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SYNTHESIS OF NEW DERIVATIVES OF CARBO(HETERO)CYCLOSPIROBUTANOIC LACTONES

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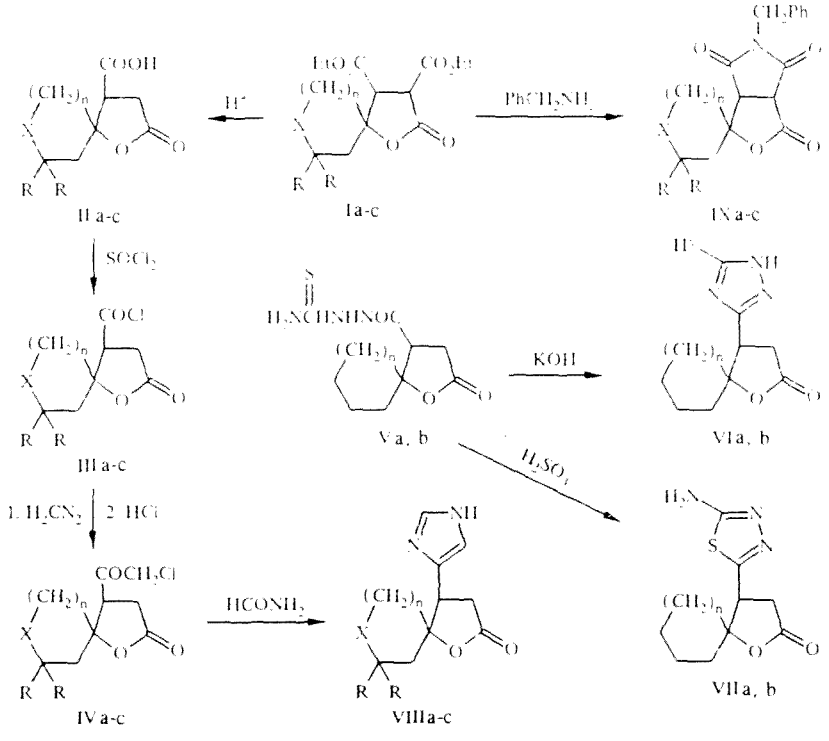
The diethyl esters of 2-oxo-1-oxaspiro[4,4]nonan-3,4-dicarboxylic, 2-oxo-1-oxaspiro[4,5]decan-3,4-dicarboxylic and 7,7-di-methyl-1,8-dioxaspiro-[4,5]decan-3,4-dicarboxylic acids (Ia-c) are transformed by hydrochloric acid into 2-oxo-1-oxa-spiro]4,4]nonan-, 2-oxo-1-oxaspiro-[4,5]decan-, and 7,7-dimethyl-1,8-dioxaspiro[4,5]decan-4-carboxylic acids (IIa-c), which are converted into the acyl chlorides IIIa-c, and the latter into the chloromethyl ketones IVa-c. Reaction of the acyl chlorides of IIa and IIb with thiosemicarbazide gives the acid thiosemicarbazides Va and Vb, which form the triazoles VIa and VIb in potassium hydroxide solution, and the thiadiazoles VIIa an VIIb in sulfuric acid. Reaction of the chloromethyl ketones IVa-c with formamide gives the imidazoles VIIIa-c. The diesters Ia-c react with benzylamine to form the N-benzylimides IXa-c.

Earlier we developed a convenient method for the synthesis of 3,4-diethoxycarbonylcarbo(heteryl)cyclospirobutanoic lactones [1, 2]. Simultaneously it was shown that the diesters could easily be transformed into the monoesters, since the deethoxycarbonylation certainly proceeds on position 3 of the butanoic lactone ring. In continuing studies of the chemical properties of 3,4-diethoxycarbonylcarbo(hetero)-cyclospirobutanoic lactones, we investigated their behavior in acidic medium. The diesters Ia-c hydrolyzed upon boiling in concentrated hydrochloric acid. At the same time, the decarboxylation of the butanoic lactone also proceeded on position 3, resulting in the formation of the monoacids IIa-c. Based upon the acids



