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SYNTHESIS OF ACYLTHIO DERIVATIVES OF PENTA-O-ACETYLGLYCYRRHIZIC ACID. ANTIFLAMMATORY AND ANTIULCEROUS PROPERTIES

L. A. Baltina, V. A. Davydova,
T. G. Tolstikova, F. A. Zarudii,
R. M. Kondratenko, and G. A. Tolstikov

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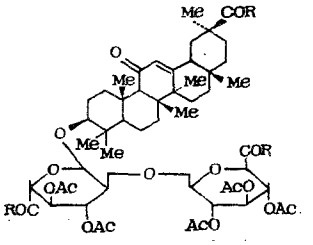
In continuation of our work on the transformation of the triterpene glycoside glycyrrhizic acid (GA) [1, 2, 5, 6] we have carried out conversions of the trichloride of penta-O-acetylglycyrrhizic acid (I) [6] with the purpose of synthesizing acylthioureas (III) and acetylthiosemicarbazides (IV), which are of interest as novel antiinflammatory agents and also as polydentate ligands for preparing complexes with bioactive metals.

As starting compound for the synthesis we used the triacylisothiocyanate of penta-O-acetylglycyrrhizic acid (II), which was obtained in a yield of 65% by refluxing trichloride I with freshly melted KSCN in acetonitrile for 1 h.

Reactions of triacylisothiocyanate II with primary amines and aniline proceed in dry chloroform in the presence of an excess of amine at room temperature with formation of corresponding triacylthioureas III in yields of 40-55%.

Compounds II react with suitable hydrazines V (equivalent amount or a slight excess) on refluxing in dichloromethane. The yields of substituted acylthiosemicarbazides IV were 45-71%.



I, II, III a-d, *IV* a-f

R=Cl(I), NCS(II), $NHCSNH(CH_2)_5CH_3$(IIIa),

$NHCSNHC_6H_{11}$-cyclo (IIIb), $NHCSNHC_6H_5$ (IIIc),

$NHCSNHCH_2C_6H_5$ (IIId), $NHCSNHNH_2$ (IVa),

$NHCSNHNHC_6H_5$ (IVb), $NHCSNHNHC_6H_4CH_3$-*o* (IVc),

$NHCSNHNHSO_2C_6H_4Me$-p (IVd), $NHCSNHNHCH_2C_6H_5$ (IVe),

$NHCSNHNHC_6H_3(NO_2)_2$-3,5 (IVf).

The structures of the prepared acylthio derivatives were confirmed by IR and UV spectra, and also by elemental analyses. Thus, IR spectra of compounds III and IV do not contain an absorption maximum of the CNS group (2050-1950 cm^{-1}), which is characteristic of starting acylisothiocyanate II, and have bands that are characteristic of NH and CONH groups (3400-3200 and 1570-1510 cm^{-1}). Intensive absorption maxima of the aglycon carbonyl group and the acetyl groups ($\nu_{C=O}$; 1660 and 1760–1750 cm^{-1}) are retained in the spectra of compounds III and IV. IR spectra of acylthioureas IIIc, d and semicarbazides IVb-e have characteristic absorption maxima of the aromatic groups (1620-1600 cm^{-1}).

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TABLE 1. Properties of Sulfur-Containing Derivatives of Penta-O-acetylglycyrrhizic Acid

