclidine nucleus (specific radioactivity 6.8 mCi/g) at a dose of 50 mg/kg on the 13th day of pregnancy. After 3 h, the animals were sacrificed and the radioactivity of the mother's blood and the embryonic tissues (including the amnion) was investigated.

The effect of phencarol on intrauterine development was investigated by administering the compound once between the first and 15th day of pregnancy. The phencarol was administered in a subtoxic dose, viz. 300 mg/kg. The experiment was performed on 310 pregnant females, 209 receiving phencarol and 101 serving as a control.

To investigate the effect of the compound on embryogenesis upon prolonged application, it was administered every day from the first to the 19th day of pregnancy at the maximum tolerable dose (for repeated administrations), viz., 110 mg/kg. Another group received diprazin, also at the maximum tolerable dose (90 mg/kg).

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