I–IX a R=H, X=CH_2, n=1; b R=H, X=CH_2, n=2; c R=Me, X=O, n=2

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obtained, we developed a method for the preparation of derivatives of carbo(hetero)-cyclospirobutanoic lactones containing a triazole, thiadiazole, or imidazole heterocycle in position 4 of the butanoic lactone ring. The acids IIa-c were transformed into the acyl chlorides IIIa-c. The reaction of IIa, b with thiosemicarbazide in pyridine at 0°C gave the acid thiosemicarbazides Va-c, which cyclized in the presence of potassium hydroxide into the triazoles VIa-c, and in the presence of concentrated sulfuric acid into the thiadiazoles VIIa, b. The triazoles and thiadiazoles obtained were crystalline materials, insoluble in the usual organic solvents. In contrast to the thiadiazoles, the triazoles were easily soluble in 10% sodium hydroxide solution. For the synthesis of the imidazoles derivatives VIIIa-c of the carbo(hetero)cyclospirobutanoic lactones, the chloromethyl ketones IVa-c, prepared from the acyl chlorides IIIa-c, were condensed with formamide. Characteristic resonance absorptions in the ^1H NMR spectra of the imidazoles VIIIa-c showed signals of the hydrogen atom of the CH=N group at 7.73 ppm.

We also developed a method for the synthesis of N-benzylimides of the carbo(hetero)cyclospirobutanoic lactones IXa-c by condensation of the diesters Ia-c with benzylamine using a small quantity of methanol. In the ^1H NMR spectra, the protons in position 3 and 4 of the butanoic lactone ring occurred in the form of a doublet at 3.36 and 3.96 ppm for IXa, 3.43 and 3.93 ppm for IXb, and 3.20 and 4.23 ppm for IXc.

The structures of the compounds obtained were confirmed by IR, ^1H NMR and mass spectrometry.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument and the ^1H NMR spectra with a Varian T-60 instrument in $CDCl_3$ (IIa, b; IIIa-c; IVa-c; VIIIa-c), CD_3OD (IXa-c), and DMSO-d_6 (IIc, Va, b, VIIa, b), and Varian T-100 in DMSO-d_6 (Va, b). The mass spectra were obtained with a MX-1303 spectrometer using direct introduction of the sample and ionization energy of 50 eV. The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates using the systems chloroform–acetone, 8:2 (IIa-c, IIIa-c, VIIIb, c); chloroform–acetone, 1:1 (VIIIa); chloroform–methanol, 8:2 (Vb, VIb, VIIIa); acetone–benzene, 5:3(Va); and chloroform–ethanol, 8:2(Vb, VIb, VIIIa); acetone–benzene, 5:3(Va); and chloroform–ethanol, 8:2, (IXa-c).

Elemental analysis data for the synthesized compounds for C, H, N, and S corresponded with the calculated values.

Characteristics of the synthesized compounds are presented in Table 1.

2-Oxo-1-oxaspiro[4,4]nonan-4-carboxylic Acid (IIa, $C_9H_{12}O_4$), 2-Oxo-1-oxaspiro[4,5]decan-4-carboxylic Acid (IIb, $C_{10}H_{14}O_4$), and 7,7-Dimethyl-2-oxo-1,8-dioxaspiro[4,5]decan-4-carboxylic Acid (IIc, $C_{11}H_{16}O_5$). A mixture of 0.1 mole of compound Ia-Ib in 148 ml of concentrated hydrochloric acid was boiled for 5 h. After cooling, the resulting crystals were filtered off and washed with a small portion of ether. Recrystallization was from water for IIa and IIb, and from ethanol for IIc.

2-Oxo-1-oxaspiro[4,4]nonan-4-carbonyl Chloride (IIIa, $C_9H_{11}ClO_3$), 2-Oxo-1-oxaspiro[4,5]decan-4-carbonyl Chloride (IIIb, $C_{10}H_{13}ClO_3$), and 7,7-Dimethyl-2-oxo-1,8-dioxaspiro[4,5]decan-4-carbonyl Chloride(IIIc, $C_{11}H_{15}ClO_4$). A suspension of 0.1 mole of acid IIIa-c in 200 ml of absolute benzene and 17.8 g (0.15 mole) of thionyl chloride was boiled for 6 h and the benzene and excess thionyl chloride were removed under reduced pressure. Seventy ml of absolute benzene was added to the residue and distilled twice, and the residue was then distilled under vacuum.