Compound	Yield, %	Mp, °C	$[\alpha]_D^t$ (dioxane)	R_f	UV spectrum λ_{max} nm (lg ε)	Empirical formula, mol. mass
IIIa	54,8	180—183	+30° (c=0,02)	0,39 (A) 0,34 (B)	243 (4,16) 312 (3,71) (A)	$C_{73}H_{114}N_6O_{18}S_3$, 1459,85
III b	47,5	197—200	+25° (c=0,02)	0,39 (A) 0,39 (B)	245 (4,29) 312 (3,90) (A)	$C_{73}H_{108}N_6O_{18}S_3$, 1453,80
IIIc	40,5	227—230	+40° (c=0,02)	0,39 (A) 0,38 (B)	238 (4,62) 312 (3,73) (A)	$C_{73}H_{90}N_6O_{18}S_3$, 1435,66
IIId	44,6	—	+30° (c=0,02)	0,39 (A) 0,34 (B)	238 (4,46) 300 (4,11) (A)	$C_{76}H_{96}N_6O_{18}S_3$
IVa	63,5	(amorph)	+30° (c=0,01)	0,42 (A) 0,46 (B)	238 (4,41) 310 (3,89) (B)	$C_{55}H_{81}N_9O_{18}S_3$, 1252,42
IV b	71,4	182—185	+44° (c=0,03)	0,43 (A)	235 (4,04) 280 (3,74) (A)	$C_{73}H_{93}N_9O_{18}S_3$, 1480,70
IVc	65,8	212—214 (dec.)	+50° (c=0,02)	0,50 (A) 0,42 (B)	233 (4,68) 286 (4,31) (A)	$C_{76}H_{99}N_9O_{18}S_3$, 1522,78
IVd	58,8	207—210 (dec.)	+32,5° (c=0,02)	0,43 (A) 0,40 (B)	228 (4,55) 308 (3,92) (A)	$C_6H_{99}N_9O_{24}S_6$, 1714,96
IVe	69,1	205—208	+40° (c=0,02)	0,45 (A) 0,41 (B)	243 (4,27) 290 (3,99) (A)	$C_{76}H_{99}N_9O_{18}S_3$,
IV f	44,8	230—234	+45° (c=0,02)	0,54 (A) 0,40 (B)	230 (4,53) 250 (4,49) 359 (4,33) (A)	$C_{73}H_{87}N_{15}O_{18}S_3$, 1558,68

Notes. A) Dioxane, B) dioxane—methanol.

The absorption maximum of the $\pi-\pi^*$ bond of unsaturated ketone —C=C—C=O of the aglycon in UV spectra of acylthioureas IIIa, b is found in the region 243-245 nm, and in the case of compounds IIIc, d it combines with the maximum of aromatic chromophores and is found at 238 nm; at the same time the extinction increases (Table 1). UV spectra of acylthiosemicarbazides IV are characterized by two maxima; the absorption of the α,β-unsaturated ketone also combines with the absorption maximum of the NHC(=S)NHCO groups (250-254 nm [7]) or aromatic chromophores (see Table 1).

The antiflammatory activity of acylthio derivatives III and IV was studied in white mongrel mice with the models of carrageenan and formaline inflammation. As preparations for comparison we used glycyrrhizic acid (GA), niglizine, and the highly active antiphlogistic orthophene, which is used in medical practice and was administered at effective doses. Results of the investigations are listed in Tables 2 and 3.

With the model of carrageenan inflammation the compounds under investigation inhibited the growth of the inflammatory edema at doses of 50 and 100 mg/kg (see Table 2). At a dose of 50 mg/kg the antiinflammatory effect of compounds IIIc, d and IVb is similar to the effect of orthophene and niglizine, and more expressed as with GA at the same dose. At a dose of

TABLE 2. Antiinflammatory Effect of Acylthio Derivatives of Penta-O-acetylglycyrrhizic Acid (carrageenan inflammation, n = 6)

Compound	Dose, mg/g	Average swelling of the paw, %	p
IIIa	50	36,2±1,0	<0,001
	25	43,0±4,0	<0,002
	15	58,5±1,9	<0,001
	8	54,8±6,8	<0,01
IIIb	100	49,4±5,5	<0,05
	50	48,2±4,6	<0,05
IIIc	100	50,8±2,4	<0,05
	50	44,8±5,7	<0,05
IIId	100	48,3±1,4	<0,002
	50	44,8±5,7	<0,05
IVa	100	54,2±6,8	<0,01
	50	54,5±6,8	<0,01
IVb	100	51,7±3,5	<0,02
	50	45,7±2,8	<0,001
IVc	100	52,6±4,6	<0,001
	50	56,0±2,8	<0,05
IVd	100	60,1±3,4	<0,02
	50	51,5±2,4	<0,05
	25	49,2±2,9	<0,01
IVf	100	62,2±3,6	<0,02
	50	46,8±3,4	<0,01
	25	59,3±2,9	<0,05
Glycyrrhizic acid	100	37,8±3,3	<0,001
	50	54,3±3,2	<0,05
Niglizine	100	43,5±2,0	<0,002
Orthophene	8	42,6±2,6	<0,001
Control	—	63,4±3,4	

TABLE 3. Antiinflammatory Activity of Acylthio Derivatives of Penta-O-acetylglycyrrhizic Acid (formaline inflammation, n = 6)

