SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF DERIVATIVES OF 2-AMINOTHIOPHENE-5-ACETIC ACIDS

I. N. Fedorova, R. D. Syubaev, V. I. Shvedov,
L. M. Alekseeva, G. Ya. Shvarts, and M. D. Mashkovskii

UDC 615.276].012.07

Despite the large number of non-steroidal antiinflammatory agents used in medicine, work is actively continuing on a search for new, better preparations, lower in toxicity and with minimum side effects [4].

One group of compounds which shows promise in this area consists of arylacetic acid derivatives; this group has contributed a large number of pharmacologically active substances, many of which are in use in medical practice [2, 15-17].

Thiophene is an isoelectric analog (isostere) of benzene, and in some cases the replacement of a benzene ring by a thiophene ring does not cause a significant decrease in biological activity. Thus, thiophenealkane acids [11] and aminothiophene derivatives have been reported to possess antiinflammatory activity [8, 21].

Of interest was the synthesis and study of the antiinflammatory activity of derivatives of aminothiopheneacetic acids.

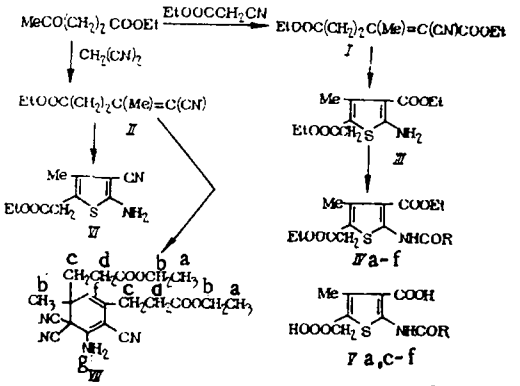
In contrast to monosubstituted thiophenes, which can readily be obtained by direct substitution reactions (either by metallization or by electrophilic substitution) [13], the synthesis of polysubstituted thiophenes is generally more complex, involving many stages. Recently, considerable success has been achieved in the development of methods of synthesis of polyfunctional derivatives of thiophene [7, 12, 13, 19, 20]. These methods are based not on the successive multistage introduction of substituents into the thiophene heterocycle, but on the condensation of two or more acyclic fragments to give a thiophene with two or three functional groups on the ring.

Continuing the study of synthetic routes to polyfunctional thiophenes [5, 6], we have studied the possibility of using Gewald's reaction [1] for the synthesis of substituted thiopheneacetic acid. The Knoevenagel—Cope condensation of the ethyl ester of levulinic acid with cyanoacetic ester or dicyanomalonic acid gave the ethyl esters of 2-cyano-3-methyl-2-hexene-1,6-dicarboxylic acid (I) and 4-methyl-5,5-dicyano-4-pentenecarboxylic acid (II). Heating the substituted acrylonitrile (I) with sulfur in ethyl alcohol in the presence of a secondary amine gave the ethyl ester of 2-amino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic acid (III), characterized as the N-acyl derivatives (IVa-f). The esters IVa, c-f were selectively hydrolyzed to the corresponding dicarboxylic acids (Va, c-f) without further purification. The reaction of the ethyl ester II with elemental sulfur in the presence of base is complicated because of the tendency of II to dimerize to 1-amino-2,2,6-tricyano-3-methyl-3,5-diethoxycarbonylethyl-4,6-cyclohexadiene (VII). This reaction, carried out in ethyl alcohol in the presence of piperidine, but without elemental sulfur, at 18-20°C, gave VII in 93.5% yield. Using the Gewald reaction conditions, with piperidine as catalyst, the thiopheneacetic acid derivative (VI) was formed in 41% yield. We found that in the Gewald reaction, use of a weaker base than piperidine (morpholine, piperazine, N-methylpiperazine) increased the yield of the thiopheneacetic acid derivative VI from 41 to 60.3%.

The structures of the thiophenes IVb, Va, c-f, and VI were confirmed by elemental analysis and infrared spectroscopy. The infrared spectra of the acylaminothiophenes IV[illegible]a, and c-f contain absorption bands with ν_{max} (cm^{-1}): 3220-3280 (NH) and 1630-1750 (CONH), and the infrared spectrum of VI: 3420, 3340, and 3215 (NH_2), 2220 (CO), 1710 (COOEt), and 760 (thiophene ring). The structure of VII was obtained by comparison with literature data [3]. The molecular weight of VII corresponds to that of a dimer of the ester II. The PMR spectrum of VII has the following signals (δ, ppm): Ha, 1.26 t ($2CH_3$); Hb, 1.43 s (CH_3); Hc and

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 19, pp. 39-45, January, 1986. Original article submitted October 23, 1984.

