Studies on the Adamantylation of *N*-Heterocycles and Nucleosides

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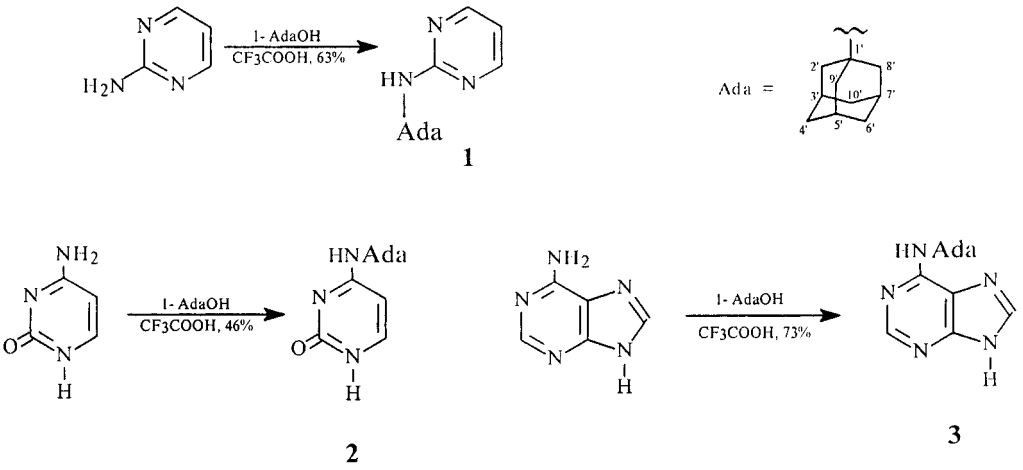
Dedicated to Prof. Dr. *Frank Seela* on the occasion of his 60th birthday

Adamantylation of several *N*-heterocycles and of two ribonucleosides (uridine and toyocamycin) was studied. The exact substitution position by the adamantyl carbocation generated from adamantan-1-ol in CF_3COOH depends on the nature of the heterocyclic substrate. Thus, adamantylation of an additional exocyclic amino group (see *Scheme 1*), *N*-adamantylation of the heterocycle (*Scheme 2*), *C*-adamantylation of the heterocycle (*Scheme 3*), as well as the formation of heterocyclic *N*-adamantylcarboxamides *via* the *Ritter* reaction (*Scheme 4*) are possible. The structures of the reaction products were determined by means of elemental analysis and NMR, UV, and IR spectroscopy.

Introduction. – Adamantane derivatives have received considerable attention because of their multifaceted biological activity. For instance, adamantan-1-amine (amantidine) has been found effective in the prophylaxis and treatment of influenza virus A infection [1]. It is also used in the treatment of *Parkinson*'s disease [2]. Many adamantane-moiety-containing compounds show distinct antimicrobial activity [3–5]. The unusual hydrophobic cage-like structure of adamantane has been employed for modification of many potentially bioactive organic compounds, *e.g.*, nucleosides and polypeptides [6][7]. Substituting heterocyclic compounds with the adamantyl group requires more stringent conditions than those used for derivatizing their aliphatic analogs [8][9]. Recently, a simple, elegant, and promising method has been developed that enables C(5)-adamantylation of barbituric acid (pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) as well as *N*-adamantylation of carboxamides and ureas [10]. This method involves heating in CF_3COOH, a condition which limits somewhat its synthetic potential because of the susceptibility of many naturally occurring compounds to the acidic medium. In the present paper, we would like to show some perspectives that have been opened by this reaction in the chemistry of heterocyclic compounds including certain ribonucleosides.

