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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NONCONDENSED THIAZOLIDONES-2 WITH POLYMETHYLENE BRIDGES

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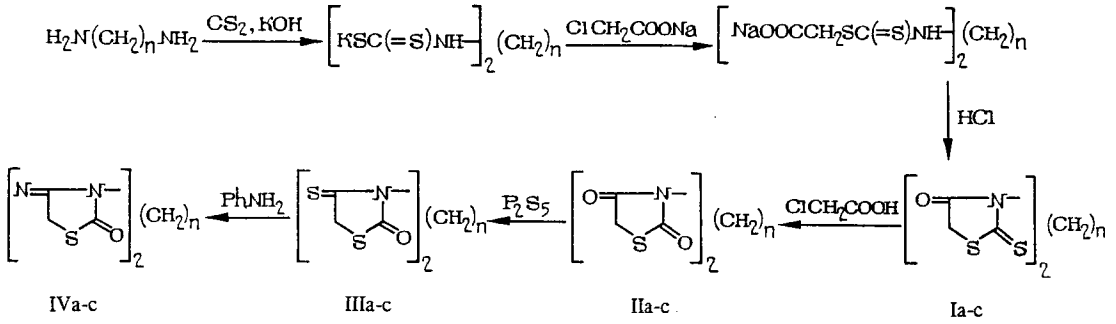
The introduction into medical practice of highly effective therapeutic agents such as the natural and semisynthetic penicillins, the antitumor agents imiphos and thioprillin, the stimulator of leukopoiesis Leukogen, and other [3, 6] agents containing thiazolidine rings demonstrates the value of searching for biologically active substances among thiazolidine derivatives. Of particular interest are the little-studied bicyclic noncondensed thiazolidones-2 with polymethylene bridges.

Bicyclic noncondensed thiazolidindiones-2,4, united by 3,3′-polymethylene bridges (II) were prepared by a method which we have perfected, from alkylenebis(2-thioxothiazolidones-4) (I) by desulfuration with aqueous solutions of monochloroacetic acid [4].

Thionylation of dioxane solutions of diones II with phosphorus pentasulfide leads to the formation of alkylenebis(4-thioxothiazolidones-2) (III). Reaction of the latter with aniline in alcohol results in the formation of the corresponding alkylenebis(4-phenyliminothiazolidones-2) (IV).



IVa-c IIIa-c IIa-c Ia-c

$n = 2(a), 4(b), 6(c)$

The structures of the compounds synthesized were demonstrated by elemental analysis, IR spectroscopy, and back synthesis [1, 5]. The purity of the compounds synthesized was checked by TLC on silica gel KCK plates, using the Dragendorf reagent as modified by Munier for detection [2].

EXPERIMENTAL (CHEMICAL)

IR spectra were taken using an IKS-29 spectrophotometer in KBr tablets, and UV spectra were recorded using a Spectromom-203 apparatus, in methanol.

The properties of compounds II-IV are shown in Table 1. Results of elemental analyses corresponded to theoretical values.

α,ω-Bis(thiazolidin-2,4-dion-3-yl)alkanes (IIa-c). Solutions of 0.4 mole of KOH in 25 ml of water and 0.4 mole of CS_2 were added to 0.2 mole of alklyenediamine in 75 ml of water dropwise over 1 h. The reaction was carried out in a flask

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TABLE 1. Physicochemical Properties of Compounds IIa-c, IIIa-c, and IVa-c

Compound	Yield, %	mp, %	Elemental formula	IR spectrum, ν_{max}, cm^{-1}				UV spectrum in methanol, λ_{max}, nm
				C=O	C—N	C—N	C=S	
IIa	64	188—0	$C_8H_8N_2O_4S_2$	1770—1710	1360			228, 287, 347
IIb	57	108—10	$C_{10}H_{12}N_2O_4S_2$	1750—1665	1365—1350			227, 286, 343
IIc	66	94—6	$C_{12}H_{16}N_2O_4S_2$	1780—1680	1350			227, 283, 338
IIIa	72	108—9	$C_8H_8N_2O_2S_4$	1710—1690	1320		1120	242, 294—295
IIIb	66	167—9	$C_{10}H_{12}N_2O_2S_4$	1740	1340		1120	243, 295
IIIc	69	67—9	$C_{12}H_{16}N_2O_2S_4$	1695	1315		1110	243, 295
IVa	51	119—21	$C_{20}H_{18}N_4O_2S_2$	1665	1370—1360	1605		241—246, 435—440
IVb	46	69—70	$C_{22}H_{22}N_4O_2S_2$	1650	1360	1620		239, 452
IVc	53	99—101	$C_{24}H_{26}N_4O_2S_2$	1650	1350	1605		238, 414—419

fitted with a mechanical stirrer, with cooling to 5-8°C. Mixing was continued until a uniform liquid formed (at least 4 h). Then, without stopping stirring, 0.4 mole of monochloroacetic acid previously neutralized with $NaHCO_3$ was added in small portions. After 30 min the reaction mix was supplemented with dilute HCl to a pH of <7.0, followed by 75 ml of boiling concentrated HCl. The resulting mixture was heated to 90°C for 15 min. The reaction was supplemented with another 0.5 mole of monochloroacetic acid and boiled until release of hydrogen sulfide stopped (5-6 h). The reaction mixture was cooled to 8-10°C and poured into water cooled to the same temperature. The precipitate was collected by filtration and recrystallized from butanol. This procedure yielded α,β-bis(thiazolidin-2,4-dion-3-yl)ethane (IIa), with $R_f = 0.41 \pm 0.02$ in a system consisting of chloroform–butanol–25% ammonia (8:5:2), α,δ-bis(thiazolidin-2,4-dion-3-yl)butane (IIb), with $R_f = 0.53 \pm 0.02$ in a system consisting of chloroform–methanol–25% ammonia (6:1:1), and α,ω-bis(thiazolidin-2,4-dion-3-yl)hexane (IIc), with $R_f = 0.38 \pm 0.01$ in a system consisting of chloroform–butanol–25% ammonia (12:8:5).