0091-150X/86/2001-0023$12.50

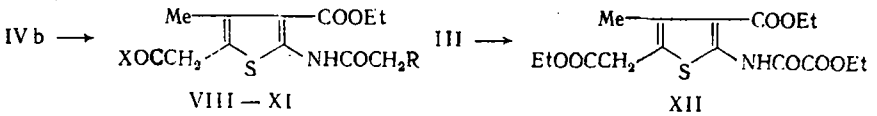


IVa, Va: R = Me; IVb: R = CH_2Cl; IVc, Vc: R = Ph; IVd, Vd: R = Bz; IVe, Ve: R = CH = CHPh; IVf, Vf: R = C_6H_4Cl-p

d, 1.6-2.6 m ($2CH_2CH_2$); He, 4.13 q ($2CH_2$); Hf, 5.14 s (H); Hg 5.62 s (NH_2). The infrared spectrum of VII contains absorption bands with ν_{max} (cm^{-1}): 3220-3380 (NH_2), 2220 (C≡N), and 1655-1730 (CO of the ester group).

Thus, we have successfully developed a method for the preparation of substituted 2-amino-5-thiopheneacetic acids based on a readily available ester of levulinic acid, which can be synthesized, for example, from furfuryl alcohol [22]. The polyfunctional thiophenes III-VI which we prepared can be regarded on the one hand as thiophene analogs of substituted phenylacetic acids and, on the other, as anthranilic acid analogs.

For pharmacological screening, a number of derivatives of thiopheneacetic acids III and VI were prepared. Heating IVb with N-methylpiperazine or piperidine gave the aminoamides (VIII and IX). One carbethoxy group of compound IX was selectively hydrolyzed and the half-ester of the dicarboxylic acid (X) was isolated as the hydrochloride.

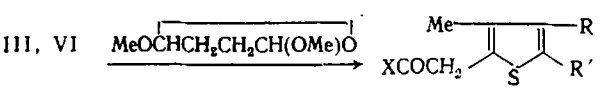


VIII — XI

VIII: R = $N(CH_2CH_2)_2NMe \cdot 2HCl$, X = OEt; IX: R = NC_5H_{10}, X = OEt; X: R = = $NC_5H_{10} \cdot HCl$, X = OH; XI: R = X = $N(CH_2CH_2)_2O$.

The reaction of IVb with morpholine led to the replacement of the chlorine atom by a morpholine group, and also the formation of a morpholide at the acetic acid group, to give the morpholide of 2-morpholino-methylcarbonylamino-2-ethoxycarbonyl-4-methyl-5-thiopheneacetic acid (XI). Refluxing the aminothiophene III with diethyloxalate gave the ethyl ester of 2-ethoxalylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic acid (XII) in 36% yield.

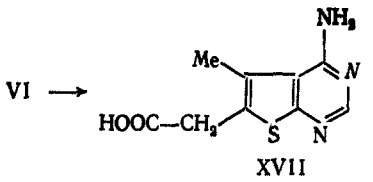
Condensation of the aminothiophenes III and VI with 2,5-dimethoxytetrahydrofuran in boiling AcOH gave chlorine-free dehydrogenated analogs of the drug piprophene [10] — ethyl esters of 2-(1-pyrrolyl)-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic acid and 2-(1-pyrrolyl)-3-cyano-4-methyl-5-thiopheneacetic acid (XIII and XV). Hydrolysis of these esters with aqueous-alkaline base gave the corresponding substituted thiopheneacetic acids (XIV and XVI).