Results and Discussion. – *Adamantylation of Exocyclic Amino Groups.* Substituted exocyclic amino groups are usually obtained from the corresponding halogeno, methylthio, and methoxy derivatives. Using adamantyl cation formation from adamantan-1-ol in refluxed CF_3COOH solution, we were able to derivatize the exocyclic NH_2 group of pyrimidin-2-amine, cytosine, and adenine to form compounds **1**, **2**, and **3**, respectively (*Scheme 1*). Aniline and phenylalanine did not react under these conditions, which shows that this adamantylation is possible only with non-protonated NH_2 groups. Heterocyclic bases are protonated at the ring heteroatoms; therefore, the acidic conditions do not hinder the trapping of the adamantyl carbocation by the

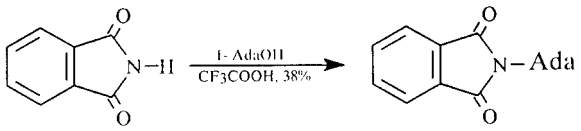
Scheme 1



exocyclic NH_2 group. Because of the relatively high solubility of the heterocyclic base in acidified aqueous medium, the use of an excess of the base allowed product purification without a column-chromatography step. NMR Spectroscopy unequivocally indicated that the substitution took place at the exocyclic NH_2 group of pyrimidin-2-amine and cytosine. Determination of the structure of the adamantylation product from adenine was not so simple: the δ(H) of H–C(2) and H–C(8) of N^6-(1-adamantyl)adenine (**3**) were separated only at 500 MHz. However, the position of the adamantyl group at the exocyclic amino group of **3** was confirmed by both NOE measurements and comparison with reference compounds obtained according to a previously described procedure [11].

N-*Adamantylation of the Heterocycle.* Another reaction observed under the above described conditions was adamantylation of the heterocyclic N-atom of certain compounds. This reaction was exemplified by adamantylation of phthalimide, 1,2-dihydropyridazine-3,6-dione, and 6-azauracil (*Scheme 2*). Phthalimide as well as 1,2-dihydropyridazin-3,6-dione underwent *N*-substitution under rather atypical conditions, giving **4** and **5**, respectively. Usually, *N*-alkylation of these compounds is performed in an alkaline medium. The results of the present study indicate that the adamantyl cation may also attack the electron-deactivated N-atom by replacing the acidic H-atom. The structure of the product was determined spectroscopically in the case of **5** and by comparison with the authentic reference compound obtained by a different method [12] in the case of **4**. Interestingly, adamantylation of 6-azauracil also yielded the N(1)-substituted derivative **6** as the sole product, *i.e.*, no *C*-substitution had occurred. The structure of **6** was determined by UV spectroscopy (both neutral and monoanionic species of N(1)- and N(3)-substituted 6-azauracils display quite different UV spectra [13]) and confirmed by NMR spectroscopy.

Scheme 2



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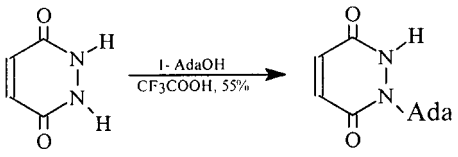

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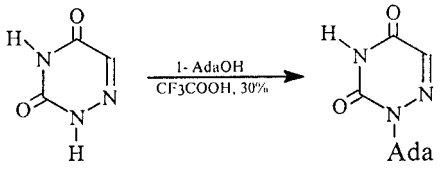

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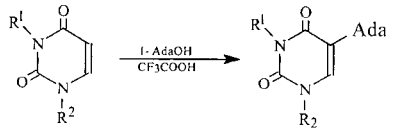
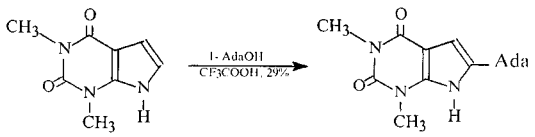
C-*Adamantylation of the Heterocycle.* Among the uracil derivatives, 1,3-dimethyluracil and uridine gave the respective 5-substituted derivatives **7** and **8** as the main products of the adamantylation (*Scheme 3*). The choice of uridine for nucleoside transformations was justified by the fact that it is the most stable nucleoside in acidic medium. However, prolonged refluxing of uridine in CF_3COOH gave a more complex mixture (TLC) that was most likely due to a cleavage of the glycosylic bond and/or anomerization of the sugar moiety. A somewhat unexpected and unexplained result was obtained in the adamantyl carbocation reaction with uracil. The ^{1}H-NMR spectrum of the product showed the presence of the H–C(6) signal (6.88 ppm) expected for 5-adamantyluracil [14], but also that of two adamantyl-type signal patterns (1.4–2.2 ppm; shifted by 0.5 ppm) instead of one, and of an additional *s* at 6.96 ppm. HPLC Analysis (*Lichrospher-RP-18* column, H_2O/MeCN 9 :1) revealed that the product consisted of two compounds (t_R 26.79 and 27.25 min). We were unable to isolate individual components of the mixture and to determine the structure of the