α,ω-Bis(thiazolidin-2-on-4-thion-3-yl)alkanes (IIIa-c). Phosphorus pentasulfide (0.1 mole) was added in portions to a hot solution of 0.04 mole of alkylene-bis(thiazolidin-2,4-dione) in 100 ml of anhydrous dioxane with mechanical stirring over 3 h. Mixing was continued for a further 2 h. The hot reaction mix was then filtered, and dioxane was evaporated until the residue was insignificant (~10-15 ml), and the mix was poured into 100 ml of propanol. The precipitate was collected by filtration and recrystallized from butanol. This procedure yielded α,β-bis(thiazolidin-2-on-4-thion-3-yl)ethane (IIIa), with $R_f = 0.70 \pm 0.01$ in a system consisting of chloroform–acetone–methanol (6:1:1), α,γ-bis(thiazolidin-on-4-thion-3-yl)butane (IIIb), with $R_f = 0.46 \pm 0.01$ in a system consisting of benzene–methanol–25% ammonia (45:10:1), and α,ω-bis(thiazolidin-2-on-4-thioxo-3-yl)hexane (IIIc), with $R_f = 0.50 \pm 0.02$ in a system consisting of chloroform–dioxane–diethylamine (60:40:5).

α,ω-Bis(thiazolidin-2-on-4-phenylimino-3-yl)alkanes (IVa-c). A mixture of 0.002 mole of alkylenebis(thiazolidin-2-on-4-thione) and 0.005 mole of aniline in 10.0 ml of butanol was boiled for 2 h. The reaction mixture was then cooled and hexane was used to precipitate a brown product. This yielded α,β-bis(4-phenyliminothiazolidin-2-on-3-yl)ethane (IVa), with $R_f = 0.57 \pm 0.02$ in a system consisting of chloroform–acetone–diethylamine (60:40:5), α,δ-bis(4-phenyliminothiazolidin-2-on-3-yl)butane (IVb), with $R_f = 0.48 \pm 0.02$ in a system consisting of benzene–dioxane–diethylamine (60:40:1), and α,ω-bis(phenyliminothiazolidin-2-on-3-yl)hexane (IVc), with $R_f = 0.39 \pm 0.01$ in a system consisting of benzene–dioxane–diethylamine (60:40:5).

EXPERIMENTAL (BIOLOGICAL)

Neuroleptic activity was assessed in terms of increases in the duration of sodium ethaminal or hexenal sleep by the compounds of interest. Experiments were carried out using white Wistar rats. Compounds were given subcutaneously at a dose of 1/10 the LD_{50}, 30 min before intraperitoneal sodium ethaminal or hexenal.

The results showed that α,ω-bis(thiazolidin-2,4-dion-3-yl)alkanes had pronounced neuroleptic activity, increasing the duration of sodium ethaminal and hexenal sleep in animals by 50-80%. Neuroleptic activity increased as the length of the polymethylene bridge increased from n = 2 to n = 6. Replacement of the oxygen atom in position 4 with sulfur and arylimino groups led to significant reduction in neuroleptic activity.

Studies of the analgesic activity were carried out using a hot-plate method, with white mice of both sexes (16-25 g). Animals were placed on a metal tray in a water bath kept at 55°C. Reactions of animals were measured in seconds to thermal discomfort (mice sinking down on their hind paws and bringing the fore and hind paws together). Initial reactions to heat were

determined, and animals were then given test substances subcutaneously, and changes in reaction to heat were determined 30, 60, 90, 120, 150, and 180 min later.

α,ω-Bis(thiazolidin-2-on-4-thion-3-yl)alkanes were found to have pronounced analgesic activity, equal to that of Analgin, through the period of study. The other compounds synthesized here had weak analgesic activity.

Studies of the antibacterial and antifungal activities of the compounds synthesized here were carried out by the twofold serial dilution method on liquid nutritive medium, using five strains of microbes: two species of Gram-positive bacteria, two species of Gram-negative bacteria, and one strain of a pathogenic fungus. Bacteria were cultivated using amino-peptide diluted twofold in distilled water pH 7.2. The test inoculum was $2.5 \cdot 10^5$ bacterial cells from an 18-h amino-peptide culture. in 1 ml of medium. The highest concentration tested was 500 μg/ml.

Fungi were grown using Saburead medium (pH 6.0-6.8). The inoculum was 500,000 reproductive bodies per ml. The highest concentration tested was 500 μg/ml.

Antimicrobial activity was assessed in terms of the minimal bacteriostatic or mycostatic concentration (in μg/ml) of the compounds of interest. Furacillin was used as a standard reference compound for antibacterial and fungicidal activity. The compounds synthesized here were found to have moderate bacteriostatic activity.

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