Synthesis of derivatives of a new heterocyclic system, 9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidine

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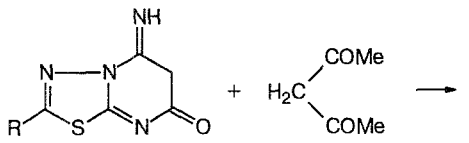
Reaction of 2-substituted 5-imino-7-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidines with pentane-2,4-dione in polyphosphoric acid yields 9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines.

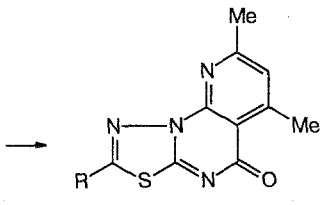
Key words: 5-imino-7-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, pentane-2,4-dione, polyphosphoric acid, cyclodehydration, 9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines.

Derivatives of 5-imino-7-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**1**) have been poorly investigated. Under conditions of the Vilsmeier—Haak reaction they are converted into 5-isocyano-7-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidines.[1] No information on the possibility of using compounds **1** for building tricyclic heterocyclic systems have been reported in the literature.

We found that compounds **1** react with an equimolar amount of pentane-2,4-dione at 90—95 °C in polyphosphoric acid (PPA) to give derivatives of previously unknown 9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidines (**2a—c**), which are close analogs of 1,3,4-thiadiazolo[2,3-*b*]quinazolines[2—4]:



1a—c



2a—c

R = H (**a**), $MeS(CH_2)_2$ (**b**), $EtS(CH_2)_2$ (**c**)

The structures of compounds **2a—c** were confirmed by ^{1}H NMR and IR spectroscopy and elemental analysis. The IR spectra of **2a—c** exhibit absorption bands at 1680—1705 cm^{-1}, due to the carbonyl group of the pyrimidine ring, and the ^{1}H NMR spectra contain no signals of methylene protons, but exhibit signals at 6.12—6.17 ppm, 2.10—2.16 ppm, and 2.42—2.50 ppm, caused by the presence of the methyne proton in position 3 and the methyl groups at the C(6) and C(8) atoms.

The signals of protons of the group R in compounds **1** and **2** are almost identical.

Experimental

IR spectra were recorded for pellets with KBr in the 400—4000 cm^{-1} range. The ^{1}H NMR spectra were obtained for DMSO-d_6 solutions on a Tesla BS-587C spectrometer operating at 100 MHz. Compounds **1a—c** were prepared by known procedures.[5,6]

Reaction of 1,3,4-thiadiazolopyrimidines (1a—c) with pentane-2,4-diones (general procedure). An equimolar mixture of **1a—c** and pentane-2,4-dione in PPA (10 mmol per 10—15 g of PPA) was heated for 5—6 h in a boiling water bath. Diluting the reaction mixture with water followed by neutralization gave **2a—c**.

6,8-Dimethyl-9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidine (2a). Colorless crystals, yield 75.5 %, m.p. 328—330 °C (from 1:5 aqueous dioxane). IR, ν/cm^{-1}: 1690 (C=O); 1545, 1490.

^{1}H NMR, δ: 9.08 (s, CH); 6.17 (s, CH); 2.50 (s, Me); 2.16 (s, Me). Found (%): C, 51.93; H, 3.33. $C_{10}H_8N_4OS$. Calculated (%): C, 51.71; H, 3.47.

6,8-Dimethyl-2-(2-methylthio)ethyl-9-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidine (2b). Colorless crystals, yield 65 %, m.p. 248—252 °C (from 1:5 aqueous dioxane). IR, ν/cm^{-1}: 2930, 1680 (C=O); 1540, 1490. ^{1}H NMR, δ: 6.12 (s, CH); 3.00 (t, CH_2); 2.68 (t, CH_2); 2.42 (s, Me); 2.10 (s, Me); 2.02 (s, Me). Found (%): C, 51.30; H, 4.37. $C_{13}H_{14}N_4OS_2$. Calculated (%): C, 50.09; H, 4.37.

6,8-Dimethyl-9-oxo-2-(2-ethylthio)ethyl-1,3,4-thiadiazolo[3,2-*a*]pyrido[3,2-*e*]pyrimidine (2c). Colorless crystals, yield 49 %, m.p. 250—252 °C (from 1:5 aqueous dioxane). IR, ν/cm^{-1}: 2935, 1685 (C=O); 1540, 1485. ^{1}H NMR, δ: 6.20 (s, CH); 3.38 (t, CH_2); 3.08 (t, CH_2); 2.76 (t, Me); 2.46 (s, Me); 2.14 (s, Me); 1.08 (s, Me). Found (%): C, 52.91; H, 5.17. $C_{14}H_{16}N_4OS_2$. Calculated (%): C, 52.4; H, 5.17.

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Effect of concentrations of salts on the formation of protein monolayers

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Effects of salts present in the subphase on the properties of monolayers, *viz.*, molecular areas of proteins and Gibbs elasticities, were studied by the monolayer method.

Key words: proteins, monolayers, molecular areas, elasticity of a monolayer.

The Langmuir—Blodgett (LB) technology is promising for the development of sensors, since it allows one to obtain oriented close-packed layers with specified characteristics.[1] The main difficulty in the preparation of LB polylayers from protein molecules is that they are soluble in the subphase; therefore, the surface pressure of an obtained monolayer is not constant and decreases with time.[2,3] Replacement of water in the subphase by an electrolyte solution (0.05 mol L^{-1} KCl) may lead to stabilization of the surface pressure. This suggests that the quantity of protein that passes to the subphase would decrease, which may finally result in the formation of stable and more close-packed monolayers.

A lot of papers have been devoted to investigation of protein monolayers; however, systematic studies of the effects of subphase salts on molecular areas of proteins are missing.[4—9] The purpose of the present work has been to study the behavior of proteins on the surface of subphases that contain no salts or contain various concentrations of salts, in order to obtain stable close-packed protein monolayers.

Experimental

Monolayers of bull serum albumin (BSA) and mouse immunoglobulin (IgG) were studied. BSA was purchased from "Sigma", and IgG was prepared by a known procedure.[10]

Protein monolayers were studied using a Joyce-Loebl set (UK) and a 200-mL bath with a surface area of 186 cm^2. Tridistilled water with pH 6.9 was used as the subphase. The effects of KCl, KNO_3, and $(NH_4)_2SO_4$ with ionic strengths μ of 0.01, 0.05, 0.1, and 0.15 were studied. Addition of a salt to the subphase resulted in an increase in the pH to 7.3—7.5.

Studies were carried out at pH 7.4, 6.5, and 5.0. For acidification, an acid having a common anion with the salt under study was used; for example, when the effect of KCl was studied, the solution was acidified by HCl (0.01 mol L^{-1}); in the calculations of the ionic strength, the concentration of the acid added was taken into account.

An aqueous solution of protein (0.01—0.05 mL) was sprayed on the surface of a subphase (288 K) and compressed to the pressure of collapse at a rate of 10 mm min^{-1}.

Three rates of compression of a protein monolayer, 10, 25, and 50 mm min^{-1}, were employed. When the rate of compression increased, the isotherms became uniform, since an inflection in the 30—35 mN m^{-1} region, typical of BSA,

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