Scheme 3



R^1, R^2 = Me
R^1 = H, R^2 = β-D-ribofuranosyl

7 R^1, R^2 = Me; 35%
8 R^1 = H, R^2 = β-D-ribofuranosyl; 34%



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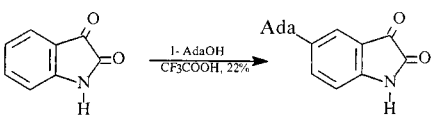

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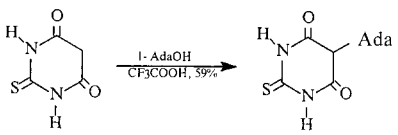

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second product because of its slow solvolysis in MeOH and its chromatographic similarity to 5-adamantyluracil. No product was detected after 2 h refluxing of thymine and 6-methyluracil with adamantan-1-ol in CF_3COOH. Also no indication of adamantylation was found in the case of benzimidazole and 3-deazauridine.

The adamantyl carbocation formed as the intermediate of the reaction under study is a weak electrophile, which explains the 5-substitution of 1,3-dimethyluracil and uridine. In 1,3-dimethyl-7-deazaxanthine, the substitution occurred at C(8) yielding **9** (*Scheme 3*), which was consistent with electrophilic acylation of this ring system [15]. *C*-Substitution also took place with isatin (= 1*H*-indole-2,3-dione), which underwent adamantylation at C(5) to give **10**, in analogy to its bromination reaction. In both cases, the substitution position was verified by NOE measurements. The use of the adamantylation reaction for modification of 2-thiouracil resulted in a highly complex product mixture. By contrast, 2-thiobarbituric acid gave a single product **11** under the same conditions; such behavior has also been observed for the parent barbituric acid [10].

It is worth mentioning that adamantylation under the same conditions as described for adamantan-1-ol did not succeed with adamantan-2-ol. This was probably because of the difference in carbocation formation between the tertiary and the corresponding secondary alcohol.

Formation of N-*Adamantylated Carboxamides. N*-(1-Adamantyl) amides can be obtained by the *Ritter* reaction of adamantan-1-ol and its derivatives with nitriles [16][17], as well as by *N*-alkylation of amides with 1-adamantyl halides [18]. In the following, the *Ritter* reaction is exemplified by the transformation of the heterocyclic carbonitriles 5-cyano-1-methyluracil and the antibiotic nucleoside toyocamycin into the substituted amides **12** and **13**, respectively (*Scheme 4*). The cyano group is more nucleophilic than other possible reaction centers, and the formation of diadamantylated derivatives of toyocamycin was negligible. However, the presence of other minor by-products was revealed by TLC.

Conclusion. – The first step of the adamantylation reaction is probably the formation of the corresponding trifluoroacetate of adamantan-1-ol; next, a carbenium ion is generated. The rather harsh acidic conditions of this reaction present a major limitation in its prospective use for derivatization of certain biologically important compounds, *e.g.*, deoxynucleosides and polypeptides. However, the aforementioned examples do not exhaust the list of possible modifications of heterocyclic compounds. Importantly, the above-described reaction provides a facile route for the synthesis of modified bases to be used in nucleoside synthesis. The results of the above studies reveal that predicting the actual substitution position at a heterocycle (*i.e., N- vs. C*-substitution, see *Schemes 2* and *3*) is not an easy task, except in the case of amino- and cyano-substituted *N*-heterocycles (*Schemes 1* and *4*).