XIII — XVI

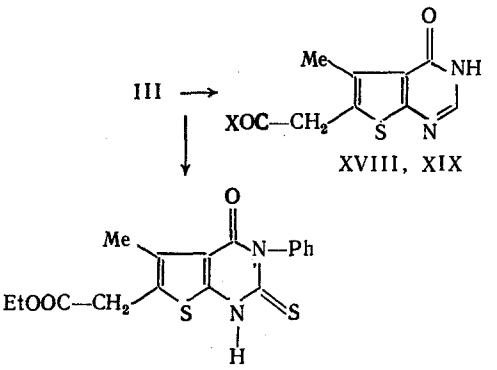
XIII — XVI: R' = pyrrolyl-1; XIII: R = COOEt, X = OEt; XIV: R = COOH, X = OH; XV: R = CN, X = OEt; XVI: R = $CONH_2$, X = OH.

The aminothiophenes III and VI, which have neighboring amino- and carbethoxy(cyan)-groups, are suitable intermediates for the synthesis of substituted thienopyrimidines. Refluxing the aminocyanothiophene VI with formamide in the presence of DMFA and HCOOH led to cyclization of the pyrimidine ring and this was accompanied by transesterification with formic acid, to give the thienopyrimidineacetic acid (XVII).



XVII

The aminocarbethoxythiophene III was also readily converted to the corresponding thienopyrimidine derivatives by reaction with H_2NCHO or phenylisothiocyanate, and the thienopyrimidineacetic acids (XVIII and XX) were also synthesized in this way. Hydrolysis of the ester XVIII led to the formation of the corresponding acids (XIX).



XX

XVIII: X = OEt; XIX: X = OH.

The structures of the thienopyrimidines XVIII, XIX, and XX were confirmed by elemental analysis, infrared, and mass-spectroscopy.

EXPERIMENTAL (CHEMICAL)

Infrared spectra (in mineral oil) were obtained on a UR-10 (GDR) spectrometer, mass-spectra on an MAT-112 (Varian, FRG), PMR spectra were determined in $CHCl_3$ with TMS as a reference using an XL-200 spectrometer (Varian, Switzerland).

Ethyl Ester of 2-Amino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (III). To a mixture of 27.36 g (0.114 mole) of the ethyl ester of 2-cyano-3-methyl-2-hexene-1,6-dicarboxylic acid [14] and 3.69 g (0.115 mole) of sulfur in 55 ml of absolute ethanol was added dropwise 9.5 g (0.11 mole) of piperidine. The mixture was refluxed until all the sulfur had dissolved, the alcohol distilled off, the residue treated with water and extracted with benzene. The benzene extract was dried over $MgSO_4$ and the benzene evaporated to give 23.38 g (75.3%) of III as an oil. Compound III was used for subsequent reactions without further purification.

2-Acetylamino-3-carboxy-4-methyl-5-thiopheneacetic Acid (Va). A mixture of 9.2 g (0.034 mole) of III, 2.78 g (0.034 mole) of sodium acetate, and 50 ml of Ac_2O was refluxed for 5 h. Water (25 ml) was added through the condenser, and refluxing was continued for another 20 min. The reaction mixture was poured onto ice, the oil which separated extracted with benzene, and the benzene extract dried over $MgSO_4$. The benzene was removed, and the residue [9.38 g (0.03 mole) of IVa] refluxed for 1 h with a solution of 4.8 g (0.12 mole) of NaOH in 62 ml of 50% of MeOH. The reaction mixture was cooled, poured into water, and acidified with concentrated HCl. The oil which precipitated was extracted with ether, and the ether extract dried. The ether was distilled off, and the residue recrystallized from water to give 4.8 g (56%) of Va, mp 184-186°C. IR spectrum, ν_{max}, cm^{-1}: 3275 (NH) and 1640 (CONH). Found, %: C 46.87, H 4.15, N 5.13, S 12.44. $C_{10}H_{11}NO_5S$. Calculated, %: C 46.67, H 4.31, N 5.45, S 12.47.

Ethyl Ester of 2-Chloroacetylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (IVb). A mixture of 10.85 g (0.04 mole) of III and 3.8 ml of $ClCH_2COCl$ in 50 ml of dry benzene was refluxed for 1 h. The benzene was removed, the residue triturated with ether, and the precipitate filtered off to give 5.67 g (41%) of IVb (from heptane), mp 118-120°C. IR spectrum, ν_{max}, cm^{-1}: 3220 (NH) and 1670 (CONH). Found, %: Cl 10.10, S 9.04. $C_{14}H_{18}ClNO_5S$. Calculated, % Cl 10.19, S 9.22.

