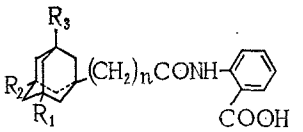
SYNTHESIS AND BIOLOGICAL ACTIVITY OF ADAMANTANE DERIVATIVES

II. N-(1-ADAMANTOYL)-ANTHRANILIC ACIDS

G. N. Danilenko, N. A. Mokhort, and F. P. Trinus

UDC 615.276:547.583.5].012.1

It was previously shown [1] that derivatives of N-[(1-adamantoyl)-phenyl]anthranilic acid display anti-inflammatory activity (by the formalin edema test), the introduction of the adamantyl residue noticeably reducing toxicity. In this connection it was of interest to study also the anti-inflammatory action of N-adamantoyl derivatives of anthranilic acid. With this objective, a series of compounds of the following structure was synthesized:



n = 0. I, $R_1 = R_2 = R_3 = H$; II, $R_1 = CH_3$, $R_2 = R_3 = H$; III, $R_1 = CH_3$, $R_2 = CH_2Br$, $R_3 = H$; IV, $R_1 = R_2 = R_3 = CH_3$; V, $R_1 = 3'4' = (CH_3)_2C_6H_3$, $R_2 = R_3 = H$.

n = 1. VI, $R_1 = R_2 = R_3 = H$; VII, $R_1 = Br$, $R_2 = R_3 = H$.

Information on the starting adamantanecarboxylic acids is given in the review of [2]. To prepare the amides, the acid chloride of the appropriate adamantanecarboxylic acid was mixed with anthranilic acid in a 1:2 molar ratio. The reaction was conducted in benzene solution at room temperature for 12 h. Then 10% hydrochloric acid was added to the reaction mixture, it was mixed well, the benzene layer was separated, and it was extracted several times with 5% sodium hydroxide solution. The combined alkaline extracts were acidified with 10% hydrochloric acid, and the precipitate of amide which fell was collected.

The toxicity of all the compounds synthesized was studied on one-time intraperitoneal injection to mice. Experiments on study of anti-inflammatory activity were carried out on rats of both sexes, weighing 160-220 g. Formalin and serotonin were selected as the provoking agents; this made it possible to study the effect of the synthesized compounds on the various links in the development of an acute inflammatory reaction [3-5]. The usual procedures in study of formalin or serotonin edema [6, 7] were used thereupon. Moreover, analgesic activity was evaluated by the method of varying the pain sensitivity threshold in mice upon hot contact paw irritation [8]. In the pharmacological tests, doses corresponding to $^1/_{10}$ LD_{50} for mice were used. The data are given in Table 1.

As is evident from Table 1, the tested amides inhibit formalin edema far more poorly than serotonin edema. Probably these amides are capable of directly inhibiting the inflammatory activity of serotonin or of blocking the serotonin receptors of the vascular wall.

The degree of suppression of serotonin edema correlates poorly with the pK values of the corresponding adamantanecarboxylic acids. Probably the geometry of the molecule plays a larger role. Introducing one methyl group into the adamantane nucleus (II) leads to a considerable increase in activity as compared

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Kiev Scientific-Research Institute of Pharmacology and Toxicology. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 10, pp. 15-17, October, 1973. Original article submitted September 19, 1972.

TABLE 1. Properties of N-(1-Adamantoyl)-anthranilic Acid Derivatives

Compound	Yield (%)	mp (deg)	N Found, %	Empirical formula	N Calc., %	LD_{50} (mg/kg)	Edema inhibition (%)		Elevation of pain sensitivity threshold
							formalin	serotonin	
I	53,6	217—218	4.54,4.72	$C_{18}H_{21}NO_3$	4.68	70	27	34	B 1,7-fold
II	65,2	144—145	4.17,4.21	$C_{19}H_{23}NO_3$	4.47	145	34	60	B 1,8 »
III	70	158—159	3.40,3.48	$C_{20}H_{24}BrNO_3$	3.45	620	0	52	None
IV	48,4	196—197	3.94,4.07	$C_{21}H_{27}NO_3$	3.81	70	0	32	B 1,1-fold
V	57,2	191—193	3.25,3.41	$C_{26}H_{29}NO_3$	3.46	220	0	20	None
VI	71,8	173—174	4.32,4.50	$C_{19}H_{23}NO_3$	4.47as above	800	0	57	»
VII	51,4	159—161	3.50,3.58	$C_{19}H_{22}BrNO_3$	3.57	165	22	6	B 1,7

Notes: Compounds I and VI were crystallized from ethyl acetate; II, III, and IV, from a mixture of petroleum ether and benzene; VII, from methanol; V, from aqueous methanol.

with that of I. Introducing three methyl groups does not break up the symmetry of the substituent, and the activities of I and IV coincide. The identical activity of the isomeric compounds II and VI causes surprise.

It is interesting to note the marked analgesic action of I, II, and VII. Among adamantane derivatives, such action has been noted only in esters of aminopropanediol or 1-hydroxymethyladamantane [9].

LITERATURE CITED

1. F. N. Stepanov, N. A. Mokhort, G. I. Danilenko, et al., Khim.-Farm. Zh., No. 10, 9 (1971).
2. S. Landa, and Z. Weidenhofer, in: Sbornik Vysoke Školy Chem.-Technol., Prague (1971), Vol. D22, p. 7.
3. C. V. Winder, J. Wax, and M. Welford, J. Pharmacol. Exp. Ther., 148, 3 (1965).
4. S. M. Shegel', Trudy Dushanbinsk Med. Inst., 49, 59 (1961).
5. D. A. Rowley and E. P. Benditt, J. Exp. Med., 103, 339 (1956).
6. F. P. Trinus and N. A. Mokhort, Farmakol. i Toksikol., No. 3, 306 (1971).
7. N. A. Mokhort, F. P. Trinus, and G. A. Get'man, Vrach. Delo, No. 11, 124 (1971).
8. E. Komlas, F. Porzasz, and J. Knoll, Acta Physiol. Acad. Sci. Hung., 1, 77 (1950).
9. J. A. Pedrazzoli and L. Dall'Asta, Farmaco Ed. Sci., 25, 822 (1970).