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4-THIAZOLIDINONES WITH CYCLIC SUBSTITUENTS IN THE 2 POSITION

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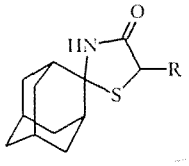
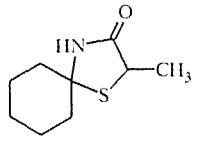
Cycloalkylspiro-4-thiazolidinones are synthesized by the reaction of several cyclic ketones with 2-mercaptopropionic or thioglycolic acids in the presence of an ammonium salt. The reaction of thioglycolic acid with N-benzylidene derivatives of adamantylalkylamines or hydroxyphenylethylamines leads to the corresponding N-substituted 5-phenyl-4-thiazolodinones. By the condensation of adamantanone thiosemicarbazide, or its hydroxy derivative, with chloroacetic acid, the corresponding substituted hydrazones are obtained.

Among thiazolidine derivatives containing a carbonyl function are found substances possessing various biological activities [1]. For this reason it was of interest to synthesize derivatives of 4-thiazolidinone with various substituents on the ring.

Previously we had obtained the first representative of this type, adamantan-2-spiro-2′-(thiazolidin-4′-one) (Ia) [2]. In a continuation of these studies, we have carried out the synthesis of new, substituted 4-thiazolidinones. Here, mercaptoalkylcarboxylic acids were used as the source of sulfur for the construction of the thiazolidine ring. By heating 2-adamantanone, cyclohexanone,3-quinuclidinone, or p-chloroacetaldehyde with 2-mercaptopropionic acid in the presence of an ammonium salt (acetate, carbonate, or oxalate) or urea, the corresponding derivatives (Ib-d) or (II) were obtained. Spirothiazolidinone (Ie) was synthesized in analogous fashion from 3-quinuclidinone and thioglycolic acid.



Ia,b



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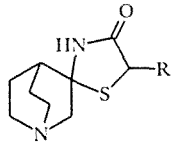
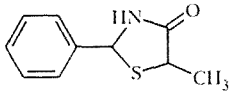
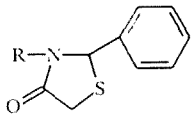


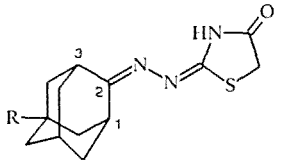
Id,e



II



IIIa-e



IVa,b

I a, e R = H, d, d R = CH_3; III a R = 1-$AdCH_2$–; b R = 3-OH-1-$AdCH_2$–; c R = 1-$AdS(CH_2)_2$–; d R = $PhCH(OH)CH_2$–; e R = O_2N–C$_6$H$_4$–$CH(OH)CH_2$–; IV a R = H, b R = OH

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TABLE 1. Characteristics of Compounds I-IV