2-Oxo-4-chloroacetyl-1-oxaspiro[4,4]nonane (IVa, $C_{10}H_{13}ClO_3$), 2-Oxo-4-chloroacetyl-1-oxaspiro[4,5]decane (IVb, $C_{11}H_{15}ClO_3$, and 7.7-Dimethyl-2-oxo-10-dioxaspiro[4,5]decane (IVc, $C_{12}H_{17}ClO_4$). To an ethereal solution of diazomethane, prepared from 41 g (0.4 mole) of N-nitrosomethyl urea, was added with stirring and cooling to −5°C and 100 ml of concentrated hydrochloric acid was added dropwise and the mixture was stirred for 1 h. The ether layer was separated and the aqueous layer, neutralized with potassium acetate, was extracted with ether. The extracts were washed with water and dried with anhydrous calcium chloride. After distillation of the solvent, the crystals formed were washed with ether and recrystallized from ethanol.

Thiosemicarbazides of 2-Oxo-1-oxaspiro[4,4]nonan-4-carboxylic Acid (Va, $C_{10}H_{15}N_3SO_3$) and 2-Oxo-1-oxaspiro[4,5]decan-4-carboxylic Acid (Vb, $C_{11}H_{17}N_3SO_3$). A suspension of 0.19 mole of thiosemicarbazide in 100 ml of dry pyridine was treated with stirring and cooling to 0°C with 0.19 mole of acryl chloride IIIa or IIIb in 100 ml of dry benzene over 30 min. The stirring was continued for an additional 4 h until complete solution of the thiosemicarbazide. The solution was kept at room temperature for 12 h, and 1.3 liters of water was added with stirring, and the stirring was continued for 2 h until complete solidification of the residue, which was then filtered, washed with 300 ml of water, and recrystallized from acetone.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp °C or bp °C(mm Hg)	R_f	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, Δ, ppm (J, Hz)	M*	Yield, %
IIa	152...153	0,41	1720 (C=O, Acid); 1810 (C=O, Lactone); 3100, 3200 (OH, Acid.)	1,36...2,43 (8H, m, 6,7,8,9-CH_2); 2,56...2,93 (2H, m, 3-CH_2); 3,13...3,40 (1H, m, 4-CH); 10,16 (1H, s, COOH)	184	35
IIb	190	0,50	1735 (C=O Acid); 1760 (C=O, Lactone.); 3100, 3200 (OH, Acid.)	1,30...1,96 (10H, m, 6,7,8,9,10-CH_2), 2,46...3,30 (3H, m, 3-CH_2 and 4-CH)	198	70
IIc	190...192	0,80	1720 (C=O, Acid); 1780 (C=O, Lactone); 3100, 3200 (OH, Acid.)	1,20 s and 1,30 s (at 3H, 7-CH_3)$_2$; 1,41 ..2,26 (4H, m, 6,10-CH_2), 2,40...2,93 (3H, m, 3-CH_2, 4-CH); 3,43 4,16 (2H, m, 9-CH_2); 11,20 (1H, s, COOH)	228	54
IIIa	163...165 (3)	–	–	1,46...2,30 (8H, m, 6,7,8,9-CH_2); 2,73...3,00 (2H, m, 3 CH_2); 3,61...4,03 (1H, m, 4-CH)	–	90
IIIb	168...171 (3)	–	–	1,13...2,36 (10-H, m, 6,7,8,9,10-CH_2); 2,73 (2H, d, 3-CH_2); 3,36...3,83 (1H, m, 4-CH)	–	94
IIIc	158...160 (3)	–	–	1,23 s and 1,30 s (at 3H, 7-(CH$_3$)$_2$); 1,50...2,16 (4H, m, 6,10-CH_2); 2,26...3,16 (2H, m, 3-CH_2); 3,33...3,96 (3H, m, 4-CH, 9-CH_2)	–	87
IVa	50...52	0,74	1720 (C=O, Ketone); 1760 (C=O, Lactone.)	1,50...2,16 (8H, m, 6,7,8,9-CH_2); 2,66...2,93 (2H, d, 3-CH_2); 3,70...3,93 (1H, m, 4-CH); 4,30 (2H, s, CH_2CO)	216/218	60
IVb	130...132	0,73	1725 (C=O, Ketone); 1750 (C=O, Lactone.)	0,80...2,00 (10H, m, 6,7,8,9,10-CH_2); 2,92...3,8 (3H, m, 3-CH_2 and 4-CH); 4,15 (2H, s, CH_2CO)	231/233	87
IVc	86	0,55	1700 (C=O, Ketone); 1760 (C=O, Lactone)	1,26 (3H, s, 7-CH_3); 1,36 (3H, s, 7-CH_3); 1,46...1,73 (2H, m, 10-CH_2); 1,90 (2H, s, 6-CH_2); 2,65...3,00 (2H, m, 3-CH_2); 3,40...4,10 (3H, m, 3-CH_2 and 4-CH)	–	45
Va	168...170	0,53	1750 (C=O, Lactone); 3200 (1H, Thioamide.)	1,30...1,63 (8H, m, 6,7,8,9-CH_2); 2,16...2,86 (3H, m, 3-CH_2, 4-CH); 7,40 (2H, d, NH_2); 13,26 (1H, s, C–NH); 14,43 (1H, s, CONH)	–	60
Vb	130...132	0,52	1460 (C=S); 1750 (C=O Lactone.); 3180...3200 (NH, Thioamide)	1,13...2,13 (10H, m, 6,7,8,9,10-CH_2); 2,55...3,15 (3H, m, 3-CH_2, 4-CH); 7,88 (2H, d, NH_2); 9,48 (1H, s, C–NH), 10,17 (1H, s, CONH)	–	72