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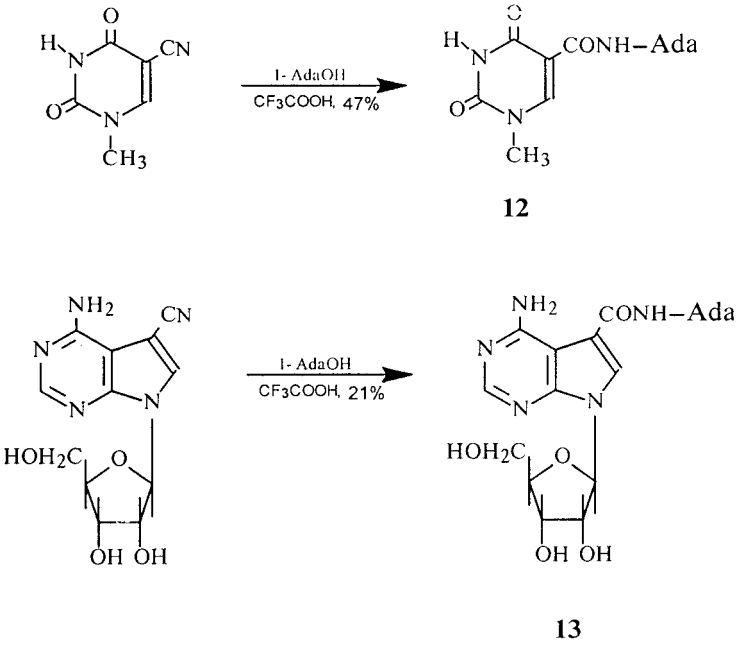
Scheme 4



Experimental Part

General. All chemicals, except solvents, were purchased from *Sigma-Aldrich* (Steinheim, Germany). Column flash chromatography (FC): silica gel *60 H (Merck*, Germany). Anal. TLC: pre-coated silica gel *60F*$_{254}$ (*Merck*, Germany). M.p.: open capillary tubes; *Gallenkamp-5* melting-point apparatus (Leicester, U.K.); uncorrected. UV Spectra: *Kontron-Uvikon-940* (Vienna, Austria) spectrometer. FT-IR Spectra (in cm^{-1}): *Perkin-Elmer-2000* apparatus (Beaconsfield, U.K.). NMR Spectra (in ppm): *Varian-Gemini-200-MHz* and *Varian-UNITYplus-500-MHz* spectrometers (Palo Alto, CA) in $CDCl_3$ and ((D_6)DMSO) solns.; NOE experiments by the truncated-driven NOE (TOE) method [19].

N-*(1-Adamantyl)pyrimidin-2-amine* (**1**). A soln. of pyrimidin-2-amine (1.15 g, 11 mmol) and adamantan-1-ol (1.52 g, 10 mmol) in CF_3COOH (10 ml) was stirred under reflux for 5 h. The mixture was poured into H_2O (50 ml) and brought to pH 7 with conc. aq. NH_3 soln. The precipitate formed was filtered and crystallized from EtOH/H_2O 1:1: **1** (1.45 g, 63%). Colorless crystals. M.p. 201–203°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.78. UV (MeOH/H_2O 1:1): 241 (17200), 311 (2500). ^{1}H-NMR ((D_6)DMSO): 1.62 (br. *s*, 6 H, Ada); 2.03 (br. *s*, 6 H, Ada); 2.37 (br. *s*, 3 H, Ada); 6.49 (*t*, H–C(5)); 8.80 (*d*, H–C(4), H–C(6)). Anal. calc. for $C_{14}H_{19}N_3$ (229.33): C 73.33, H 8.35, N 18.32; found: C 73.24, H 8.38, N 18.25.

N^4-*(1-Adamantyl)cytosine* (**2**). As described for **1**, with cytosine (330 mg, 2.5 mmol), adamantan-1-ol (610 mg, 4 mmol), and CF_3COOH (3.5 ml). The precipitate was washed with a small amount of petroleum ether and crystallized from EtOH: **2** (280 mg, 46%). Colorless crystals. M.p. >320° (dec.) TLC (CH_2Cl_2/MeOH 8:2): R_f 0.85. UV (MeOH/H_2O 2:8): pH 1: 285 (10900); pH 7: 268 (7700); pH 13: 281 (6500). ^{1}H-NMR ((D_6)DMSO): 1.61 (br. *s*, 6 H, Ada); 2.03 (br. *s*, 6 H, Ada); 2.48 (overlapped signal, DMSO); 5.57 (*d*, H–C(5)); 7.17 (*d*, H–C(6)). Anal. calc. for $C_{14}H_{19}N_3O$ (245.33): C 68.54, H 7.81, N 17.13; found: C 68.66, H 7.90, N 17.07.