Compound	Dose, mg/kg	Average swelling of paw, %	p
IIIa	50	48,6±3,7	<0,05
	25	58,6±2,6	<0,05
IIIb	100	50,7±4,8	<0,05
	50	51,3±2,1	<0,05
IIIc	100	46,4±3,4	<0,001
	50	48,7±4,6	<0,05
IIId	100	46,4±3,4	<0,001
	50	48,7±4,6	<0,02
IVc	100	42,8±1,5	<0,02
	50	47,3±3,3	<0,05
IVe	100	44,7±1,9	<0,001
	50	50,8±1,9	<0,05
IVd	50	51,0±3,2	<0,001
IVf	100	46,1±2,6	<0,001
Glycyrrhizic acid	100	42,8±1,5	<0,001
	50	47,0±2,8	<0,05
Niglizine	100	50,4±3,6	<0,05
Orthophene	8	51,4±3,9	<0,05
Control	—	69,5±2,9	—

50 mg/kg acylthiourea IIIa surpasses in antiinflammatory activity the comparison preparations and has an antiinflammatory effect that is similar to that of orthophene, also at a dose of 25 mg/kg. Increasing the dose of the preparations to 100 mg/kg gives a lowering of the antiinflammatory effect of acylthio derivatives; a high activity is found with the comparison preparations GA and niglizine.

In the case of inflammation evoked by formaline, at doses of 50 and 100 mg/kg acylthio derivatives III and IV have antiinflammatory activity similar to that of niglizine and orthophene (see Table 3). In this model of edema, compounds IVc and IVd are the most active ones

TABLE 4. Antiulcerous Activity (dose 200 mg/kg) of Thio Derivatives of Glycyrrhizic Acid in Rats (n = 7)

Compound	Average number of destructions of the stomach, evoked by			
	indomethacin	p	cinchophen	p
IIId	11,6±1,0	<0,05	4,6±0,5	<0,01
IVe	9,5±1,0	<0,05	3,1±0,7	<0,001
Cimetidine	16,8±2,2	<0,05	5,1±0,8	<0,05
Glycyrrhizic acid	13,6±2,0	<0,05	5,0±0,4	<0,01
Control	18,3±2,1		8,5±0,9	

at a dose of 50 mg/kg. The antiflammatory effect of these compounds is similar to that of GA. It should be noted that the thio derivatives in question are more active at a dose of 100 mg/kg in the model of formaline inflammation.

In contrast to orthophene, thio derivatives of GA are less toxic compounds and do not irritate the mucous membrane of the stomach but, on the contrary, have a protecting effect on it.

We have studied the antiulcerous effect of two sulfur-containing derivatives of glycyrrhizic acid, IIId and IVe, on two experimental ulcers of rat stomach in comparison with known antiulcerous agents, cimetidine and glycyrrhizic acid (Table 4).

Single administration into the stomach of compounds IIId and IVe at a dose of 200 mg/kg one hour before producing the ulcer protects the mucous membrane of the stomach against ulceration. The protecting effect of acylsemicarbazide IVe was 1.7 times that of the same dose of cimetidine.

The LD_{50} of a series of acylthio derivatives in the case of oral administration, determined by the method of Kerber [3], varied between 1000 and 5000 mg/kg in dependence of the structure, which makes it possible to classify these compounds with the 3rd class of moderately dangerous compounds.

Thus, the pharmacological investigations lead to the conclusion that novel acylthio derivatives of glycyrrhizic acid are moderately toxic compounds that combine high antiinflammatory activity with a protective effect on the mucous membrane of the stomach, which favorably distinguishes them from known antiphlogistics that are widely used in medical practice.

EXPERIMENTAL

Thin-layer chromatography was carried out on Silufol plates (Czechoslovakia) in the systems benzene—alcohol, 5:1 (A) and chloroform—alcohol, 10:1 (B). Spots were visualized with a 20% solution of phosphotungstic acid in alcohol and heating at 110°C. Compounds were purified by crystallization and reprecipitation from dichloromethane—hexane, chloroform—hexane, or alcohol.

