SYNTHESIS AND BIOLOGICAL ACTIVITY OF ADAMANTANE DERIVATIVES. VI. ANTIINFLAMMATORY ACTION OF PYRIDINECARBOXYLIC ACID ADAMANTYLAMIDES

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The antiinflammatory action of several N-adamantylamides of isonicotinic and nicotinic acid has been disclosed in the patent literature [1]. The action of adamantyl-substituted amides of the 1 oxides of pyridinecarboxylic acids has not been studied, but it is known that conversion of isonicotinic acid hydrazide into its 1 oxide reduces its toxicity without altering its antitubercular activity [2]. It is also known that nicotinic acid diethylamide is excreted from the organism in the form of its 1 oxide [3]. In view of this, it would be of interest to study the antiinflammatory, analgesic and antipyretic activity of the following compounds:

R_1–NHCO–R_2

R_1 \ R_2					
Ad-[4]	I	VI	XI	XIV	-
Ad-C$_6$H$_4$- [5]	II	VII	XII	XV	XIX
Ad-CH(CH$_3$)-[6]	III	VIII	-	XVI	XX
Ad-CH$_2$-	IV	IX	-	XVII	XXI
Ad-(CH$_2$)$_2$-	V	X	XIII	XVIII	XXII

Ad = 

The starting 1-(2-aminoethyl)adamantane is prepared by reducing adamantane-1-acetamide with lithium aluminum hydride.

Amides I-XXII (Table 1) are formed by reacting pyridinecarboxylic acid chlorides with the calculated amount of the corresponding amine in pyridine solution. The technique used to test for antiinflammatory activity has been described in [7]. The data are given in Table 2.

As can be seen from Table 2, there is no correlation between structure and the degree of suppression of serotonin edema. The antiinflammatory action of the test compounds is probably due to the pyridinecarboxamide residue.

The compounds containing a p-adamantylphenyl group (XII, VII, II, XV, and XIX) proved to have the highest analgesic activity, this activity increasing on passing from isonicotinic to picolinic acid. Introduction of an oxygen atom into the 1 position of the pyridine ring leads to a decrease in analgesic activity.

Substituted picolinamide XIII has the highest antipyretic activity. Amides in which there is a phenylene or monomethylene group between the adamantane nucleus and the amide nitrogen atom all give a large temperature decrease.

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TABLE 1. Properties of Adamantyl-Substituted Pyridinecarboxamides

Compound	Yield (%)	Melting point (deg)*	Found (%)	Empirical formula	Calculated (%)
I	63,2	132—133	11,06, 11.14	$C_{16}H_{20}N_2O$	10,94
II	61,8	230—1	7,59, 7,83	$C_{22}H_{24}N_2O \cdot HCl$	7,60
III	57,0	215—7	8,93, 8,88	$C_{18}H_{24}N_2O \cdot HCl$	8,74
IV	33,3	258—60	9,14, 9,27	$C_{17}H_{22}N_2O \cdot HCl$	9,13
V	50,0	229—31	8,52, 8.67	$C_{18}H_{24}N_2O \cdot HCl$	8,74
VI	50,7	131—2	10,74, 10,82	$C_{16}H_{20}N_2O$	10,94
VII	73,0	272—4	7,87, 7,77	$C_{22}H_{24}N_2O \cdot HCl$	7,60
VIII	49,8	149—50	9,91, 10,07	$C_{18}H_{24}N_2O$	9,86
IX	65,3	111—2	10,22, 10.11	$C_{17}H_{22}N_2O$	10,37
X	52,2	84—6	9,82, 9,94	$C_{18}H_{24}N_2O$	9,86
XI	32,3	104—6	10,87, 11,06	$C_{16}H_{20}N_2O$	10,94
XII	49,2	214—6	7,87, 8,02	$C_{22}H_{24}N_2O \cdot HCl$	7,60
XIII	29,8	330—2	8,86, 9,02	$C_{18}H_{24}N_2O \cdot HCl$	8,75
XIV	34,4	215—7	9,51, 9,26	$C_{16}H_{20}N_2O \cdot HCl$	9,09
XV	55,2	298—300	7,14, 7,32	$C_{22}H_{24}N_2O_2 \cdot HCl$	7,29
XVI	37,0	290—2	7,94, 8,07	$C_{18}H_{24}N_2O_2 \cdot HCl$	8,33
XVII	70,0	200—2	9,65, 9,85	$C_{17}H_{22}N_2O_2 \cdot HCl$	9,79
XVIII	37,0	187—9	8,57; 8,64	$C_{18}H_{24}N_2O_2 \cdot HCl$	8,33
XIX	23,6	230—2	7,02, 7,14	$C_{22}H_{24}N_2O_2 \cdot HCl$	7,29
XX	65,0	290—2	8,73, 8.62	$C_{18}H_{24}N_2O_2 \cdot HCl$	8,33
XXI	41,7	289—1	8,92. 8,99	$C_{17}H_{22}N_2O_2 \cdot HCl$	8,70
XXII	67,0	230—2	7,99, 8,14	$C_{18}H_{24}N_2O_2 \cdot HCl$	8,33

*Compound I was crystallized from n-hexane; II-V, VII and XII-XXII (hydrochlorides) from water; VI, X and XI from n-heptane; and VIII and IX from alcohol.