N^6-*(1-Adamantyl)adenine* (**3**). A suspension of adenine (1.62 g, 12 mmol) and adamantan-1-ol (1.52 g, 10 mmol) in CF_3COOH (15 ml) was stirred under reflux for 8 h. The mixture was poured into H_2O (100 ml) and brought to pH 7 with conc. aq. NH_3 soln. The precipitate was filtered off, washed with H_2O and crystallized from

EtOH: **3** (1.68 g, 73%), spectrally and chromatographically identical with a sample obtained according to [11]. Colorless powder. M.p. 348–350°. TLC (CH_2Cl_2/MeOH 8:2): R_f 0.90. UV (MeOH/H_2O 2:8): pH 1: 261 (13700); pH 7: 262 (14100); pH 13: 262 (13500). ^{1}H-NMR ((D_6)DMSO): 1.75 (br. *s*, 6 H, Ada); 2.19 (br. *s*, 6 H, Ada); 2.40 (br. *s*, 3 H, Ada); 7.65 (br. *s*, NH–C(6)); 8.19, 8.21 (2*s*, H–C(2), H–C(8)). NOE: irrad. 8.20 (H–C(2), H–C(8)) → no NOE; irrad. 1.75 (CH_2(2′), CH_2(8′), CH_2(9′)) → 4% (NH–C(6)), 7% (H–C(3′), H–C(5′), H–C(7′)); 7% (CH_2(4′), CH_2(6′), CH_2(10′)). ^{13}C-NMR ((D_6)DMSO): 174.0 (C(6)); 150.1 (C(4)); 149.2 (C(2)); 138.8 (C(8)); 119.9 (C(2)); 57.5, 40.7, 35.5, 28.9 (C(Ada)).

N-*(1-Adamantyl)phthalimide* (**4**). A soln. of phthalimide (900 mg, 6 mmol) and adamantan-1-ol (910 mg, 6 mmol) in CF_3COOH (6 ml) was stirred under reflux for 12 h. The mixture was poured into H_2O/EtOH 8:2 (60 ml), the precipitate filtered off, adsorbed onto silica gel, and chromatographed (silica gel, column 3 × 15 cm, hexane/$CHCl_3$ 10:2). Crystallization from MeOH yielded **4** (615 mg, 38%). Colorless plates. TLC (hexane/$CHCl_3$ 5:2): R_f 0.59. M.p. 138–139° ([12]: 140°). UV (MeOH/H_2O 1:1): 224 (28600), 297.5 (1900). ^{1}H-NMR ($CDCl_3$): 1.75 (br. *s*, 6 H, Ada); 2.16 (br. *s*, 6 H, Ada); 2.51 (br. *s*, 3 H, Ada); 7.63–7.78 (*m*, 4 arom. H).

1-(1-Adamantyl)-1,2-dihydropyridazine-3,6-dione (**5**). A soln. of pyridazine-3,6-diol (335 mg, 3 mmol) and adamantan-1-ol (910 mg, 6 mmol) in CF_3COOH (6 ml) was stirred under reflux for 4 h. The mixture was evaporated and the residue adsorbed onto silica gel and chromatographed (silica gel, column 3 × 12 cm, $CHCl_3$ (200 ml), then $CHCl_3$/MeOH 9:1). The product was crystallized from MeOH: **5** (410 mg, 55%). Colorless plates. M.p. 282–284°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.48. UV: (MeOH/H_2O 2:8): pH 7: 316 (3200); pH 12: 225 (7400), 338 (2900). ^{1}H-NMR ((D_6)DMSO): 1.65 (br. *s*, 6 H, Ada); 2.09 (br. *s*, 6 H, Ada); 2.26 (br. *s*, 3 H, Ada); 6.73, 6.95 (2*d*, H–C(3), H–C(4)). Anal. calc. for $C_{14}H_{18}N_2O_2$ (246.31): C 68.27, H 7.37, N 11.37; found: C 68.15, H 7.26, N 11.40.

