SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF STRUCTURAL ANALOGS OF 1-(3-DIMETHYLAMINOPROPIONYL)-4-METHOXYBENZENE

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1-(3-Dimethylaminopropionyl)-4-methoxybenzene (Ib) shows high antiinflammatory activity (AA) and is little toxic [2]. With the aim of studying the relationship between chemical structure and AA, and also of searching for new medicines, we have studied analogs of Ib, aminoketones (Ic-e), which up to now have not been studied for AA. For answering the question whether the AA is shown by aminoketones Ic-e or by their metabolites, we have studied the metabolism of the most active aminoketone Ic in the organism of the rabbit and the AA of its metabolites III and IV.

p-ROC_6H_4(Ia-e II — IV)
Ia-e R=H(a), Me(b), Et(c), Pr(d), Bu(e);
X=$COCH_2CH_2NMe_2$;
II — IV: X=$COCH_2CH_2Cl$(II), $COCH_2CH_2NHMe$(III), $CH(OH)CH_2CH_2NMe_2$(IV), R=Et(II — IV).

Aminoketone III was synthesized by reacting $MeNH_2$ with chloroketone II. Aminoalcohol IV was prepared by reduction of aminoketone Ic with $NaBH_4$ in MeOH.

The structure of the novel compounds prepared was confirmed by UV, IR, and PMR spectral data; compounds Ia [4], Ic-e [3], and II [6] were described earlier.

EXPERIMENTAL (CHEMICAL)

UV spectra were recorded on a Specord UV-VIS spectrometer (FRG) in ethanol, IR spectra on a Specord M-80 spectrometer (FRG) in KBr disks, and PMR spectra on a Tesla BS-487C spectrometer (80 MHz, Czechoslovakia) in deuteromethanol with TMS as internal standard.

Data of elemental analyses corresponded with calculated values.

Hydrochloride of 1-(3-dimethylaminopropionyl)-4-ethoxybenzene (III). A solution of 10.6 g (50 mmole) of chloroketone II and 6.2 g (200 mmole) of $MeNH_2$ in 80 ml of benzene is stored at 20°C for 10 days, extracted with Na_2CO_3 solution, dried over Na_2SO_4, the benzene is evaporated under vacuum, the residue is dissolved in acetone, dry HCl is bubbled through the solution, the precipitate is separated off, and recrystallized from acetone. Yield 7.9 g (65%) of the hydrochloride of III, $C_{12}H_{17}NO_2 \cdot HCl$, mp 143-156°C. UV spectrum, λ_{max}, nm (lg ε): 220 (4.03), 276 (4.26). IR spectrum, ν_{max}, cm^{-1}: 1666 (C=O), 3324 (NH). PMR spectrum, δ, ppm: 1.38 t (3H, CH_3, J ~ 7 Hz), 2.10 s (3H, CH_3N), 3.25-3.56 m (4H, CH_2CH_2), 4.08 q (2H, CH_2O, J ~ 7 Hz), 6.93 d (2H, 3-H, 5-H, J ~ 9 Hz), 7.92 d (2H, 2-H, 6-H, J ~ 9 Hz).

Hydrochloride of 3-dimethylamino-1-(4-ethoxyphenyl)-1-propanol (IV). To a solution of 7.7 g (30 mmole) of the hydrochloride of aminoketone Ic in 50 ml of MeOH is added at 0-5°C 1.5 g (40 mmole) of $NaBH_4$, the mixture is stirred at 20°C for 2 h, 100 ml of water is added, MeOH is evaporated under vacuum, the residue is extracted with benzene, dry HCl gas is bubbled through the dried extract, the precipitate is separated off, and recrystallized from a 1:1 mixture of acetone and 2-propanol. Yield 5.9 g (76%) of the hydrochloride of IV, $C_{13}H_{21}NO_2 \cdot HCl$, mp 205-207°C. UV spectrum, λ_{max}, nm (lg ε): 226 (4.02), 268 (shoulder), 263 (3.38), 270 (shoulder). IR spectrum, ν_{max}, cm^{-1}: 3480 (OH). PMR spectrum, δ, ppm: 1.38 t (3H, CH_3 J ~ 7 Hz), 1.95-2.20 m (2H, CH_2), 2.88 s (6H, CH_3H), 3.09-3.40 (2H, CH_2N), 4.00 q (2H, CH_2O, J ~ 7 Hz), 4.11-4.40 m (1H, CH), 6.83 d (2H, 3-H, 5-H, J ~ 9 Hz), 7.23 d (2H, 2-H, 6-H, J ~ 9 Hz).

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TABLE 1. Acute Toxicity and AA of the Hydrochlorides of Compounds Ia-e, III, and IV in the Case of Subcutaneous Administration at a Dose of 50 mg/kg

Compound	LD_{50}, mg/kg	Average percentage of reduction of the inflammation	
		carrageenan	bentonite
Ia	553 (490—590)	29,2	36,2
Ib	258 (192—307)	47,1	65,0
Ic	160 (114—224)	68,0	89,5
Id	198 (175—211)	59,9	65,9
Ie	146 (126—169)	49,3	68,9
III	380 (325—445)	10,0	25.7
IV	1650 (1138—2393)	13,4	14,7
Lysine acetylsalicylate	1000 (890—1130)	18,4 63,2*	8,6 58,4*

Note. In parentheses the limits of variation for $p \leq 0.05$. Asterisk means dose 200 mg/kg.