TABLE 1 (continued)

VIa	255...256	0.56	1680 (C=O, Lactone); 3100 (NH)	–	–	93
VIb	170...172	0,41	1690 ((C=O, Lactone); 3200 (NH)	–	253	91
VIIa	235...236	0,56	1680 (C=O, Lactone; 3100 (NH_2)	1,00...1,90 (8H, m, 6,7,8,9-CH_2); 2,40...2,70 (1H, m, 4-CH); 2,85...4,30 (2H, m, 3-CH_2)	239	76
VIIb	182...185	0,43	1690 (C=O, Lactone); 3100...3200 (NH_2)	1,02...2,00 (10H, m, 6,7,8,9,10-CH_2); 2,45...2,85 (1H, m, 4-CH); 2,90...3,55 (2H, m, 3-CH_2)	253	74
VIIIa	167...168	0,50	1600 (C=C); 1650 (C=N); 1750 (C=O, Lactone); 3100 (NH, Imidazole)	1,33...2,33 (8H, m, 6,7,8,9-CH_2); 2,80...3,03 (2H, m, 3-CH_2); 3,21...3,40 (1H, m, NH); 3,60...4,00 (1H, m, 4-CH); 7,06 (1H, s, 5'-C=CH); 7,73 (1H, s, 2-N=CH)	206	70
VIIIb	160...162	0,64	1580 (C=C); 1650 (C=N); 1760 (C=O, Lactone); 3110 (NH, Imidazole)	0,73...2,13 (10H, m, 6,7,8,9,10-CH_2); 2,73...3,13 (2H, m, 3-CH_2); 3,23...3,76 (2H, m, NH, 4-CH); 7,10 (1H, s, 5'-C=CH); 7,73 (1H, s, 2-N=CH)	220	70
VIIIc	Amorph.	0,55	1600 (C=C); 1650 (C=N); 1760 (C=O, Lactone); 3100...3110 (NH, Imidazole)	1,23 (3H, s, 7-CH_3); 1,36 (3H, s, 7-CH_3); 1,30...1,60 (2H, m, 10-CH_2); 1,70 d and 1,90 d (at 1H, 6-CH_2); 2,70...3,10 (2H, m, 3-CH_2); 3,20...3,50 (1H, m, NH); 3,60...3,80 (1H, m, 4-CH); 7,09 (1H, s, 5'-C=CH); 7,71 (1H, s, 2-N=CH	–	72
IXa	120...122	0,67	1580...1600 (C=C, Aromatic); 1695, 1750 (C=O, Imide); 1780 (C=O, Lactone)	1,53...2,06 (8H, m, 6,7,8,9-CH_2); 3,43 (1H, d, J = 8, 4-CH); 3,93 (1H, d, J = 8, 3-CH); 4,56 (2H, s, N–CH_2); 7,13...7,16 (5H, m, C_6H_5)	299	50
IXb	128...130	0,64	1600 (C=C, Aromatic); 1695, 1755 (C=O, Imide); 1780 (C=O, Lactone)	1,40...1,86 (10H, m, 6,7,8,9,10-CH_2); 3,36 (1H, d, J = 8, 4-CH); 3,96 (1H, d, J = 8, 3-CH); 4,60 (2H, s, N–CH_2); 7,23...7,40 (5H, m, C_6H_5)	313	40
IXc	194...195	0,60	1580...1610 (C=C, Aromatic); 1690, 1750 (C=O, Imide); 1780 (C=O, Lactone)	0,86 (3H, s, 7-CH_3); 0,96 (3H, s, 7-CH_3); 1,1...2,00 (4H, m, 6,10-CH_2); 3,20 (1H, d, J = 8, 4-CH); 3,30...3,60 (2H, m, 9-CH_2); 4,23 (1H, d, J = 8, 3-CH); 4,40 (2H, s, N–CH_2)	343	42

