Synthesis of some new derivatives of 6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene

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Reactions of ethyl 6-substituted 4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates with Lawesson's reagent, hydrazine hydrate and lithium aluminum hydride are described.

Key words: 6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulenes, thiones, Lawesson's reagent, synthesis

INTRODUCTION

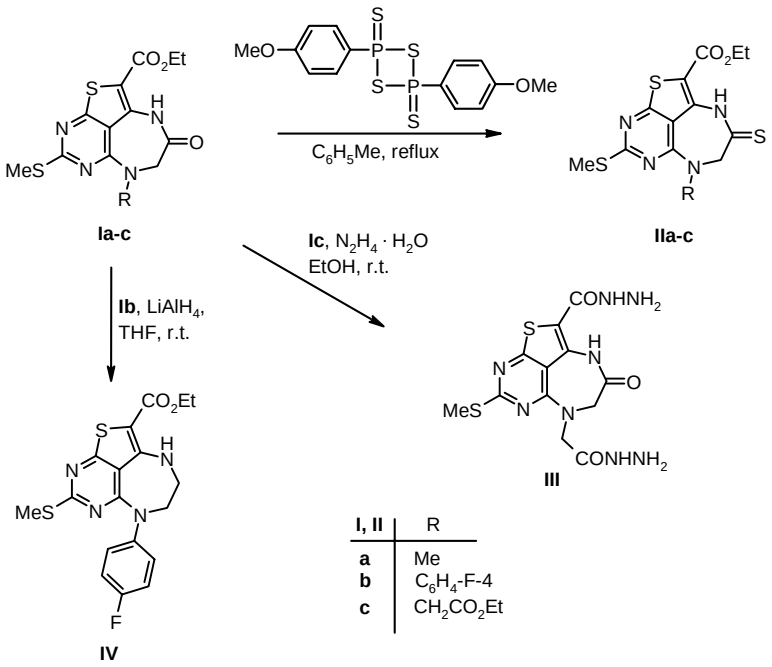
The importance of fused pyrimidines, which are common sources for the development of new potential therapeutic agents, is well known. Among them the thienopyrimidines and their tri- and tetracyclic relatives as well as fused diazepines are of considerable interest and many of them have been shown to possess diverse biological activity [1–10]. Recently we have described the preparation of novel heterocycles in which the thienopyrimidine is *ortho-peri* fused with 1,4-diazepine [11, 12] or 1,2,4-triazepine moieties [13]. However, no work has been done on the chemical properties of these tricyclic heterosystems. In this connection we present herein the results of a study of some 6-substituted ethyl 4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates with Lawesson's reagent, hydrazine hydrate and lithium aluminum hydride. Taking into account that the compounds studied bear such functional groups as ester, amide and methylthio groups capable of interacting with the selected reagents, it was of interest to identify the most reactive sites in the molecules as well.

RESULTS AND DISCUSSION

Ethyl 6-substituted 4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates (**I a–c**) have been synthesised by the acylation reaction of the corresponding ethyl 4,5-diaminothieno[2,3-*d*]pyrimidine-6-carboxylates with chloroacetyl chloride and subsequent intramolecular cyclocondensation of the obtained 5-chloroacetylaminothienopyrimidines in the presence of potassium carbonate [11, 12].

Two most often used reagents for the conversion of the carbonyl group into the corresponding thioxo group are phosphorous pentasulfide and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent). Although phosphorous pentasulfide in the reactions with carbonyl compounds usually gives good results, its selectivity is poor when several carbonyl groups are present in the molecule. Taking into account that there are two different carbonyl groups in compounds **I a–c** and in order to synthesise monothioxo derivatives, we chose Lawesson's reagent as more selective in these reactions [14].

