SYNTHESIS OF TRI- AND TETRAMETHYLENE[b]PYRROLE DERIVATIVES FROM 2-(1-ETHOXY-2-BROMOETHYL)CYCLO-ALKANONES

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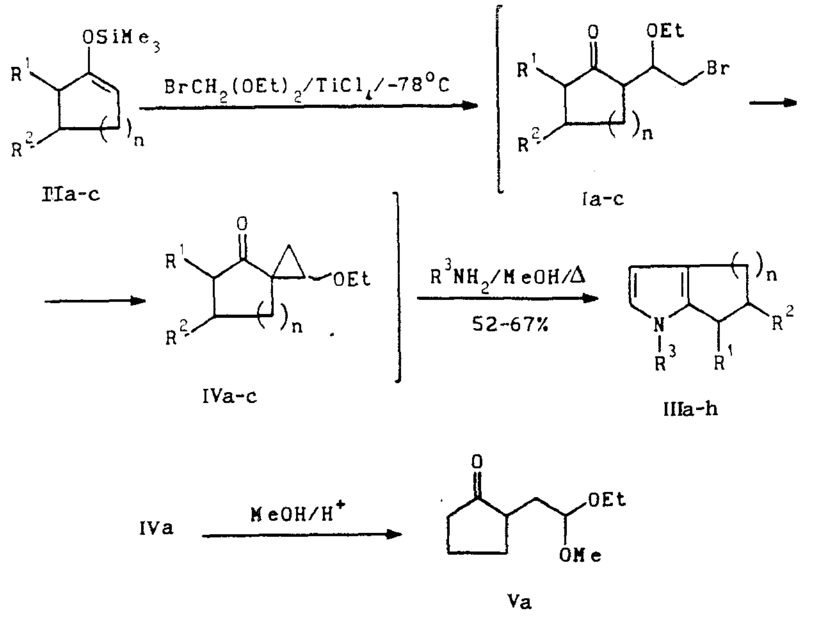
Tri- and tetramethylene[b]pyrrole derivatives were synthesized by treatment of the corresponding 2-(1-ethoxy-2-bromoethyl)cycloalkanones with an aqueous solution of sodium hydroxide and a methanol solution of a primary amine. The transformation proceeds through a step involving 1,3-dehydrobromination and opening of the three-membered ring in the intermediately formed spirocyclic ketones.

Many effective methods for obtaining pyrroles are based on the use of aliphatic compounds as the starting substances [1-3]. In a recently proposed approach to the synthesis of pyrroles aryl 3-bromo-2-methoxypropyl ketones, which are obtained by the reaction of aryl allyl ketones with N-bromosuccinimide and are readily converted to pyrrole derivatives by the action of primary amines, were used as the starting substrates [4].

We have found that a similar approach can be used successfully in the synthesis of pyrroles condensed with cyclopentane and cyclohexane rings. The corresponding 2-(1-ethoxy-2-bromoethyl)cycloalkanones Ia-c were obtained in this case in analogy with [5] by condensation of silyl ethers IIa-c of cyclic enols with bromoacetaldehyde diethylacetal in the presence of titanium tetrachloride. Good yields of the corresponding pyrrole derivatives IIIa-c (see Table 1) were obtained in a two-step synthetic scheme that includes the reaction



I, II, IVa $n = 1$, $R^1 = R^2 = H$; b $n = 2$, $R^1 = R^2 = H$; c $n = 2$, R^1, $R^2 = C_4H_4$; IIIa $n = 1$, $R^1 = R^2 = H$, $R^3 = CH_3$; b $n = 1$, $R^1 = R^2 = H$, $R^3 = C_6H_5CH_2$; c $n = 2$, $R^1 = R^2 = H$, $R^3 = CH_3$; d $n = 2$, $R^1 = R^2 = H$, $R^3 = C_6H_5$; e $n = 2$, $R^1 = R^2 = R^3 = H$; g $n = 2$, $R^1 = R^2 = C_4H_4$, $R^3 = CH_3$; h $n = 2$, $R^1 = R^2 = C_4H_4$, $R^3 = C_6H_5CH_2$

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TABLE 1. Characteristics of Tri- and Tetramethylene[b]pyrroles IIIa-h

Compound	n_D (T, °C)	PMR spectrum, δ, ppm (J, Hz)	Yield,* %
III a	1,5171 (20)	2,2...2,5 (6H, m); 3,36 (3H, s); 5,68 (1H, d J = 3); 6,18 (1H, d J = 3)	60
III b	1,5410 (19)	2,0...2,56 (6H, m); 4,66 (2H, s); 5,60 (1H, d, J = 3); 6,23 (1H, d J = 3); 6,67...7,16 (5H, m)	61
IIIc	1,5492 (19)	1,33...1,90 (4H, m); 2,10...2,43 (4H, s); 3,23 (3H, s); 5,51 (1H, d J = 3); 6,10 (1H, d J = 3)	66
IIId	1,5892 (21)**	1,56...1,80 (4H, m); 2,26...2,60 (4H, m); 5,76 (1H, d, J = 3); 6,46 (1H, d J = 3); 7,10 (5H, d)	52
IIIe	—***	1,33...1,90 (4H, m); 2,10...2,53 (4H, s); 5,57...5,73 (1H, m); 6,16...6,30 (1H, m); 5,56...7,40 (1H, m NH)	62
IIIg	1,5315 (20)	2,33...2,83 (4H, m); 3,63 (3H, s); 5,66 (1H, d, J = 3); 6,13 (1H, d, J = 3); 6,56...7,18 (4H, m)	67
III h	1,5600 (22)	2,30...2,81 (4H, m); 5,10 (2H, s); 5,81 (1H, d J = 3); 6,23 (1H, d J = 3); 6,56...7,20 (9H, m)	52

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*The yields are based on IIa-c.