1-(1-Adamantyl)-6-azauracil (= *2-(1-Adamantyl)-1,2,4-triazine-3,5(2*H*,4*H*)-dione*; **6**). As described for **5**, with 6-azauracil (340 mg, 3 mmol), adamantan-1-ol (910 mg, 6 mmol), and CF_3COOH (4 ml) (6 h). FC (silica gel, column 3 × 10 cm, $CHCl_3$, then $CHCl_3$/MeOH 8:2) and crystallization from MeOH/H_2O gave **6** (220 mg, 30%). Colorless plates. M.p. 268–269°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.80. UV (MeOH/H_2O 2:8): pH 7: 275 (7200); pH 12: 267 (6400). ^{1}H-NMR ((D_6)DMSO): 1.64 (br. *s*, 6 H, Ada); 2.11 (br. *s*, 6 H, Ada); 2.18 (br. *s*, 3 H, Ada); 7.39 (*s*, H–C(5)). Anal. calc. for $C_{13}H_{17}N_3O_2$ (247.30): C 63.14, H 6.93, N 16.99; found: C 63.02, H 7.01, N 17.10.

5-(1-Adamantyl)-1,3-dimethyluracil (**7**). As described for **5**, with 1,3-dimethyluracil (285 mg, 2 mmol), adamantan-1-ol (610 mg, 4 mmol), and CF_3COOH (4 ml) (3 h). FC (silica gel, column 3 × 10 cm, $CHCl_3$, then $CHCl_3$/MeOH 9:1) and crystallization from MeOH/H_2O gave **7** (190 mg, 35%). Colorless plates. M.p. 208–210°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.80. UV (MeOH/H_2O 1:1): 270 (8800). ^{1}H-NMR ($CDCl_3$): 1.74 (br. *s*, 6 H, Ada); 1.95 (br. *s*, 6 H, Ada); 2.05 (br. *s*, 3 H, Ada); 3.32, 3.38 (2*s*, 2 Me), 6.82 (*s*, H–C(6)). Anal. calc. for $C_{16}H_{22}N_2O_2$ (274.31): C 70.04, H 8.08, N 10.21; found; C 70.16, H 8.08, N 10.11.

5-(1-Adamantyl)uridine (**8**). A soln. of uridine (970 mg, 4 mmol) and adamantan-1-ol (1.21 g, 8 mmol) in CF_3COOH (6 ml) was stirred under reflux for 2 h. The mixture was poured into ice/water (50 ml). The precipitate formed was filtered and chromatographed (silica gel, column 4 × 15 cm, $CHCl_3$ (250 ml), then $CHCl_3$/MeOH 9:1 (250 ml) and $CHCl_3$/MeOH 8:2). The product was crystallized from EtOH: **8** (510 mg, 34%). Colorless crystals. M.p. 178–180°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.37. UV: pH 7: 267 (9100); pH 12: 265 (7100). ^{1}H-NMR ((D_6)DMSO): 1.65 (br. *s*, 6 H, Ada); 1.86 (br. *s*, 6 H, Ada); 1.97 (br. *s*, 3 H, Ada); 3.57 (*m*, 2 H–C(5′)); 3.7–4.1 (*m*, H–C(2′), H–C(3′), H–C(4′)); 5.81 (*d*, H–C(1′)); 7.53 (*s*, H–C(6)); 11.10 (*s*, NH). ^{13}C-NMR ((D_6)DMSO): 162.4 (C(4)); 150.4 (C(2)); 135.5 (C(6)); 121.6 (C(5)); 87.7 (C(1′)); 84.9 (C(4′)); 73.7 (C(2′)); 70.4 (C(3′)); 60.9 (C(5′)); 40.8, 39.7, 34.8, 28.0 (C(Ada)). Anal. calc. for $C_{19}H_{26}N_2O_6$ (378.43): C 60.30, H 6.93, N 7.40; found: C 60.17, H 7.01, N 7.29.