Compound	Molecular formula	T_{mp}, °C	PMR spectrum*, δ, ppm, SSCC (J) Hz	Yield, %
Ib	$C_{13}H_{19}NO$	215...216	1,6...2,2 (14H, m, 2-Ad), 1,34 (3H, d, CH_3, $J_{CH,CH3}$ = 7,3), 3,76 (1H, q, CH), 9,05 (1H, s, NH)	93
Ic	$C_9H_{15}NOS$	143...145	1,2...1,8 (10H, m, C_6H_{10}), 1,38 (3H, d, CH_3, $J_{CH,CH3}$ = 7,1), 3,69 (1H, q, CH), 8,65 (1H, s, NH)	84
Id · HCl*2	$C_{10}H_{16}N_2OS \cdot HCl$	270...272	A: 1,42 (3H, d, CH_3, $J_{CH,CH3}$ = 7,3), ~3,9 (1H, m, CH), 9,34 (1H, s, NH); B: 1,38 (3H, d, CH_3, $J_{CH,CH3}$ = 7,3), ~3,9 (1H, m, CH), 9,38 (1H, s, NH), 11,4 (1H, br.s, NH^+Cl^-)	77
Ie · HCl	$C_9H_{14}N_2OS \cdot HCl$	298...299	1,9...3,2 (11H, m, $C_7H_{11}N$), 3,48 & 3,65 (1H, d, αCH & 1H, d, βCH), J_{gem} = 15,4) 9,43 (1H, s, NH), 11,2 (1H, br.s, NH^+Cl^-)	85
II*2	$C_{10}H_{10}ClNOS$	211...212	A: 1,55 (3H, d, CH_3), 3,93 (1H, q, CHCH$_3$, $J_{CH,CH3}$ = 6,9), 5,70 (1H, s, CH), 7,52 (1H, br. s, NH), 7,31 (2H, d, αCHPh), 7,36 (2H, d, βCHPh, $J\alpha\beta$ = 9,1); B: 1,56 (3H, d, CH_3), 3,92 (1H, q, CHCH$_3$), 5,71 (1H, s, CH), 7,62 (1H, br.s, NH), 7,31 (2H, d, αCHPh), 7,36 (2H, d, βCHPh), J identical to J of isomer A	75
IIIa	$C_{20}H_{25}NOS \cdot H_2O$	126...131	1,4...2.2 (15H, m, Ad), 3,17 (1H, d, CH_2–Ad), 3,39 (1H, d, CH_2–Ad, J_{gem} = 14.3), 3,68 (1H, d, CH_2S), 3,71 (1H, d, CH_2S, J gem = 16,0), 5,81 (1H, s, CHPh), 7,2...7,4 (5H, m, C_6H_5)	81
IIIb	$C_{20}H_{25}NO_2S$	151...152	1,3...2,1 (14H, m, Ad), 2,13 (1H, d, CH_2–Ad), 3,38 (1H, d, CH_2–Ad, J_{gem} = 13.9), 3,64 (1H, d, CH_2S), 3,75 (1H, d, CH_2S, Jgem = 15,9), 5,79 (1H, s, CHPh), 7,2...7,4 (5H, m, C_6H_5)	89
IIIc	$C_{21}H_{27}NOS_2$	91...92	2,0...2,6 (15H, m Ad), 2,44 & 3,66 (2H, m, CH_2N), 2,67 & 2,90 (2H, m, CH_2SAd), 3,71 (1H, d, CH_2S), 3,82 (1H, d.d CH_2S, Jgem = 15,6, $^4J_{CH,CH}$ = 1,8), 5,78 (1H, br.s, CH), ~7,4 (5H, m, C_6H_5)	93
IIId*2	$C_{17}H_{17}NO_2S$	103...105	A: 2,63 (1H, d.d, CH_2N, J_{cis} = 5.5), 3,96 (1H, d.d CH_2N, J_{trans} = 7.7, J_{gem} = 13.9), ~4,9 (1H, m, CHOH), 3,58 (1H, d, CH_2), 3,72 (1H, d.d, CH_2S, J_{gem} = 15.7, $^4J_{CH,CH}$ = 1,8), 4,6 (1H, br.s, OH), 5,40 (1H, d, CHPh), 7,3...7,4 (10H, m, $2C_6H_5$); B: 2,79 (1H, d.d, CH_2N), 3,76 (1H, d.d, CH_2N), ~4,9 (1H, m, CHOH), ~3,6 (1H, d, CH_2S), 3,7 (1H, d, CH_2S), 4,80 (1H, br.s, OH), 6,03 (1H, d, CHPh), 7,3...7,4 (10H, m, $2C_6H_5$), J identical to J of isomer A	80
IIIe*2	$C_{17}H_{14}N_2O_4S$	175...177	A: 2,96 (1H, d.d, CH_2N, J_{cis} = 3,3), 3,90 (1H, d.d, CH_2N, J_{trans} = 7.7, J gem = 14.6), 5,03 (1H, m, CHOH), 3,73 (1H, d, CH_2S), 3,84 (1H, d.d CH_2S, J gem = 15.7), 3,7 (1H, br.s, OH), 5,64 (1H, br.s, CHPh), ~7,4 (5H, m, C_6H_5), 7,43 (2H, d, αCHPh), 8,17 (2H, d, βCHPh, $J\alpha\beta$ = 8,8), 3,53 (1H, d.d, CH_2N), 3,21 (1H, d.d, CH_2N), 4,86 (1H, m, CHOH), 3,73 (1H, CH_2S), 3,84 (1H, CH_2S), ~3,7 (1H, br.s, OH), 5,54 (1H, d, CHPh), ~7,4 (5H, m, C_6H_5), 7,37 (2H, d, αCHPh), 8,17 (2H, d, βCHPh), J identical to J of isomer A	90
IVa	$C_{13}H_{17}N_3OS$	201...203	2.59 (1H, m, C_1H); 3,56 (1H, m, CH_3H), 1.7...2,00 (12H, m remaining protons of 2-Ad 3,70 (2H, br.s, CH_2), 11,5 (1H, br.s, NH)	76
IVb	$C_{13}H_{17}N_3O_2S$	194...197	2,30 (1H, br.s, OH), 2,85 (1H, m, $C_{(1)}H$), 3,66 (1H, br.s, $C_{(3)}H$), 1,8...1,9 (11H, m, remaining protons of 2-Ad), 3,77 (2H, s, CH_2), 9,2 (1H, br.s, NH)	75