**According to [9], n_D^{20} 1.5960.

***According to [10], mp 50°C.

of cycloalkanones Ia-c with an aqueous solution of sodium hydroxide and treatment of the resulting spiro ketones IVa-c with a methanol solution of the corresponding primary amine or ammonium hydroxide. The yields of pyrroles IIIa-c ranged from 52% to 67% based on the starting silyl ethers of the enol forms of cyclopentanone (IIa), cyclohexanone (IIb), and tetralone (IIc).

Compounds IVa-c are unstable, and their isolation in the individual state was difficult; the PMR spectra of the reaction mixtures, in contrast to those for alkyl 2-methoxycyclopropyl ketones [6], were not sufficiently informative. Judgment in favor of the formation of spiro ketones IVa-c was arrived at in the case of spiro[2,3]-1-ethoxy-4-heptanone (IVa) from the characteristic (for activated vicinally oriented p-electron-donor and π-electron-acceptor substituents of cyclopropanes) acid-catalyzed methanolysis [7, 8], which leads to 2-(2-methoxy-2-ethoxyethyl)-1-cyclopentanone (Va) in 52% yield based on silyl ether IIa (see the Experimental).

EXPERIMENTAL

The PMR spectra of 10% solutions of the investigated substances in CCl_4 were recorded with a Tesla BS 467-A spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The purity of the investigated compounds was monitored by TLC on Silufol plates with development by iodine vapors.

2-(1-Ethoxy-2-bromoethyl)cycloalkanones (Ia-c). A 2.85-g (15 mmole) sample of titanium tetrachloride was added dropwise at −78°C in a stream of argon to a solution of 1.97 g (10 mmole) of bromoacetaldehyde diethylacetal in 150 ml of dichloromethane, after which 11 mmole of enol silyl ether IIa-c was added, and the reaction mixture was stirred at this temperature for 2 h. It was then poured into cold saturated sodium bicarbonate solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 × 50 ml). The combined organic layers were dried with calcium chloride, the drying agent was removed by filtration, and the solvent was removed in vacuo. The residue was used in the subsequent transformations. PMR spectra: Ia: 0.8-1.1 (3H, m, CH_3), 1.5-2.6 (7H, m, $3CH_2$, CH), 3.2-4.1 ppm (5H, m, $2CH_2$, CH); Ib: 1.0 (3H, m, J = 7 Hz, CH_3), 1.3-2.6 (9H, m, $4CH_2$, CH), 3.1-3.9 ppm (5H, m, $2CH_2$, CH); Ic: 0.8-1.1 (3H, m, CH_3), 1.93-2.1 (2H, m, CH_2), 2.2-2.9 (3H, m, CH_2, CH), 3.0-3.6 (4H, m, $2CH_2$), 3.8-4.3 (1H, m, CH), 6.7-7.3 (3H, m, 3CH), 7.5-8.0 ppm (1H, m, CH).

Tri- and Tetramethylene[b]pyrrole Derivatives (IIIa-h). Diethyl ether (25 ml) and 75 ml of 2% aqueous NaOH were added to the cycloalkanones Ia-c obtained via the method presented above, and the mixture was stirred for 1 h. The ether layer was separated, and the aqueous layer was extracted with ether (3 × 25 ml). The combined ether extracts were dried with

Na_2SO_4, the drying agent was removed by filtration, and the ether was removed in vacuo at a bath temperature of 20-25°C. The residue was mixed with 30 mmole of a primary amine in 15 ml of methanol (with 15 ml of 25% ammonium hydroxide in the preparation of IIIe), and the mixture was refluxed for 1 h. The methanol was then removed in vacuo, 50 ml of ether was added to the residue, and the resulting solution was washed successively with saturated sodium bicarbonate solution and water. To obtain IIIe the reaction mixture was extracted with ether (3 × 10 ml). The combined ether extracts were dried with Na_2SO_4, after which the drying agent was removed by filtration, the solvent was removed, and the residue was chromatographed with a column packed with silica gel (40/100) by elution with hexane—ether (20:1).

2-(2-Methoxy-2-ethoxyethyl)-1-cyclopentanone (Va). The solvent was removed at a bath temperature of 20-25°C from the ether solution of spiro[2,4]-1-ethoxy-4-heptanone (IVa) obtained via the method presented above from 11 mmole of silyl ether IIa and 10 mmole of bromoacetaldehyde diethylacetal, the residue was dissolved in 15 ml of methanol, several small crystals of p-toluenesulfonic acid were added, and the reaction mixture was maintained at room temperature for 1 h. The methanol was removed in vacuo, the residue was dissolved in 20 ml of ether, and the solution was washed successively with saturated sodium bicarbonate solution and water and dried with Na_2SO_4. The solvent was removed, and the residue was fractionally distilled in vacuo to give 0.91 g (52%) of cyclopentanone Va with bp 68-70°C (5 mm) and n_D^{20} 1.4550. PMR spectrum, δ, ppm: 1.0 (3H, t, J = 7 Hz), 1.3-2.5 (9H, m), 3.10 (3H, s), 3.3-3.5 (2H, m), 4.40 (1H, t, J = 6 Hz).

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