8-(1-Adamantyl)-1,3-dimethyl-7-deazaxanthine (= *6-(1-Adamantyl)-3,9-dihydro-1,3-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4-dione*; **9**). A suspension of 1,3-dimethyl-7-deazaxanthine [20] (560 mg, 3 mmol) and adamantan-1-ol (910 mg, 6 mmol) in CF_3COOH (5 ml) was stirred under reflux for 5 h. The deep red mixture was evaporated and adsorbed onto silica gel. FC (silica gel, column 3 × 15 cm, $CHCl_3$ (200 ml), then $CHCl_3$/MeOH 95:5) and crystallization from a small amount of acetone gave **9** (180 mg, 29%). Colorless crystals. M.p. >320° (dec. >260°). TLC (CH_2Cl_2/MeOH 9:1): R_f 0.51. UV (MeOH/H_2O 1:1): 249 (8400), 283 (6700). ^{1}H-NMR ((D_6)DMSO): 1.71 (br. *s*, 6 H, Ada); 1.87 (br. *s*, 6 H, Ada); 2.01 (br. *s*, 3 H, Ada); 3.18, 3.46 (2*s*, 2 Me); 5.93 (*s*, H–C(7)); 10.93 (*s*, NH). NOE: irrad. NH → 1% (3.46, Me–N(3)), 2% (1.71, CH_2(2′), CH_2(8′), CH_2(9′)); irrad. Me–N(1) → no NOE; irrad. H–C(7)) → 1% (10.93, NH), 3% (1.71, CH_2(2′), CH_2(8′), CH_2(9′); irrad. CH_2(2′), CH_2(8′), CH_2(9′) → 10% (10.93, NH), 6% (5.93, H–C(7)), 7% (1.87, CH_2(4′), CH_2(6′), CH_2(10′)), 7% (2.01, H–C(3′), H–C(5′), H–C(7′)). Anal. calc. for $C_{18}H_{23}N_3O_2$ (313.40): C 68.98, H 7.40, N 13.41; found: C 69.00, H 7.51, N 13.54.

5-(1-Adamantyl)isatin (= *5-(1-Adamantyl)-1*H*-indole-2,3-dione*; **10**). A soln. of isatin (1.47 g, 10 mmol) and adamantan-1-ol (1.21 g, 8 mmol) in CF_3COOH (10 ml) was stirred and refluxed for 6 h. The deep red mixture was brought to r.t. and diluted with EtOH/H_2O 2:8 (30 ml). The red precipitate was filtered off and chromatographed (silica gel, column 4 × 15 cm, $CHCl_3$ (250 ml), then $CHCl_3$/MeOH 95:5). The product-containing fractions were evaporated and the residue crystallized from EtOH/H_2O: **10** (620 mg, 22%). Red plates. M.p. 273–275°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.55. UV (MeOH/H_2O 1:1): 246 (22900), 305 (3900). ^{1}H-NMR ($CDCl_3$): 1.74 (br. *s*, 3 H, Ada); 1.79 (br. *s*, 3 H, Ada); 1.86 (br. *s*, 6 H, Ada); 2.11 (br. *s*, 3 H, Ada); 6.92 (*d*, H–C(7)); 7.57 (*m*, H–C(6)); 7.64 (*d*, H–C(4)); 8.83 (*s*, NH). NOE: irrad. NH → 2% (6.92, H–C(7)), 2% (1.79, CH_2(2′), CH_2(8′), CH_2(9′)); irrad: H–C(4) and H–C(6) → 2% (6.92, H–C(7)), 3% (1.86, CH_2(4′), CH_2(6′), CH_2(10′)). Anal. calc. for $C_{18}H_{19}NO_2$ (281.36): C 76.84, H 6.81, N 4.98; found: C 76.75, H 6.69, N 4.97.

5-(1-Adamantyl)-2-thiobarbituric Acid (= *5-(1-Adamantyl)-dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione*; **11**). A suspension of 2-thiobarbituric acid (1.73 g, 12 mmol) and adamantan-1-ol (1.52 g, 10 mmol) in CF_3COOH (15 ml) was stirred under reflux. After 3 h, the suspension was entirely dissolved, and 2 h later, the mixture was poured into H_2O (30 ml). The precipitate formed was filtered off and washed with acetone/H_2O 1:1 (20 ml). Crystallization from EtOH yielded **11** (1.63 g, 59%). Pale yellow plates. M.p. 270°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.70. UV (MeOH/H_2O 1:9): pH 1: 244 (11500), 291 (30400); pH 7: 239 (15900), 292 (14800). ^{1}H-NMR ((D$_6$)DMSO): 1.59 (br. *s*, 12 H, Ada); 1.95 (br. *s*, 3 H, Ada); 2.76 (*s*, H–C(5)); 12.18 (*s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 180.1 (C(2)); 166.9 (C(4)), (C(6)); 61.8 (C(5)); 28.3, 35.9, 39.0, 39.8 (C(Ada)). Anal. calc. for $C_{14}H_{18}N_2O_2S$ (278.32): C 60.42, H 6.52, N 10.07; found: C 60.45, H 6.63, N 9.97.