2-Benzoylamino-3-carboxy-4-methyl-5-thiopheneacetic Acid (Vc). A mixture of 7.3 g (0.027 mole) of III and 3.6 ml of PhCOCl was refluxed in 20 ml of dry benzene for 2 h. Water was added to the reaction mixture, the benzene layer separated, and the aqueous layer extracted with benzene. The combined extracts were evaporated, and the residue was refluxed for 50 min with a solution of 4.3 g (0.108 mole) of NaOH in 55 ml of 50% MeOH. The reaction mixture was cooled, poured into water, and acidified with concentrated HCl. The oily material which separated crystallized on standing to give 6.67 g (76.8%) of Vc (from alcohol), mp 230-231°C. IR spectrum, ν_{max}, cm^{-1}: 3280 (NH) and 1640 (CONH). Found, %: C 56.11, H 4.13, S 10.09. $C_{15}H_{13}NO_5S$. Calculated, %: C 56.42, H 4.10, S 10.04.

2-Phenylacetylamino-3-carboxy-4-methyl-5-thiopheneacetic acid (Vd) was obtained by the same method as Vc from a mixture of 10.85 g (0.04 mole) of III and 6.15 g (0.04 mole) of $PhCH_2COCl$, yield 7.73 g (57.8%) (from ethanol), mp 248-250°C. IR spectrum, ν_{max}, cm^{-1}: 3260 (NH) and 1640 (CONH). Found, %: C 57.25, H 4.34, S 10.18. $C_{16}H_{15}NO_5S$. Calculated, %: C 57.64, H 4.54, S 9.62.

2-(Cinnamoyl)-3-carboxy-4-methyl-5-thiopheneacetic Acid (Ve). A mixture of 10.85 g (0.04 mole) of III and 13.26 g (0.08 mole) of cinnamoyl chloride in 200 ml of pyridine was refluxed for 1.5 h, then cooled, poured into water, and extracted with $CHCl_3$. The chloroform layer was separated, treated with HCl, and the chloroform evaporated off. The residue was refluxed for 50 min with 6.4 g (0.16 mole) of NaOH in 85 ml of 50% MeOH, the mixture poured into water and acidified with concentrated HCl. The precipitated material was separated, washed with water, and dried to give 10.42 g of Ve (75.5%) (from ethanol), mp 236-237 °C (decomp.). IR spectrum, ν_{max}, cm^{-1}: 3240 (NH) and 1670 (CONH). Found, %: C 59.00, H 4.32, S 9.33. $C_{17}H_{15}NO_5S$. Calculated, %: C 59.12, H 4.54, S 9.62.

2(p-Chlorobenzoylamino)-3-carboxy-4-methyl-5-thiopheneacetic acid (Vf) was obtained by the same method as Vc from 10.85 g (0.04 mole) of III and 8 ml of p-chlorobenzoyl chloride in 69.9% yield (10 g) (from ethanol), mp 221-222°C. IR spectrum, ν_{max}, cm^{-1}: 3260 (NH) and 1630 (CONH). Found, %: C 51.00, H 3.4, Cl 10.03. $C_{15}H_{22}ClNO_5S$. Calculated, %: C 50.92, H 3.42, Cl 10.02.

1-Amino-2,2,6-tricyano-3-methyl-3,5-diethoxycarbonylethyl-4,6-cyclohexadiene (VII). To 2 g of the ethyl ester of 4-methyl-5,5-dicyano-4-pentenoic acid (bp 135-138°C/0.8 mm Hg) II in 5 ml of absolute ethanol was added dropwise 0.5 ml of piperidine at 18-20°C. The reaction mixture was stirred for 30 min, the precipitated material filtered off and washed with ether to give 1.87 g (93.5%) of VII (from ethanol), mp 154-156°C. Found, %: N 14.43, M^+· 384. $C_{20}H_{24}N_4O_4$. Calculated, %: N 14.56, M 384.

