Formation of Oxazolo[3,2-*a*]purinones from Propynyluracils

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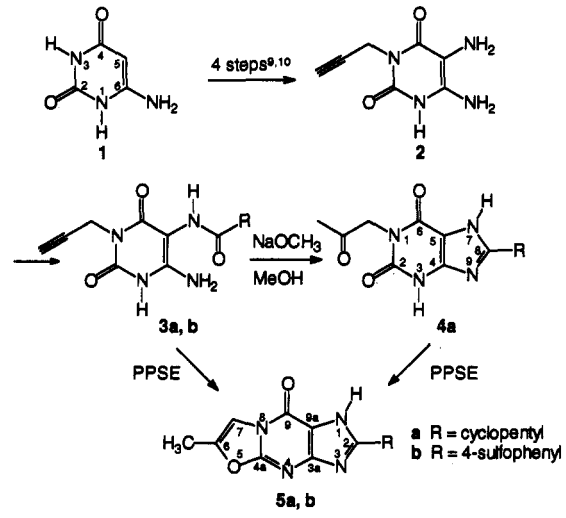
Xanthines (7*H*-imidazo[4,5-*d*]pyrimidine-2,6(1*H*,3*H*)-diones) are the classical and still most important class of adenosine receptor antagonists.[1] Xanthine and non-xanthine antagonists with high potency and selectivity for one subtype of adenosine receptors, the A1 adenosine receptor, have been developed.[2,3] Up to now, only few antagonists with selectivity for the A2 adenosine receptor have been described.[4] A 2-propynyl (propargyl) substitutent in the 1-position of the xanthine heterocycle proved to be favorable for selectivity of such compounds for A2 adenosine receptors.[3] 3,7-Dimethyl-1-propargylxanthine (DMPX) has been one of the first A2-selective adenosine receptor antagonists.[5] In addition, certain propargylxanthines have recently been shown to be several-fold as potent as caffeine in releasing Ca^{2+} from intracellular stores.[6] Therefore, part of our program directed toward the synthesis of novel xanthine derivatives as adenosine receptor antagonists has been the preparation of various 1-propargylxanthines.[7,8]

Our synthetic approach was the introduction of the propargyl group in the 3-position of 6-aminouracil by iodine-catalyzed alkylation of silylated 6-aminouracil with propargyl bromide.[9] The purine ring system was subsequently built according to the classical Traube purine synthesis.[10] The ring closure of the imidazole ring, however, did not proceed in aqueous alkaline solution, due to the lacking of a substitutent in the 1-position of the uracil derivatives. This caused anion formation in alkaline solution and hence a lowering of the nucleophilicity of the 6-amino group. A variety of condensing agents was investigated for the ring closure of those compounds. It was observed that several acidic (HCOOH, $POCl_3$) and alkaline reagents ($NaOCH_3$, 20% aqueous NaOH) caused an unexpected hydration of the triple bond of the propargyl substituent as a side reaction.[8,10]

Unusual hydration of triple bonds by strong acids could be explained to proceed via the formation of a vinyl cation, followed by nucleophilic addition of the acid to form an enol ester, which is then cleaved by the acid to yield a ketone.[11,12]

Hydration by $NaOCH_3$/MeOH, on the other hand, may proceed via nucleophilic addition of methoxide to the triple bond to form an enol ether (Favorskii–Shostakovskii reaction[13]) and subsequent hydrolysis of the unstable vinyl ether.[14,15]

When polyphosphoric acid trimethylsilyl ester (PPSE), reported to be a powerful condensing agent,[16–18] was used for the imidazole ring closure of **3a** and **3b**, new tricyclic compounds, oxazolo[3,2-*a*]purinones, **5a** and **5b** were obtained. To elucidate the mechanism of the formation



1 2 3a, b 4a 5a, b

of compounds **5**, 8-cyclopentyl-1-(2-oxopropyl)xanthine (**4a**), obtained by imidazole ring closure and hydration of **3a** with 30% methanolic $NaOCH_3$ solution, was treated with PPSE. Under these conditions, condensation occurred, and oxazolopurinone **5a** was obtained. We therefore conclude that the formation of oxazolopurinones **5** from 1-(2-propynyl)uracils by PPSE may proceed via a two-step mechanism, an initial hydration of the triple bond, followed by a condensation to form the oxazole ring. Surprisingly, condensation of 1-(2-oxopropyl)-substituted xanthines by $NaOCH_3$ (30% in MeOH) or 20% aqueous NaOH solution to form the oxazole ring does not occur, even after prolonged heating under reflux.