IR spectra were taken on a UR-20 spectrometer from dispersions in paraffin oil. UV spectra were recorded on a Specord M40 spectrometer. The specific rotation was measured on a Perkin—Elmer 241 MC polarimeter in cells with a length of 1 dm. Acetonitrile, dichloromethane, and chloroform were distilled from P_2O_5. Data of elemental analyses corresponded with calculated values.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-isothiocyanato-11-oxo-30-norolean-12-ene-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-isothiocyanatoglucopyranosyl])-α-D-(3,4-di-O-acetyl-6-oxo-6-deoxy-6-isothiocyanatoglucopyranozide (II). To a solution of 8.8 g (8.9 mmole) of the trichloride of penta-O-acetylglycyrrhizic acid I [6] in 200 ml of dry acetonitrile is added 2.6 g (26.9 mmole) of freshly melted KSCN powder and the mixture is refluxed with stirring for 1 h. The solvent is evaporated under vacuum, the residue is dissolved in 200 ml of chloroform, extracted with water, and dried over $MgSO_4$. After evaporation of the solvent there was obtained 8.4 g of product II, which was recrystallized from chloro—hexane. Yield 6.2 g (65%), mp 210-213°C, $[\alpha]_D^{20} = +47 \pm 5°$ (c0.05, MeOH); R_f 0.42 (A), 0.44 (B). IR spectrum, ν, cm^{-1}: 2050-1950 (NCS), 1750 (OAC), 1660 (C_{11}=O).

UV spectrum λ_{max}^{MeOH} (log ε): 244 nm (4.17); 294 nm (4.12). UV spectrum, $\lambda_{max}^{alc-diox}$ (log ε): 244 nm (4.47), 340 nm (4.00). $C_{57}H_{69}N_3O_{18}S_3$. Mol. mass 1179.85.

[1-O-[3β, 20β)-20-Oxo-20-deoxy-20-(N^1-alkylthioureido)-11-oxo-30-norolean-12-en-3-yl]-2-O-[β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-(N^1-alkylthioureido)glucopyranosyl]-α-D-3,4-di-O-acetyl-6-oxo-6-deoxy-(N^1-alkylthioureido)glucopyranozides (compounds IIIa-d). To a solution of 0.59 g (0.5 mmole) of triacylisothiocyanate II in 50 ml of dry chloroform is added 0.5 ml of distilled amine, the mixture is stirred at room temperature for 1 h, extracted with water, 5% HCl solution, and again with water. The extract is dried over $MgSO_4$, evaporated to half the volume and the product is precipitated with hexane. After crystallization from chloroform—hexane and drying at 50°C the desired compounds are obtained in yields of 45-55% as light-yellow or light-brown powders that are homogeneous according to TLC. Properties of the prepared compounds are listed in Table 1.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-thiosemicarbazide-11-oxo-30-norolean-12-en-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-thiosemicarbazidoglucopyranosyl)-α-D-(3,4-di-O-acetyl-6-oxo-6-deoxy-6-thiosemicarbazido)glucopyranozide (IVa). To a solution of 0.59 g (0.5 mmole) of acetylisothiocyanate II in 30 ml of dry dichloromethane and 5 ml of dioxane is added a solution of 0.5 g of 85% hydrazine hydrate and the mixture is refluxed for 15 min. The solvents are evaporated under vacuum and the residue is reprecipitated from dimethylformamide—water.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-phenylthiosemicarbazido-11-oxo-30-norolean-12-en-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-phenylthiosemicarbazido-glucopyranosyl)-α-D-3,4-di-O-acetyl-6-oxo-6-deoxy-6-phenylthiosemicarbazidoglucopyranozide (IVb). To a solution of 0.59 g (0.5 mmole) of acylisothiocyanate II in 30 ml of dry dichloromethane is added 0.43 g (4 mmole) of phenylhydrazine, the mixture is refluxed for 15 min, extracted with water, dried over $MgSO_4$, and evaporated under vacuum. The residue is crystallized from chloroform—hexane, dried, and recrystallized from aqueous ethanol.