Ethyl Ester of 2-Amino-3-cyano-4-methyl-5-thiopheneacetic Acid (VI). To a stirred suspension of 0.325 g (0.01 mole) of sulfur and 1.92 g (0.01 mole) of II in 5 ml of absolute ethanol at 50-60°C was added dropwise 0.1 ml of N-methylpiperazine. The reaction mixture was heated at this temperature until all the sulfur had dissolved, then cooled and the precipitated material filtered off and washed with ether to afford 1.36 g (60.3%) of IV (from ethanol), mp 118-119°C. IR spectrum, ν_{max}, cm^{-1}: 3420, 3340, and 3215 (NH_2), 2220 (CN), 1710 (CO), and 760 (thiophene ring). Found, %: C 53.62, H 5.23, N 12.59. $C_{10}H_{12}N_2O_2S$. Calculated, %: C 53.54, H 5.39, N 12.49.

Hydrochloride of the Ethyl Ester of 2-(4-Methylpiperazinyl-1-acetylamino)-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (VIII). A mixture of 5.67 g (0.016 mole) of IVb and 20 ml of N-methylpiperazine was refluxed for 1 h, the reaction mixture poured into water, and extracted with benzene. The benzene extract was dried with potassium carbonate and the benzene removed. The residue was dissolved in ethanol and alcoholic HCl added. The hydrochloride was filtered off and washed with ether to give 5.91 g (74.9%) of VIII (from absolute ethanol), mp 207-209°C (decomp.). Found, %: Cl 14.82, M^+· 411. $C_9H_{29}N_3O_5S \cdot 2HCl$. Calculated, %: Cl 14.65, M 411.

Hydrochloride of 2-Piperidinomethylcarbonylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (IX). A mixture of 5.67 g (0.016 mole) of IVb and 20 ml of piperidine was refluxed for 1.5 h, then poured into water and extracted with benzene. The benzene was distilled off, and the residue was refluxed for 50 min with a solution of 2.64 g (0.066 mole) of NaOH in 35 ml of 50% MeOH. When cool, the reaction mixture was poured into water and acidified with concentrated HCl. The oil which separated was extracted with ethyl acetate and the solvent removed to give 3.5 g (53%) of IX (from ethanol), mp 175-176°C. Found, %: Cl 8.85, N 6.53, M^+· 368. $C_{17}H_{24}N_2O_5S \cdot HCl$. Calculated, %: Cl 8.75, N 6.9, M 368.

Morpholide of 2-Morpholinomethylcarbonylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (IX). A mixture of 5.67 g of IVb and 20 ml of morpholine was refluxed for 1.5 h, then poured into water and extracted with $CHCl_3$. The solvent was evaporated and the residue recrystallized from ether to give 2.79 g (39%) of XI, mp 169-170°C (from ethanol). Found, %: C 54.44, H 6.56, N 9.51, $M^{+\cdot}$ 439. $C_{20}H_{29}N_3O_6S$. Calculated, %: C 54.65, H 6.65, N 9.56, M 439.

Ethyl Ester of 2-Ethoxyalylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic Acid (XII). A mixture of 12.1 g of III and 6 ml of diethyloxalate was refluxed for 3 h. The excess diethyloxalate was removed *in vacuo* and the residue allowed to crystallize at room temperature for 48 h. The material was triturated with alcohol, filtered, and washed with water to give 5.96 g (36%) of XII, mp 96-97°C (from heptane). Found, %: C 52.20, H 5.20, S 8.68, $M^{+\cdot}$ 371. $C_{16}H_{21}NO_7S$. Calculated, %: C 51.74, H 5.7, S 8.63, M 371.

2-(Pyrrolyl-1)-3-carboxy-4-methyl-5-thiopheneacetic Acid (XIV). A mixture of 10.1 g (0.037 mole) of III and 7.35 g (0.056 mole) of 2,5-dimethoxytetrahydrofuran in 80 ml of AcOH was refluxed for 1 h. The AcOH was removed and XIII extracted with petroleum ether. The solvent was removed and the residue refluxed for 50 min with a solution of 2 g (0.05 mole) of NaOH in 26 ml of 50% MeOH. When cool, the reaction mixture was poured into water and acidified with concentrated HCl. The precipitated material was separated and washed with water to give 2.49 g (25.2%) of XIV, mp 181-183°C (from water). Found, %: C 54.40, H 4.20, N 5.51, S 12.09. $C_{12}H_{11}NO_4S$. Calculated, %: C 54.33, H 4.18, N 5.28, S 12.09.