5-{[(1-Adamantyl)amino]carbonyl}-1-methyluracil (= N-*(1-Adamantyl)-1,2,3,4-tetrahydro-1-methyl-2,4-dioxopyrimidine-5-carboxamide*; **12**). As described for **5**, with 5-cyano-1-methyluracil [21] (305 mg, 2 mmol), adamantan-1-ol (330 mg, 2.2 mmol) and CF_3COOH (4 ml) (30 min). FC (silica gel, column 2 × 10 cm, $CHCl_3$ (100 ml), then $CHCl_3$/MeOH 95:5) and crystallization from EtOH gave **12** (285 mg, 47%). Colorless crystals. M.p. >320° (dec.). TLC (CH_2Cl_2/MeOH 9:1) R_f 0.65. UV (MeOH/H_2O 1:9): pH 7: 225 (9900), 280 (12700); pH 12: 230 (12000), 279 (10600). ^{1}H-NMR ((D$_6$)DMSO): 1.61 (br. *s*, 6 H, Ada); 1.95 (br. *s*, 6 H, Ada); 2.01 (br. *s*, 3 H, Ada); 3.32 (*s*, Me); 8.34 (*s*, H–C(6)); 8.16 (br. *s*, NH). FT-IR: 1697 (CONH). Anal. calc. for $C_{14}H_{18}N_2O_2$ (303.36): C 63.35, H 6.98, N 13.85; found: C 63.40, H 7.01, N 13.74.

N-*(1-Adamantyl)-4-amino-7-(β-*D*-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide* (= N^{amido}-*(1-Adamantyl)sangivamycin*; **13**). As described for **5**, with toyocamycin (= 4-amino-7(*β*-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile; 760 mg, 4 mmol) adamantan-1-ol (1.22 g, 8 mmol), and CF_3COOH (4.5 ml) (1 h). FC (silica gel, column 4 × 15 cm, $CHCl_3$ (300 ml), then $CHCl_3$/MeOH 9:1) and crystallization from EtOH/AcOEt gave **13** (380 mg, 21%). Colorless wool-like crystals. M.p. 248°. TLC (CH_2Cl_2/MeOH 9:1): R_f 0.38. UV (MeOH/H_2O 1:9): pH 7: 282 (11800); pH 1: 237 (13200), 281 (10400). ^{1}H-NMR ((D$_6$)DMSO): 1.66 (br. *s*, 6 H, Ada); 2.08 (br. *s*, 6 H, Ada); 2.10 (br. *s*, 3 H, Ada); 3.57 (*m*, 2 H–C(5′)); 3.94 (*q*, H–C(4′)); 4.11 (*m*, H–C(3′)); 4.35 (*t*, H–C(2′)); 6.10 (*d*, H–C(1′)); 7.83 (br. *s*, NH_2); 8.40, 8.45 (2 *s*, H–C(2), H–C(6)). ^{13}C-NMR ((D$_6$)DMSO): 163.1 (C=O); 153.0 (C(4)); 148.7 (C(2)); 145.9 (C(7a)); 126.7 (C(6)); 113.9 (C(5)); 100.9 (C(4a)); 86.7 (C(1′)); 85.5 (C(4′)); 73.8 (C(2′)); 70.1 (C(3′)); 61.4 (C(5′)); 28.7, 39.0, 40.8, 52.3 (C(Ada)). FT-IR: 1692 (CONH). Anal. calc. for $C_{22}H_{29}N_5O_5$ (443.50): C 59.58, H 6.59, N 15.79; found: C 59.47, H 6.63, N 15.68.

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