TABLE 2. Pharmacological Action of Pyridinecarboxylic Acid Adamantylamides

Compound	LD_{50} (mg/kg)	Depression of serotonin edema (%)	Elevation of pain threshold (%)	Maximum temperature decrease (deg)	Compound	LD_{50} (mg/kg)	Depression of serotonin edema (%)	Elevation of pain threshold (%)	Maximum temperature decrease (deg)
I	325	38	37	0,6	XII	980	37	256	0
II	1500	32	97	2,2	XIII	750	4	0	2,8
III	910	50	81	1,4	XIV	150	26	24	0,4
IV	650	38	26	1,7	XV	1150	6	33	1,2
V	570	50	47	2,0	XVI	225	1	57	0,1
VI	910	39	56	1,0	XVII	350	21	25	1,6
VII	700	40	144	1,3	XVIII	225	40	40	1,2
VIII	1500	2	107	0,6	XIX	700	60	0	0
IX	1500	40	0	1,7	XX	165	40	52	1,2
X	530	50	33	1,0	XXI	265	51	11	1,4
XI	1000	5	36	0	XXII	360	32	34	0,7

The toxicity of the test compounds varies over a wide range (150-1500 mg/kg), the 1 oxides being more toxic than the corresponding pyridine bases. The only exceptions to this are amides VII and XV.

EXPERIMENTAL

1-(2-Aminoethyl)adamantane. A suspension of 19.3 g of adamantane-1-acetamide in 200 ml anhydrous ether was added over 2 h to a stirred suspension of 4.2 g lithium aluminum hydride in 300 ml ether. The mixture was boiled for 55 h, treated with water to decompose excess hydride, and filtered. The filtrate was evaporated and the residue distilled at 97-98°/2 mm to give 13.6 g (76%) of product. Found, %: N 7.79, 7.91. $C_{12}H_{21}N$. Calculated, %: N 7.82.

Amides I-XXII. A mixture of 0.05 mole of the pyridinecarboxylic acid and 20 ml thionyl chloride was boiled for 2 h. The excess thionyl chloride was distilled off under vacuum and the residue dissolved in 50 ml anhydrous puridine. The solution was stirred at 0° while adding a solution of 0.05 mole of the corresponding amine in 50 ml pyridine over 1 h. The

mixture was left overnight, the solvent distilled off under vacuum, and the residue washed with water and crystallized. Data on the compounds obtained are given in Table 1.

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FLUOROSTEROIDS.

IV. A STUDY OF THE HYDROLYTIC FISSION REACTION OF THE 16α,17α-OXIDE RING IN THE 5-BROMO-6-FLUOROPREGNANE SERIES

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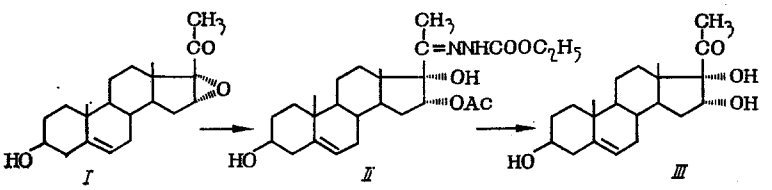
In the course of an investigation on the synthesis of 6-fluoro-16α,17α-dihydroxypregnanes, which are intermediates in the synthesis of highly active corticosteroids such as flunizolone acetonide, we studied the conversion of 5α-bromo-6β-fluoro-16α,17α-epoxypregnan-3β-ol-20-one (I) into 5α-bromo-6β-fluoropregnane-3β,16α,17α-triol-20-one (IV) and its 16α, 17α-acetonide (VI). From the methods of forming 16α,17α-cis diols described in the literature starting from 16α,17α-epoxysteroids one of the most promising is the method proposed by V. Petrov and coauthors [1] and modified by A. A. Akhrem and A. V. Kamernitskii [2, 3]. This method includes the interaction of 20-keto-16α,17α-epoxypregnanes with carbethoxyhydrazine in acetic acid [1-3] or aqueous dioxan solution containing sulfuric acid [4]. On carrying out the reaction in acetic acid the 16 acetate (II) was formed which, after saponification and removal of carbethoxyhydrazone protection by heating with pyruvic acid, was converted into the ketodiol (III) according to the following scheme:



In the second variant (in aqueous dioxan solution containing sulfuric acid) (III) was formed in one step in 78% yield.

On investigating the latter variant with a series of 5α-bromo-6β-fluoro substituted pregnanes we established that the carbethoxyhydrazone of ketoepoxide (V), which is first formed during the reaction, underwent cis fission of the epoxide ring and was converted into the carbethoxyhydrazone of ketodiol (VI). In this way up to 70% of the latter and only a small quantity of diol (VII) were contained in the reaction mixture after 20 h [chromatographic check on silufol using (V-VII) as reference markers].

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