Ethyl ester of 2-(pyrrolyl-1)-3-cyano-4-methyl-5-thiopheneacetic acid (XV) was obtained by the same method as XIII in 30% yield, mp 66-68°C (from cyclohexane). Found, %: S 12.11, $M^{+\cdot}$ 274. $C_{14}H_{14}N_2O_2S$. Calculated, %: S 11.7, M 274.

2-(Pyrrolyl-1)-3-carbamoyl-4-methyl-5-thiopheneacetic Acid (XVI). A mixture of 0.27 g of XV and 0.08 g of NaOH in 1.1 ml of 50% MeOH was refluxed for 50 min, then cooled, poured into water, and acidified with concentrated HCl. The precipitated material was separated and washed with water to give 0.1 g (41.3%) of XVI, mp 234-237°C. Found : $M^{+\cdot}$ 264. $C_{12}H_{12}N_2O_3S$. Calculated: M 264.

4-Amino-5-methylthieno[2,3-d]pyrimidine-6-acetic Acid (XVII). A mixture of 2.24 g of VI, 15 ml of formamide, 5 ml of DMFA, and 2 ml of 85% HCOOH was refluxed for 4 h. When cool, the material which precipitated was filtered off and washed with alcohol to give 1.96 g (87.9%) of XVII, mp 267-268°C (from DMFA). IR spectrum, ν_{max}, cm^{-1}: 3120, 3305, and 3410 (NH_2), 1660 (CO), 785 (thiophene ring), and 990 (pyrimidine ring). Found, %: C 47.93, H 4.69, $M^{+\cdot}$ 223. $C_9H_9N_3O_2S$. Calculated, %: C 48.41, H 4.06, M 223.

4-Oxo-5-methylthieno[2,3-d]pyrimidine-6-acetic Acid (XIX). A mixture of 13.38 g (0.049 mole) of III and 100 ml of formamide was refluxed for 3 h, then cooled and poured into water and extracted with ethyl acetate. The solvent was removed and the residue (10.37 g of XVIII) was refluxed with a solution of 3.14 g (0.0785 mole) of NaOH in 40 ml of 50% MeOH for 50 min, then poured into water and acidified with concentrated HCl. Extraction with ethyl acetate and evaporation of the solvent gave 3.78 g (34%) of XIX, mp 277-279°C. IR spectrum, ν_{max}, cm^{-1}: 3100, 3150, 3200 (NH), 1690 (CO), 1000 (pyrimidine ring). Found, %: C 48.36, H 3.25, N 12.98, S 14.13. $C_9H_8N_2O_3S$. Calculated, %: C 48.42, H 3.16, N 12.55, S 14.36.

Ethyl Ester of 2-Thio-3-phenyl-4-oxo-5-methylthieno[2,3-d]pyrimidine-6 Acetic Acid (XX). A mixture of 18.64 g (0.083 mole) of III and 11.8 g (0.088 mole) of phenylisothiocyanate was heated for 13 h at 130°C, then cooled and alcohol added. The precipitated material was separated and washed with alcohol to give 4 g (16%) of XX, mp 245-246°C (from ethanol). IR spectrum, ν_{max}, cm^{-1}: 3100, 3300 (NH), 1680, 1740 (CO), 1200 (C=S). Found, %: C 56.66, H 4.39, N 7.86. $C_{17}H_{16}N_2O_3S_2$. Calculated, %: C 56.64, H 4.47, N 7.77.

PHARMACOLOGICAL STUDY

The acute toxicity of the compounds was studied on male mice weighing 18-20 g; compounds were administered orally. The LD_{50} was determined by the method given in [18].

The antiinflammatory action of the compounds was studied on male rats weighing 100-120 g using models of acute inflammation caused by the subplantar injection of 0.1 ml of 1% carrageenan [23]. The analgesic action was studied on models of the pain of spasms in male mice weighing 20-22 g on intraperitoneal injection of 0.2 ml of 0.75% AcOH [9]. The anti-

TABLE 1. Acute Toxicity, Antiinflammatory, and Analgesic Activity of Derivatives of 2-Amino-5-thiopheneacetic Acid

