REACTIONS OF 3-(β-HYDROXYETHYL)-8-THIAXANTHINE

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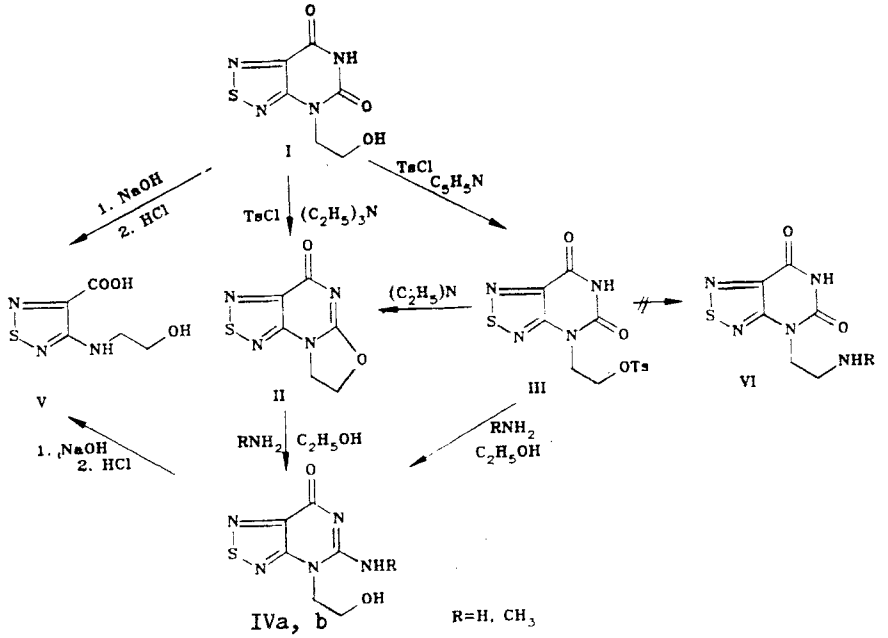
Depending on the base used, reaction of 3-(β-hydroxyethyl)-8-thiaxanthine with p-toluenesulfonylchloride either stops at the stage of formation of the tosylate or gives 1,2,5-thiadiazolo[3,4-d]oxazolidino[2,3-b]pyrimidin-9(4H)-one. Upon treatment with ammonia or methylamine, both of these compounds react to give 3-(β-hydroxyethyl)-8-thiaguanines.

Carbo- and heteroanalogs of purines are known to show antiinflammatory, antitumor, and other forms of biological activity [1]. The number of compounds finding practical application is relatively small, but the volume of investigations in this area has not diminished in recent years. In fact, the number of new structures has grown along with particular interest in their potential antimetabolite activity. Purine thio analogs have been little studied, but among the thiadiazoles and sulfur-containing purines some radio-protective properties have been reported [2, 3].

The aim of this work is to investigate the possible use of 3-(β-hydroxyethyl)-8-thiaxanthine [4] as a synthon for preparing novel 1,2,5-thiadiazoles and, in particular, 8-thiaguanines as potential, physiologically active substances.

We have shown that reaction of 3-(β-hydroxyethyl)-8-thiaxanthine (I) with toluenesulfonylchloride (TsCl), depending on the base used, can either stop at the intermediate tosylate ester III (as seen when the reaction is carried out in pyridine) or the ester III can take part in an intramolecular alkylation of the lactam form of the pyrimidine ring.



With triethylamine as base 1,2,5-thiadiazolo[3,4-d]oxazolidino[2,3-b]pyrimidin-9(4H)-one (II) is produced. Chromatographic monitoring of the reaction (in ethanol—chloroform—hexane) shows that the reaction occurs via an initial tosylation of the β-hydroxyethyl group. Upon heating to 40-50°C with alcoholic solutions of ammonia or methylamine, compound II is converted to 3-(β-hydroxyethyl)-8-thiaguanines (IV). The reaction observed is

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TABLE 1. Spectral Data for the Synthesized Compounds