*The spectra of compounds II, IIIc, IIIe, and IVb were taken in $CDCl_3$, of IIId in deuteroacetone, and the rest in DMSO-d_6.

*2The compounds exist as a mixture of two diastereoisomers: A) major, B) minor; for Id.HCl, A:B = 3:2; for II, A:B = 5:4; for IIId, A:B = 4:1; for IIIe, A:B = 8.1.

The corresponding N-substituted phenylthiazolidinones (IIIa-e) were synthesized by reaction of thioglycolic acid with N-benzylidine derivatives of adamantyl-(or hydroxyadamantyl)alkylamines. The starting compound for the synthesis of product IIIc, S-(1-ad-amantyl)mercaptoethylamine was prepared from adamantanol and mercaptoethylamine hydrogen chloride in methanesulfonic acid. Adamantylidinhydrazonothiazolidinone (IVa) and its 5-hydroxy derivative (IVb) were synthesized by reaction of the corresponding adamantanone thiosemicarbazides with chloroacetic acid.

The structures and purity of the compounds obtained were confirmed by elemental analyses, IR, and PMR spectra. Thus, the IR spectra of compounds IIIa-e contain bands that are absent in the starting materials and characteristic of a carbonyl group at 1670 (IIIa), 1650 (IIIb), 1655 (IIIc), 1645 (IIId), 1640 (IIIe), and 1700 cm^{-1} (IVa and IVb). From the PMR spectra, compounds Id.HCl, II, IIId, and IIIe exists as a mixture of diastereoisomers (see Table 1).

EXPERIMENTAL

The course of the reaction and the purity of the products were followed by means of TLC on Silufol UV-254 plates in an ethanol–ethyl acetate–hexane-25% ammonia solution system with varying ratios of the components. IR spectra (KBr tablets), were taken on a Perkin–Elmer 398 spectrophotometer; PMR spectra, on a Bruker WP-200 SY spectrometer with TMS as an internal standard.

The elemental analyses for C, H, N, S, and Cl agree with the calculated values.

Adamantan-2-spiro-2′-(5-methyl-4′-thiazolidinone) (Ib), Cyclohexanspiro-2′-(5′-methyl-4′-thiazolidinone) (Ic), Quinuclidin-3-spiro-2′-(5′-methyl-4′-thiazolidine) (Id), and 2-(4-Chlorophenyl)-5-methyl-4-thiazolidinone (II). A. A mixture of 1.5 g (0.01 mole) or 2-adamantanone, 1.27 g (0.012 mole) of 2-mercaptopropionic acid, and 1 g of ammonium acetate in 25 ml of benzene is boiled for three hours with a Dean–Stark trap until water no longer separates out. The benzene is distilled off, sodium bicarbonate solution added to the residue which is then filtered off, washed with water, and dried to obtain 2.2 g of product Ib.