Compound	Toxicity (LD_{50}, mg/kg)	Antiinflammatory action		Analgesic action	
		ED_{50}, mg/kg	relative activity	ED_{50}, mg/kg	relative activity
IVb	1500	159	0,63	580	0,3
Vc	1000	—	0	356	0,45
Vd	1200	256	0,39	485	0,33
Ve	1000	—	0	670	0,24
VI	950	435	0,23	—	0
VIII	1500	250	0,4	270	0,59
XI	1000	830	0,12	340	0,47
XII	1500	170	0,59	500	0,3
XIV	800	—	0	286	0,56
XVII	1000	113	0,89	340	0,47
XIX	1000	—	0	—	0
XX	1000	—	0	—	0
Acetylsalicylic acid (ASA)	1600	100	1	160	1

inflammatory and analgesic activity of the test compounds were obtained from the magnitude of the ED_{50} — the dose causing suppression of the inflammation reaction in 50% of cases compared with the control. Compounds in doses of 30, 100, and 300 mg/kg were injected 1 h before the induction of inflammation or pain, to groups of 8-10 animals. The activity was compared with that of acetylsalicylic acid, which was assumed to have an activity of one.

From the data presented in Table 1 it can be seen that all the compounds tested had low toxicity, since their LD_{50}'s was in the range 800-1500 mg/kg. Compounds IVb, VIII, and XII differed little in toxicity from acetylsalicylic acid, while the rest were 1.3-2 times more toxic.

Compounds VI, Vd, IVb, VIII, XI, and XVII possess varying amounts of antiinflammatory activity, equivalent to 12-89% of the activity of acetylsalicylic acid. The most active is compound XVII (4-amino-5-methylthieno[2,3-d]pyrimidine-6-acetic acid).

All the compounds, apart from compounds VI, XIX, and XX possess moderate analgesic activity, amounting to 30-50% of the analgesic activity of acetylsalicylic acid. The most active of the compounds was compound VIII [hydrochloride of the ethyl ester of 2-(4-methylpiperazinyl-1)acetylamino-3-ethoxycarbonyl-4-methyl-5-thiopheneacetic acid].

This study has thus established that the derivatives of 2-amino-5-thiopheneacetic acid, which we studied, were not very toxic and were active antiinflammatory and analgesic agents; however, they were less effective than the non-steroid drug acetylsalicylic acid. The most active compound — XVII (4-amino-5-methylthieno[2,3-d]pyrimidine-6-acetic acid) — was approximately as effective as acetylsalicylic acid as an antiinflammatory agent but, like the remaining compounds, had only half the analgesic activity of acetylsalicylic acid.

LITERATURE CITED

1. K. Geval'd, Khim. Geterosikl. Soedin., No. 10, 1299-1315 (1976).
2. R. G. Glushkov, S. S. Liberman, and L. N. Yakhontov, Zh. Vsesoyuz. Khim. O-va im. D. I. Mendeleeva, 15, No. 2, 185-193 (1970).
3. B. A. Rigerte and E. Yu. Gubrinietse, Izv. AN LatvSSR. Ser. Khim., No. 5, 601-603 (1977).
4. G. Ya. Shvarts, Khim.-farm. Zh., No. 9, 22-41 (1980).
5. V. I. Shvedov and A. N. Grinev, Zh. Organ. Khim., 1, No. 12, 2228-2231 (1965).
6. V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 1, 58-61 (1974).
7. V. I. Shvedov and O. A. Safonova, Khim.-farm. Zh., No. 11, 53-56 (1978).
8. H. G. Alperman, Arzneimittel. — Forsch., 20, 293-294 (1970).
9. C. Cashin, W. Dawson, and E. Kitchen, J. Pharm. Pharmacol., 29, 330-336 (1977).
10. R. E. Dionne and S. S. Weber, Drug Intell., 17, 894-897 (1983).
11. H. Fujimura, K. Tsurumi, Y. Hiramaisi, et al., Chem. Abstr., 83, N 188321 (1975).
12. K. Gewald, Z. Chem., 2, 305-306 (1962).
13. S. Gronowitz, Adv. Heterocycl. Chem., 1, 1 (1963).