Compound	Mass spectrum, m/z (I_{rel}, %)	IR spectrum, ν, cm^{-1}
I	214 (2), 185 (4), 184 (7), 183 (3), 171 (23), 141 (7), 140 (22), 85 (62), 83 (100)	3520, 1720, 1560, 1500
II	196 (5), 170 (6), 140 (10), 125 (9), 101 (100), 100 (46), 87 (31), 86 (92)	3000...2500, 1680, 1630, 1545, 1470, 1440, 1050
III	368 (5), 213 (14), 198 (11), 197 (48), 196 (100), 183 (8), 172 (12), 171 (6), 170 (11), 161 (25), 160 (40), 149 (44), 140 (49), 136 (44), 112 (12), 85 (65), 83 (99)	3270, 3120, 1720, 1540, 1490, 1350, 1170
IVa	213 (1), 183 (2), 171 (2), 170 (6), 169 (5), 140 (8), 87 (12), 85 (59), 83 (100)	3285...3050, 1650, 1620, 1550
IVb	227 (6), 210 (23), 209 (34), 208 (31), 197 (12), 196 (16), 184 (68), 183 (100), 171 (10), 168 (14), 167 (11), 140 (89), 128 (13), 125 (12), 124 (16), 112 (14), 86 (23), 85 (16), 83 (45)	3350...3150, 1630, 1590, 1530
V	189 (32), 171 (5), 158 (95), 145 (4), 140 (100), 86 (8), 85 (7), 83 (6)	3435, 3300, 1690, 1560, 1490, 1455

analogous to that seen for 2,2-anhydronucleosides in which treatment of the latter with bases causes fission of the C-nucleotide bond to form substitution products [5]. 8-Thiaguanines IV, as well as the starting 8-thiaxanthine I, form 3-(β-hydroxyethylamino)-1,2,5-thiadiazole-4-carboxylic acid (V) under alkaline hydrolysis. It might have been expected that reaction of the tosylate ester (III) with reactive amines would lead to formation of the corresponding β-aminoethyl derivatives VI. However, the reaction media yielded compounds IVa, b, which pointed to a preference for an intramolecular O-alkylation.

The structure of the thiadiazoles II, III was confirmed by spectroscopic data (Table 1). The mass spectra of the compounds synthesized showed the presence of molecular ion peaks. Dissociation under electron impact of purines containing the hydroxyethyl group (II, IV) is accompanied by β-fission of the hydroxyethyl fragment with elimination of the NHCO molecule. In addition, the tosylated ester III loses the groups Ts·, OTs·, and TsOH. The molecular ion for the tricycle II loses CN· and CH_2O stepwise. Compound V splits off the molecules H_2O, CH_2OH, and CO_2.

As might be expected, the IR spectrum of III, when compared with I, loses the strong hydroxyl band for the hydroxyl group and shows intense bands for the asymmetric (1350) and symmetric (1170 cm^{-1}) SO_2 stretching vibrations.

The intramolecular alkylation process is confirmed by the absence of the absorption band in the region for amide protons and the presence of the stretching band for the ether bond at 1050 cm^{-1} (compound II). Heteroanalogs of guanine are characterized by absorption at 3350-3050 cm^{-1}, due to the stretching vibrations of the amino and hydroxyl group protons.

EXPERIMENTAL

The purity of the compounds was monitored by TLC on Silufol UV-254-vis plates. Mass spectra were recorded on a Varian MAT-112 instrument with direct sample introduction at 200-250°C, an ionization temperature of 220°C, and ionization intensity of 70 eV. IR spectra were recorded on an IKS-29 instrument for KBr tablets.

4-(β-Tosylethyl)-1,2,5-thiadiazolo[3,4-d]pyrimidine-5,7(4H, 6H)-dione (III, $C_{13}H_{12}N_4S_2O_5$). A solution of TsCl (2.8 g, 15 mmoles) in tetrahydrofuran (THF) was added with stirring and cooling to 4-(β-hydroxyethyl)-1,2,5-thiadiazolo[3,4-d]pyrimidine-5,7(4H, 6H)-dione (I) in dry pyridine (70 ml). The reaction mixture was slowly heated to reflux, the solvent distilled off under reduced pressure, and the residue treated with cold water. The precipitate was filtered off and recrystallized from tetrahydrofuran to give 2.0 g (56%) with mp 238-240°C.