1-O-[3β, 20β)-20-Oxo-20-deoxy-20-ortho-tolylthiosemicarbazido-11-oxo-30-norolean-12-en-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-ortho-tolylthiosemicarbazidoglucopyranosyl)-α-D-3,4-di-O-acetyl-6-oxo-6-deoxy-6-ortho-tolylthiosemicarbazidoglucopyranozide (IVc). To a solution of 0.59 g (0.5 mmole) of triacylisothiocyanate II in 30 ml of dry dichloromethane is added a freshly prepared solution of ortho-tolylhydrazine prepared from 0.35 g (1.5 mmole) of o-$CH_3C_6H_4NHNH_2 \cdot HCl$ by treating with one equivalent of triethylamine in 20 ml of dichloromethane, and the mixture is refluxed for 1 h. After working-up as described above for IVb and reprecipitation from chloroform—hexane, 0.5 g of compound IVc is obtained as a light-brown powder.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-tosylthiosemicarbazido-11-oxo-30-norolean-12-en-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-tosylsemicarbazidoglucopyranosyl)-α-D-3,4-di-O-acetyl-6-oxo-6-deoxy-6-tosylthiosemicarbazidoglucopyranozide (IVd). To a solution of 0.59 g (0.5 mmole) of triacylisothiocyanate II in 30 ml of dry dichloromethane is added 0.33 g (1.5 mmole) of tosylhydrazine and the mixture is refluxed for 1 h. To the reaction mixture is added 10 ml of methanol to solve the precipitate and the product is precipitated with 50 ml of hexane. After drying, triacylthiosemicarbazide IVd is recrystallized from chloroform—hexane. Yield 0.5 g.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-benzylthiosemicarbazido-11-oxo-30-norolean-12-en-3-yl]-2-O-(β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6- benzylthiosemicarbazidoglucopyranosyl)-α-D-3,4-di-O-acetyl-6-oxo- 6-deoxy-6-benzylthiosemicarbazidoglucopyranozide (IVe). Under the conditions described for IVb, from 0.59 g (0.5 mmole) of triacylisothiocyanate and 0.6 ml of benzylhydrazine is obtained 0.47 g of triacylthiosemicarbazide IVe, which was reprecipitated from dichloromethane—hexane.

1-O-[(3β, 20β)-20-Oxo-20-deoxy-20-(2,4-dinitrophenylthiosemicarbazido)-11-oxo-30-norolean-12-en-3-yl]-2-O-[β-D-2,3,4-tri-O-acetyl-6-oxo-6-deoxy-6-(2,4-dinitrophenylthiosemicarbazido)glucopyranosyl]-α-D-3,4-di-O-acetyl-6-oxo-6-deoxy-6-(2,4-dinitrophenylthiosemicarbazido)glucopyranozide (IVf). Under the conditions described for IVd, from 0.59 g (0.5 mmole) of triacylisothiocyanate II and 0.3 g (1.5 mmole) of 2,4-dinitrophenylhydrazine is obtained 0.36 g of product (IVf), crystallized from chloroform—hexane.

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SYNTHESIS AND ANTIINFLAMMATORY AND ANALGESIC ACTIVITIES OF QUINOLINO[2,1-b]QUINAZOLINE DERIVATIVES

A. I. Mikhalev, M. E. Konshin, O. A. Yanborisova, A. S. Zaks, and V. V. Yushkov

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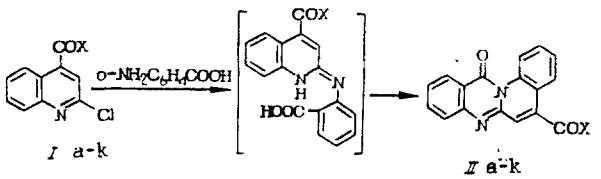
Among derivatives of pyrido[2,1-b]quinazolin-10-one there are compounds that have various biological activities [1, 2].

In this work, with the purpose of synthesizing derivatives of quinolino[2,1-b]quinazolin-12-ones, which are novel potentially biologically active compounds structurally related to pyrido[2,1-b]quinazolin-10-one, we have carried out the reaction of 2-chloroquinolinic acid and its derivatives with anthranilic acid.



X=OH (Ia, IIa), OC_2H_5 (Ib, IIb), NRR', R=H (Ic, e-k, IIc, e-k) R'=CH_3 (Ic, IIc), tert-C_4H_9 (Ie, IIe); C_6H_5 (If, IIf); m-$CH_3C_6H_4$ (Ig, IIg) o-$CH_3C_6H_4$ (Ih, IIh); p-BrC_6H_4 (Ii, IIi); 2,4-$Cl_2C_6H_3$ (Ij, IIj); m-$COOHC_6H_4$ (Ik, IIk); R=R'=C_2H_5 (Id, IId).

The reaction is carried out by heating (130-140°C, metal bath temperature) equimolar amounts of the starting compounds in concentrated acetic acid and proceeds probably via the stage of intermediary 2-(2-carboxyanilino)quinoline, of which formation is made possible by the proton-donating solvent.

The prepared compounds are yellow or light-green crystalline substances, of which the IR spectra contain valence vibrations bands at 1615-1690 (CO) and 3220-3450 (NH) cm^{-1}. In the PMR spectra of compounds IIIa-ℓ we find signals of the aromatic protons of the heterocycle, a multiplet centered at 7.43-7.60 ppm, and also singlets of the secondary amino group in the region 8.12-11.80 ppm.

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