Thus, heating compounds **I a–c** with 0.62 equivalent of Lawesson's reagent in the aprotic solvent toluene afforded the 8-thioxo derivatives **II a–c** in 57–63% yields as the only reaction products. The structure assignments of **II a–c** were based on their spectral data. In the ^{1}H NMR spectra chemical shifts of signals of the ethoxy group were practically the same as those of compounds **I a–c**, whereas the signal due to the CH_2(C = S) group was downfield shifted for *ca.* 0.3 ppm in comparison with the corresponding signal of the CH_2(C = O) group of **I a–c** [11, 12]. Moreover, in the IR spectra of compounds **II a–c** one absorption band of the carbonyl group disappeared and the thiolactam absorption band was found in a region 1452–1444 cm^{-1} instead. Ethyl 2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates (**I a–c**) were found to be rather inert to-



wards hydrazine hydrate. Compounds **I a, b** did not give satisfactory results even after prolonged heating with hydrazine hydrate without solvent. Only in the reaction of **Ic** with an excess of hydrazine hydrate, hydrazinolysis of both ester groups occurred to give compound **III**. Reduction of compounds **I a–c** with lithium aluminum hydride was ambiguous again. The reactions proceeded with the formation of complex inseparable mixtures. We succeded in isolating the product in a low 9% yield only from the reaction of **Ib** with lithium aluminum hydride. According to the ^{1}H NMR and IR spectra (see Experimental) it appeared to be ethyl 6-(4-fluorophenyl)-4-methylthio-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylate (**IV**).

EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls on a Perkin-Elmer FT-IR Spectrum BX II spectrophotometer. ^{1}H-NMR spectra were recorded with a Tesla BS 587A spectrometer (80 MHz) using tetramethylsilane as internal standard. All reactions and purity of the synthesized compounds were monitored by TLC using silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light.

***Ethyl 6-substituted 4-methylthio-8-thioxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[cd]azulene-1-carboxylates* (II a–c).** *Typical procedure*. A mixture of the corresponding compound **Ia-c** (1.0 mmol) and Lawesson's reagent (0.25 g, 0.62 mmol) in toluene (30 ml) was refluxed for 3.5–6.5 h. After cooling to room temperature the precipitate was filtered off and the filtrate was concentrated to 1/3 of the initial volume. The solid was collected, combined with that earlier obtained and recrystallized to give compounds **II a–c**.

IIa: The reaction time 5 h. Yield 63%, m. p. 221–223 °C (from toluene). IR (cm^{-1}): 3240 (NH), 1673 (C = = O), 1450 (C = S). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.40 (3H, t, J = 7 Hz, CH_3), 2.59 (3H, s, SCH_3), 3.38 (3H, s, NCH_3), 4.40 (2H, q, J = 7 Hz, OCH_2), 4.48 (2H, s, CH_2CS), 11.73 (1H, br. s, NH). Elemental analysis data: found, %: C 44.28; H 3.80; N 15.73; formula $C_{13}H_{14}N_4O_2S_3$; calculated, %: C 44.05; H 3.98; N 15.81.

IIb: The reaction time 3.5 h. Yield 57%, m. p. 179–180 °C (from ethyl acetate). IR (cm^{-1}): 3201 (NH), 1671 (C =O), 1444 (C = S). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.42 (3H, t, J = 7 Hz, CH_3), 2.30 (3H, s, SCH_3), 4.41 (2H, q, J = 7 Hz, OCH_2), 4.87 (2H, s, CH_2CS), 6.8–7.5 (4H, m, aromatic prot.), 11.83 (1H, br. s, NH). Elemental analysis data: found, %: C 50.02; H 3.43; N 13.10; formula $C_{18}H_{15}FN_4O_2S_3$; calculated, %: C 49.75; H 3.48; N 12.89.

IIc: The reaction time 6.5 h. Yield 57%, m. p. 186.5–187.5 °C (from ethyl acetate). IR (cm^{-1}): 3246 (NH), 1735 (C = O), 1675 (C=O), 1452 (C = S). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.30 (3H, t, J = 7 Hz, CH_3), 1.43 (3H, t, J = 7 Hz, CH_3), 2.54 (3H, s, SCH_3), 4.21–4.47 (4H, m, $2OCH_2$), 4.47 (2H, s, CH_2CS), 4.64 (2H, s, NCH_2), 11.80 (1H, br. s, NH). Elemental analysis data: found, %: C 45.28; H 4.24; N 13.01; formula $C_{16}H_{18}N_4O_4S_3$; calculated, %: C 45.06; H 4.25; N 13.14.