1,2,5-Thiadiazolo[3,4-d]oxazolidino[2,3-b]pyrimidin-9(4H)-one (II, $C_6H_4N_4SO_2$). A. Compound III (3.7 g, 10 mmoles) was refluxed for 0.5 h in a mixture of THF-triethylamine. The precipitate was recrystallized from chloroform to give 1.6 g (80%) with mp 179-181°C. B. A mixture of I (2.14 g, 10 mmoles) and TsCl (2.8 g, 15 mmoles) was refluxed in a mixture of THF-triethylamine. The precipitate was recrystallized from chloroform to give 1.5 g (77%) with mp 179-180°C.

4-(β-Hydroxyethyl)-5R-amino-1,2,5-thiadiazolo[3,4-d]pyrimidin-7(4H)-one (IVa, $C_6H_7N_5SO_2$). A solution of III (0.37 g, 1 mmole) in THF was added dropwise with stirring to a saturated solution of ammonia (methylamine) in dry ethanol (80 ml). The mixture was heated to 40-50°C while continuing passage of ammonia. The precipitate

was filtered off and recrystallized from DMSO to give IVa (0.14 g, 67%, mp 269-270°C) and IVb (0.16 g, 69%, mp 260-262°C).

3-(β-Hydroxyethylamino)-1,2,5-thiadiazole-4-carboxylic Acid (V, $C_5H_7N_3SO_3$). Compound I (0.2 g, 1 mmole) was refluxed in NaOH solution (2N, 5 ml) for 1 h, cooled, and acidified with HCl until precipitation began. This was filtered and recrystallized from water to give 0.18 g (96%) with mp 149-151°C.

Guanines IVa, b were hydrolyzed under analogous conditions to give V.

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SYNTHESIS OF MACROHETEROCYCLIC ANALOGS OF DIBENZO-CROWN COMPOUNDS.

6.* HYDROXYLATED 16-MEMBERED OXAAZA-CROWN COMPOUNDS

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High-dilution cycloacylation of 2-acetoxy-1,3-bis-(2-aminophenoxy)propane with the diacid chlorides of glutaric, diglycollic, thiodiglycollic, and N-tosyliminodiacetic acids gives the macrocyclic diamides. Subsequent reduction with boron hydride affords 16-membered dibenzodiaza-crown compounds.

Crown compounds bearing functional groups are of considerable interest, since their complexing properties differ from those of their unsubstituted analogs [2], and the presence of functional groups at the periphery of these macrocycles enables them to be modified in various ways [3, 4].

Two methods are used to obtain substituted crown compounds, namely introduction of substituents into the ready-formed macrocycle, and the cyclization of compounds already bearing the required substituents. The first method is that normally used to introduce substituents into the aromatic nucleus in benzo-crown compounds. The range of substituents which can be introduced is quite large (alkyl, acyl, halo, nitro, and sulfo), but the type of macrocycle is restricted to oxygen-containing benzo-crown compounds only [5].

In order to obtain benzo-crown compounds with substituents in the macrocyclic moiety, pyrocatechol or related compounds have been cycloannelated with glycol derivatives, often in the presence of template ions [3, 6-9].

In heterocyclic systems containing nitrogen, compounds with functional groups are relatively easy to obtain, albeit only by substitution at nitrogen [10, 11]. Compounds with functional groups attached to carbon atoms ofthe macrocycle appear to be unknown.

Sixteen-membered dioxadiaza-crown compounds have been reported previously [1]. Continuing a systematic search for highly selective macrocyclic compounds suitable for the extraction of heavy and transition metals, we have synthesized a range of hydroxy-crown compounds based on 6,7;15,16-dibenzo-3-hydroxy-1,5-dioxa-8,14-diazacyclohexadecane, containing additional donor atoms (oxygen, sulfur, or nitrogen) in the 11-position of the macroheterocycle (IVa-d).

*See [1] for communication 5.

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