B. A mixture of 0.75 g (0.005 mole) of 2-adamantanone, 0.6 g (0.0056 mole) of 2-mercaptopropionic acid, and 0.9 g (0.015 mole) of urea is held at 130-140°C for 15 min. After the reaction is over (evolution of gas bubbles stops) the reaction mass is cooled, an aqueous solution of sodium bicarbonate is added, the residue is filtered off, washed with water, and dried to obtain 1.0 g of product identical to that synthesized by procedure A (melting point, elemental analysis, PMR spectrum).

In a manner analogous to procedure A, compound Ic is synthesized from cyclohexanone and 2-mercaptopropionic acid; Id (isolated as the hydrogen chloride, Id·HCl) from 3-quinuclidinone and 2-mercaptopropionic acid; and compound II from p-chloroacetaldehyde and 20-mercaptopropionic acid.

Quinuclidin-3-spiro-2′-(4-thiazolidinone) hydrogen chloride (Ie·HCl) is synthesized from 2.5 g (0.02 mole) of 3-quinuclidinone, 2.3 g (0.025 mole) of thioglycolic acid, and 1.6 g of ammonium acetate by procedure A.

S-(1-Adamantyl)mercaptoethylamine Hydrogen Chloride. To a solution of 6.1 g (0.04 mole) of 1-adamantanol in 35 ml of methanesulfonic acid is added slowly with stirring 4.5 g (0.04 mole) of mercaptoethylamine hydrogen chloride. The solid is allowed to dissolve for 3 h, the reaction mass is poured onto ice, and the starting adamantanol is extracted with ether. The aqueous acidic layer, is made basic and extracted with ether.

S-(1-Adamantyl)mercaptoethylamine. The extract is dried with sodium sulfate, poured into alcohol saturated with HCl, and the desired hydrogen chloride salt filtered off. mp 241-243°C (MeOH–ether). Lit.: mp 242-244°C [3].

3-(Adamantyl-1-methyl)-2-phenylthiazolidin-4-one (IIIa), 3-(3-Hydroxyadamantyl-1-methyl)-2-phenylthiazolidin-4-one (IIIb), 3-(Adamantyl-1-thioethyl)-2-phenylthiazolidin-4-one (IIIc), 3-(2-Hydroxy-2-phenylethyl)-2-phenylthiazolidin-4-one (IIId), and 3-[2-Hydroxy-2-(4-nitrophenyl)ethyl]-2-phenylthiazolidin-4-one (IIIe). A mixture of 0.42 g (0.002 mole) of S-(1-adamantyl)mercaptoethylamine and 0.2 g (0.002 mole) of benzaldehyde in 20 ml of benzene is boiled under reflux until the evolution of water stops, 0.2 g (0.0022 mole) of thioglycolic acid is then added, and the boiling continued with a Dean–Stark trap until water no longer separates out. The benzene is distilled off, a sodium bicarbonate solution is added to the residue, the precipitate of product IIIc that has formed after 2 h is filtered off, washed with water, and dried. Compound IIIa is synthesized in analogous fashion from the N-benzylidine derivative of 1-aminomethyladamantane and thioglycolic acid; compound IIIb from the N-benzylidine derivative of 3-hydroxy-1-aminomethyladamantane and thioglycolic acid; compound IIId from the N-benzylidine derivative of 2-hydroxy-2-(4-nitrophenyl)ethylamine and thioglycolic acid; and compound IIIe from 2-hydroxy-2-(4-nitrophenyl)ethylamine and thioglycolic acid.

2-Adamantylidinhydrazono-2′-thiazolidin-4′-one (IVa) and 5-Hydroxy-2-adamantylidinhydrazono-2′-thiazolidin-4′-one (IVb). A mixture of 0.45 g (0.002 mole) of 2-adamantanone thiosemicarbazone, 0.2 g (0.002 mole) of chloroacetic acid, and 0.32 g (0.004 mole) of anhydrous sodium acetate is boiled with stirring for 4 h in 5 ml of absolute ethanol, then cooled, and the precipitated product IVa filtered off. Compound IVb is synthesized analogously from 5-hydroxy-2-adamantanone and chloroacetic acid.

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