***Hydrazide of 6-(hydrazinocarbonylmethyl)-4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[cd]azulene-1-carboxylic acid* (III).** A mixture of compound **Ic** (0.15 g, 0.365 mmol), ethanol (5 ml) and hydrazine hydrate (0.071 ml, 1.42 mmol) was stirred at room temperature for 14 h. The precipitate was filtered off and recrystallized to give 0.05 g (36%) of compound **III**, m. p. 270 °C (dec.) (from DMF). IR (cm^{-1}): 3378–3111 (NH, NH_2), 1674 (C = = O), 1657 (C = O), 1621 (C = O). ^{1}H NMR (CF_3COOD, δ, ppm): 2.40 (3H, s, SCH_3), 4.36 (2H, s, CH_2CO), 4.84 (2H, s, NCH_2). Elemental analysis data: found, %: C 37.82; H 3.55; N 29.41; formula $C_{12}H_{14}N_8O_3S_2$; calculated, %: C 37.69; H 3.69; N 29.30.

***Ethyl 6-(4-fluorophenyl)-4-methylthio-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[cd]azulene-1-carboxylate* (IV).** To a solution of compound **IIb** (0.35 g,

0.84 mmol) in tetrahydrofurane (10 ml) a solution of lithium aluminum hydride (0.038 g, 1.0 mmol) in tetrahydrofurane (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3.5 h. Then an additional amount of lithium aluminum hydride (0.038 g, 1.0 mmol) was added and the reaction mixture was stirred for 12 h. An excess of lithium aluminum hydride was decomposed with ethyl acetate and then water (0.2 ml) was added. The reaction mixture was filtered off, the filtrate was concentrated under reduced pressure to dryness. The obtained solid was dissolved in chloroform and chromatographed on a column using silica gel (40–100 μm) as a sorbent and a mixture of chloroform and hexane (19:1) as an eluent. Fraction with R_f 0.43 was collected. After the evaporation of solvents, the residue was recrystallized to give 0.03 g (9%) of compound **IV**, m. p. 226–227 °C (from benzene). IR (cm^{-1}): 3378 (NH), 1649 (C = = O). ^{1}H NMR ($CDCl_3$, δ, ppm): 1.37 (3H, t, J = 7 Hz, CH_3), 2.13 (3H, s, SCH_3), 3.75–3.97 (4H, m, CH_2CH_2), 4.30 (2H, q, J = 7 Hz, OCH_2), 7.20–7.40 (4H, m, aromatic prot.), 8.10 (1H, br. s, NH). Elemental analysis data: found, %: C 53.21; H 4.39; N 13.52; formula $C_{18}H_{17}FN_4O_2S_2$; calculated, %: C 53.45; H 4.24; N 13.85.

CONCLUSION

Reaction of 6-substituted ethyl 4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates with Lawesson's reagent has been found to give the 8-thioxo derivatives as the only reaction products. Reactions of ethyl 6-(ethoxycarbonylmethyl)- or 6-(4-fluorophenyl)-4-methylthio-8-oxo-6,7,8,9-tetrahydro-2-thia-3,5,6,9-tetraazabenz[*cd*]azulene-1-carboxylates with hydrazine hydrate or lithium aluminum hydride afforded the corresponding dihydrazide or 6,7,8,9-tetrahydro derivative.

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KAI KURIŲ NAUJŲ 6,7,8,9-TETRAHIDRO-2-TIA-3,5,6,9-TETRAAZABENZ[cd]AZULENO DARINIŲ SINTEZĖ

S a n t r a u k a

Reaguojant etil 6-pakeistiems 4-metiltio-8-okso-6,7,8,9-terahidro-2-tia-3,5,6,9-teraazabenz[*cd*]lazulen-1-karboksilatams su Lavesono reagentu susidaro atitinkami 8-tiokso dariniai. Etil 6-(etoksikarbonilmetil)- ar 6-(4-fluorfenil)-4-metiltio-8-okso-6,7,8,9-tetrahidro-2-tia-3,5,6,9-tetraazabenz[*cd*]lazulen-1-karboksilatai reakcijose su hidrazinhidratu ar ličio aliuminio hidridu sudaro atitinkamą dihidrazidą arba 6,7,8,9-tetrahidrodarinį.