2-Oxo-4-(5′-mercapto-1′,2′,4′-triazol-3′-yl)-1-oxaspiro[4,5]nonane (VIa, $C_{10}H_{13}N_3SO_2$) and 2-Oxo-4-(5′-mercapto-1′,2′,4′-triazol-3′-yl)-1-oxaspiro[4,5]decane (VIb, $C_{11}H_{15}N_3SO_2$). A mixture of 0.02 mole of thiosemicarbazide Va or Vb and 1.75 g (0.032 mole) of potassium hydroxide in 25 ml of water was boiled for 2 h, filtered, cooled, acidified with acetic acid, and kept overnight. The resulting crystals were filtered off and recrystallized from methanol.

2-Oxo-4-(2′-amino-1′,3′,4′-triazol-5′-yl)-1-oxaspiro[4,4]nonane (VIIa, $C_{10}H_{13}N_3SO_2$) and 2-Oxo-4-(2′-amino-1′,2′,4′-triazol-5′yl))-1-oxaspiro[4,5]decane (VIIb, $C_{11}H_{15}N_3SO_2$). A mixture of 0.03 mole of the thiosemicarbazide Va or Vb in 42 ml of concentrated sulfuric acid was stirred until complete solution, then poured into 250 ml of ice water. The crystals were filtered off washed with 75 ml of water and recrystallized from methanol.

4-(Imidazolyl-4′-yl)-2-oxo-1-oxaspiro[4,4]nonane (VIIIa, $C_{11}H_{14}N_2O_2$ and 4-(Imidazolyl-4′-yl)-2-oxo-1-oxaspiro[4,5]decane (VIIIb, $C_{12}H_{16}N_2O_2$ and 7,7-Dimethyl-4-(imidazolyl-4′-yl)-2-oxo-1,8-dioxaspiro[4,5]decane (VIIIc, $C_{12}H_{18}N_2O_3$. A mixture of 0.07 mole of the corresponding IVa-c in 86 ml of formamide was boiled for 2 h. After cooling, 140 ml of 3 N hydrochloric acid and 5 g of activated charcoal were added, and the mixture was boiled for 15 min. The mother liquor was filtered off, cooled, and 50 ml of 25% ammonia solution was added, and the mixture was kept in a refrigerator overnight. The resulting crystal were filtered and recrystallized from a 1:1 mixture of benzene–petroleum ether.

N-Benzyl-2-oxo-1-oxaspiro[4,4]nonan-3,4-dicarboximide (IXa, $C_{17}H_{17}NO_4$), N-Benzyl-2-oxo-1-oxaspiro-[4,5]decan-3,4-dicarboximide (IXb, $C_{18}H_{19}NO_4$), and N-Benzyl-7,7-dimethyl-2-oxo-1,8-dioxaspiro[4,5]decan-3,4-dicarboximide (IXc, $C_{19}H_{21}NO_5$). A mixture of 0.2 mole of the corresponding diethyl ester Ia-c, 0.02 mole of benzylamine and 5 ml of methanol was stirred at 55-60°C in a water bath for 1 h. Then the heating was continued for an additional hour under reduced pressure and the residue was dissolved in ether, washed with 15% hydrochloric acid solution, water, and saturated sodium bicarbonate solution. The solution was dried with magnesium sulfate, concentrated, and the residue was dissolved in 30 ml of absolute ether and kept overnight. The resulting crystals were separated and recrystallized from ethanol (cf. Table 1).

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