The new compounds can be envisaged as oxa analogs of the wye base, the base of the naturally occurring nucleoside wyosine, which had been identified as a rare constituent of the t-RNA of yeast, rat liver, and other sources.[19–22]

The structures of compounds **5** were elucidated by MS, ^{1}H-NMR, ^{13}C-NMR, FT-IR spectroscopy, and elemental analysis. Spectral data could be unambiguously assigned, based on a comparison with data for wyosine[20,22] and 1,8-disubstituted xanthines[8] (see Experimental Section).

Compound **5a** was tested in A1 and A2a adenosine receptor binding studies at rat brain membranes and showed specific binding to the receptors. In Table 1

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Table 1. Adenosine Receptor Affinity of Oxazolo[3,2-*a*]purinone 5a in Comparison with Analogous Xanthines

compound	K_i (μM) A1 adenosine receptors [^{3}H]*R*-PIA binding, rat cortical membranes	K_i (μM) A2 adenosine receptors [^{3}H]NECA binding, rat striatal membranes
5a	0.77 ± 0.05	20.6 ± 1.8
1-propyl-8-cyclopentylxanthine	0.014 ± 0.03	0.58 ± 0.18
4a	2.5 ± 0.3	9.7 ± 2.3

binding data of **5a** are compared with those of 8-cyclopentyl-1-propylxanthine and 8-cyclopentyl-1-(2-oxopropyl)xanthine (**4a**).[8] Compound **5a** can be envisaged as a sterically restricted analog of 8-cyclopentyl-1-propylxanthine. Compared to that compound, **5a** is considerably less potent at both receptor subtypes (55-fold at A1, 36-fold at A2a). This result may have implications on molecular modeling studies of adenosine receptors.

Experimental Section

Melting points were measured with a Büchi 510 apparatus and are uncorrected. NMR spectra were run on a Bruker AC-250 spectrometer. DMSO-d_6 was used as solvent and TMS as standard. IR spectra were determined with a Perkin-Elmer 1750 FT-IR spectrometer. Elemental analyses were performed by the Institute of Chemistry, University of Tübingen.

Synthesis. 3-Propargyl-6-aminouracil was prepared by iodine-catalyzed alkylation of silylated 6-aminouracil as described[9] and converted to 3-propargyl-5,6-diaminouracil (**2**) by nitrosation followed by reduction of the nitroso function with $Na_2S_2O_4$.[10] 6-Amino-5-cyclopentanecarboxamido-3-propargyluracil (**3a**) was prepared by condensation of the diaminouracil **2** with cyclopentanecarboxylic acid in the presence of a carbodiimide as described.[8]

3-Propargyl-5-[(4-sulfobenzoyl)amino]-6-aminouracil (3b). A suspension of 5,6-diamino-3-propargyluracil **2** (0.77 g, 4.3 mmol), 4-sulfobenzoic acid potassium salt (1.08 g, 4.5 mmol), and *N*-(dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.86 g, 4.5 mmol) in 50% aqueous MeOH (40 mL) is prepared and stirred at rt overnight. The solution gradually becomes clear and subsequently the product separates. The precipitate is collected by filtration and washed with MeOH: yield 1.44 g (92%); mp >300°C; ^{1}H-NMR δ 3.00 (t, 1H, propynyl CH, J = 2.1 Hz), 4.43 (d, 2H, propynyl CH_2, J = 2.1 Hz), 6.28 (br s, 2 H, NH_2), 7.73 (dd, 4H, aromat, J = 8.3 Hz), 8.91 (s, 1H, exocycl NH), 10.63 (br s, 1H, N1-H); ^{13}C-NMR δ 28.9 (NCH_2), 72.4 (propynyl C2'), 80.1 (propynyl CH), 86.8 (C5), 125.2, 127.5, 134.6, 149.3, 150.4, 150.9 (C_{aromat} + C2, C4), 159.7 (C6), 166.2 (exocycl C=O). Anal. Calcd for $C_{14}H_{13}N_4O_6S$ (364.33): C, 46.1; H, 3.32; N, 15.4; S, 8.8. Found: C, 45.9; H, 3.30; N, 15.3; S, 8.8.