EXPERIMENTAL (PHARMACOLOGICAL)

The compounds (hydrochlorides) under investigation were administered subcutaneously as 1% aqueous solutions. We used mongrel white mice weighing 18-25 g, white rats weighing 150-230 g, and rabbits of the race chinchilla weighing 2.5-3.5 kg.

The acute toxicity for mice was determined by the method of Litchfield and Wilcoxon, modified by Roth [1]. The AA was studied by using the models of carrageenan [8] and bentonite [5] edema of rat paws. Table 1 gives the average percentage of reduction of the edema (in comparison with the control) at 1, 2, 3, and 5 h after administration of the compounds under investigation.

The metabolism of aminoketone Ic was studied in rabbits by means of investigating the composition of the urine, which was collected for 2 days (till ending of the excretion of metabolites) after a single subcutaneous administration of the hydrochloride of Ic at a dose of 16 mg/kg (1/10 of LD_{50} for mice). The urine was kept at −20°C, then acidified with HCl to pH 1.0, extracted with ether, the acid layer was alkalized with NaOH to pH 10.0, and extracted with ether. By TLC on Silufol plates (Czechoslovakia) in the concentrated ethereal extract were found three compounds that are not natural metabolites. The R_f values in the system conc. NH_4OH—ethanol, 1:9 (visualization with iodine vapor) are: 0.32 (III), a small amount; 0.54 (IV), the main metabolite; and 0.60 (Ic). The alkaline layer was acidified with H_2SO_4 to pH 1.0, kept at 90°C for 8 h, neutralized with NaOH to pH 7.0, and extracted with CH_2Cl_2. In the concentrated extract on the plates mentioned above we identified compound Ia, R_f 0.42 in the same system.

It was found that the highest AA among aminoketones Ic-e is displayed by ethoxy derivative Ic, which considerably surpasses in that respect lysine acetylsalicylate, and the other aminoketones Ib, d, e differ little with respect to their AA and acute toxicity. Replacement of the alkoxy substituent in aminoketones Ic-e by hydroxyl (Ia), just as reduction of the ketone group to hydroxyl (IV), leads to a sharp lowering of AA and toxicity (see Table 1).

It was shown that the high AA is displayed by the dimethylaminoketones themselves and not by their metabolites because dimethylaminoketone Ic undergoing in the organism of the rabbit reduction, O- and N-dealkylation, gives less active (and little toxic) compounds Ia, III, and IV (see Table 1). The found courses of the metabolism of β-dimethylaminoketone Ic correspond with those of earlier investigated α- [7] and β-dialkylaminoketones [2].

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF [7-AMINO-S-TRIAZOLE[1,5-C]PYRMIDIDYL-5]-THIOACETIC ACID DERIVATIVES

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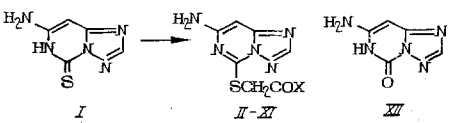
The s-triazole[1,5-c]pyrimidines constitute a limited and relatively little-studied class of compounds. Nevertheless, substances have been found among them that display a broad range of pharmacological activity, including bronchodilating [4], sedative, hypotensive [6], anti-inflammatory, and analgesic [5, 6] properties. This makes the synthesis and search for new biologically-active substances in the s-triazole[1,5-c]pyrimidine series particularly worthwhile.

The present work deals with the synthesis of (7-amino-s-triazole[1,5-c]pyrimidyl-5)-thioacetic acid (II) and its substituted derivatives (compounds III-XI) and cites the results obtained from investigating their antitumor, antiviral, and radiation-protective effects.

5(6H)Thio-7-amino-s-triazole[1,5-c]pyrimidine (I), which the authors have obtained in a previous investigation [2], was used as the starting reagent for the synthesis of compounds II-XI.

Acid II was synthesized by the reaction of compound I with chloro(bromo)acetic acid, the action of triazolepyrimidinethione with chloroacetic acid in 2 N NaOH at room temperature producing a low yield (~30%). When the reaction temperature was increased, a second product was formed (in addition to acid II), which was identified from analytical and spectral data as 5(6H)oxo-7-amino-s-triazole[1,5-c]pyrimidine (XII). Its IR spectrum contained an intensive carboxyl group absorption band at 1770 cm^{-1}. Proton signals for the pyrimidine and triazole rings and the amino group appeared in the PMR spectrum. Mass spectrometry revealed that the most intensive peak belongs to the M^+ (m/z 151) molecular ion, whose fragmentation occurs with the formation of the $M-HNCO^+$ (m/z 108) ion. When bromoacetic acid was used instead of chloroacetic, compound II was obtained with a yield of more than 70%.



I II-XI XII

X=OH (II), OMe (III), OEt (IV), NH_2 (V), NHMe (VI), NMe_2 (VII), $NHNH_2$ (VIII), $NHN=CHC_6H_4NO_2$-4 (IX), $NHN=CNC_6H_4OH$-2 (X), $NHN=CHCBr\cdot CHC_6H_5$ (XI)

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