14. O. Jeger, R. Murza, V. Prelog, et al., Helv. Chim. Acta, 2295-2301 (1954).
15. P. F. Juby, in: Antiinflammatory Agents, R. A. Scherrer and M. W. Whitehouse (eds.), Vol. 1, New York (1974), pp. 91-93.
16. P. F. Juby, Drugs of the Future, 3, 924-925 (1978).
17. P. F. Juby, Ibid., 4, 373-375 (1979).
18. I. Litchfield and F. Wilcoxon, J. Pharmacol. Exp. Ther., 96, 99-113 (1949).
19. C. N. Meltz and R. A. Volkmann, Tetrahedron Lett., 24, 4507-4510 (1983).
20. O. Meth-Cohn, Comprehensive Organic Chemistry, Vol. 3, P. G. Sammes (ed.), Pergamon, Oxford (1979), pp. 789-790.
21. M. Perrissin, C. Lun Duc, F. Bakri-Logeais, and F. Hugnet, Europ. J. Med. Chem., 15, 563-565 (1980).
22. R. Pummerer and W. Gump, Ber. Dtsch. Chem., 56, 999-1008 (1923); R. Pummerer, O. Gugot, and L. Birkofer, Ibid., 68, 480-493 (1935).
23. C. Winter, E. Risley, and G. Nuss, Proc. Soc. Exp. Biol. (N.Y.), 544-545 (1962).

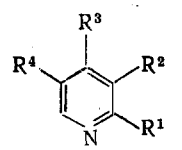
SYNTHESIS AND PSYCHOPHARMACOLOGICAL AND ANTIHYPOXIC ACTIVITY OF SOME β-SUBSTITUTED PYRIDINECARBOXYLIC ACIDS

L. G. Stolyarova, R. A. Akhundov, I. Kh. Rakhmankulova, T. A. Voronina, L. D. Smirnov, and K. M. Dyumaev

UDC 615.272.2.014.425.012.1

A study was recently proposed to test pyridine carboxylic acid derivatives for biological activity, in particular antiinflammatory activity and hypolipodynamic activity. The compounds selected for study were the β-hydroxypyridine carboxylic acids [3, 5, 6], which have a phenolic hydroxyl group in the β-position, characteristic of vitamin B_6 group compounds; in addition, unsubstituted pyrididinecarboxylic acids constitute part of a number of drugs and vitamins.

As a part of the study, we have synthesized some derivatives of 5-hydroxynicotinic acid (II, III), 3-hydroxyisonicotinic acid (IV, V), and 5-bromo- and 5-aminonicotinic acid (VI-IX). The psychopharmacological and antihypoxic activities of these compounds have been studied and compared with those of related compounds — nicotinamide (X), 3-hydroxypyridine (I), and others.



I: $R^1 = R^3 = R^4 = H$, $R^2 = OH$; II: $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = CONH_2$;
III: $R^1 = R^2 = OH$, $R^3 = H$, $R^4 = COOH$; IV: $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = COOH$;
V: $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = COONa$; VI: $R^1 = R^3 = H$, $R^2 = Br$, $R^4 = CONH_2$;
VII: $R^1 = R^3 = H$, $R^2 = Br$, $R^4 = COOH$; VIII: $R^1 = R^3 = H$, $R^2 = COOC_2H_5$, $R^4 = NHCOC_6H_5$;
IX: $R^1 = R^3 = H$, $R^2 = COOC_2H_5$, $R^4 = NHCOC_6H_2(OCH_3)_2$; X: $R^1 = R^2 = R^3 = H$, $R^4 = CONH_2$

The amide of 5-hydroxynicotinic acid (II) was obtained by the action of aqueous ammonia on the ethyl ester of 5-hydroxynicotinic acid. The acyl derivatives of 5-aminonicotinic acid (VIII, IX) were synthesized by condensation of an ester of 5-aminonicotinic acid with an arylcarboxylic acid chloride in the presence of pyridine. Synthesis of 5,6-dihydroxynicotinic acid (III) was carried out by the replacement of an iodine atom by a hydroxyl group in 6-iodo-5-hydroxynicotinic acid. The starting compounds, 5-hydroxynicotinic acid, 5-bromonicotinic acid, 5-aminonicotinic acid, and 3-hydroxyisonicotonic acid, and also compounds V-VII were obtained by standard methods [7-10]. The purity of the compounds was checked by TLC.

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 1, pp. 45-47, January, 1986. Original article submitted September 20, 1985.

0091-150X/86/2001-0029$12.50