2-Cyclopentyl-6-methyl-1,9-dihydro-1*H*-oxazolo[3,2-*a*]purin-9-one (5a). Method A: A suspension of **3a** (2.0 g, 7.2 mmol) in PPSE (15 mL) is prepared, and the mixture is heated at 160–180 °C for 2 h. After it is cooled, methanol (100 mL) is added and the residue collected by filtration and purified by column chromatography (silica gel, Merck) using CH_2Cl_2:MeOH = 9:1 as an eluent; yield: 1.39 g (83%).

Method B: A suspension of 8-cyclopentyl-1-(2-oxopropyl)-xanthine (**4a**) (0.200 g, 0.72 mmol) in 10 mL of PPSE is heated at 160–180 °C for 2 h. The solution is cooled, H_2O (30 mL) is added, the resulting mixture is extracted with CH_2Cl_2, and the organic layer is dried over $MgSO_4$. After evaporation of the solvent, white crystals are obtained, which are washed with MeOH: yield: 0.12 g (64%).

Purification is achieved by dissolving the compound in 2 N NaOH and subsequent precipitation by neutralizing with 2 N HCl: mp 282 °C dec; IR (KBr) 3425, 3121, 2958, 1687, 1598, 1577, 1370, 1165 cm^{-1}; MS (EI) m/z = 258 (M^+, 19%), 217 (100%); ^{1}H-NMR δ 1.90–2.01 (m, 8H, cyclopentyl CH_2), 2.35 (d, 3H, CH_3, J = 1.5 Hz), 3.07 (m, 1H, cyclopentyl C1'-H), 7.75 (quart, 1H, oxazole C-H, J = 1.5 Hz), 12.94 (br s, 1H, N1-H); ^{13}C-NMR δ 11.1 (CH_3), 25.0 (cyclopentyl C3', C4'), 31.6 (cyclopentyl C2', C5'), 39.0 (cyclopentyl C1'), 106.4 (C9a), 144.2 (oxazole CH), 149.0 (C3a), 151.8 (C4a), 152.4 (CCH_3), 153.6 (C9), 157.2 (C2). Anal. Calcd for $C_{13}H_{14}N_4O_2$ (258.28): C, 60.4; H, 5.46; N, 21.7. Found: C, 60.0; H, 5.46; N, 21.6.

2-(4-Sulfophenyl)-6-methyl-1,9-dihydro-1*H*-oxazolo[3,2-*a*]purin-9-one (5b). Compound **5b** is prepared from **3b** (2.5 g, 6.8 mmol) using 15 mL of PPSE as described for the synthesis of **5a** (method A). After the mixture is cooled, methanol (50 mL) is added and the precipitated product is collected by filtration. Purification is achieved by column chromatography (silica gel, Merck) with CH_2Cl_2:MeOH = 3:1 as an eluent. The compound is recrystallized from H_2O: yield 1.1 g (69%); well soluble in acetone:H_2O = 2:1; mp > 300 °C; IR (KBr) 3441, 1703, 1582, 1563, 1377, 1179 cm^{-1}; ^{1}H-NMR δ 2.37 (d, 3H, CH_3, J = 1.4 Hz), 7.75 (d, 2H, aromat, J = 8.3 Hz), 7.82 (quart, 1H, oxazole C-H, J = 1.4 Hz), 8.10 (d, 2 H, aromat, J = 8.3 Hz), 13.70 (br s, 1H, N1-H). Anal. Calcd for $C_{14}H_{10}N_4O_5S$ (346.32): C, 48.5; H, 2.91; N, 16.2; S, 9.3. Found: C, 48.0; H, 3.00; N, 15.9; S, 9.2.

Receptor Binding Assay. Inhibition of binding of [^{3}H]-(*R*)-N^6-(phenylisopropyl)adenosine (*R*-PIA) to A1 adenosine receptors of rat brain cortical membranes and inhibition of binding of [^{3}H]-1-(6-amino-9*H*-purin-9-yl)-1-deoxy-*N*-ethyl-β-D-ribofuranuronamide (NECA) to A2 adenosine receptors of rat striatal membranes in the presence of 50 nM N^6-cyclopentyladenosine (CPA) were assayed as described.[2]

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