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SYNTHESIS OF GUANINE 7-OXIDE, AN ANTITUMOR ANTIBIOTIC FROM STREPTOMYCES SPECIES

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Abstract —— The first synthesis of the antitumor antibiotic guanine 7-oxide (VI) has been achieved via a 4-step route starting from phenacyl bromide (I) and the nitropyrimidone III and proceeding through the intermediates IVe and Ve.

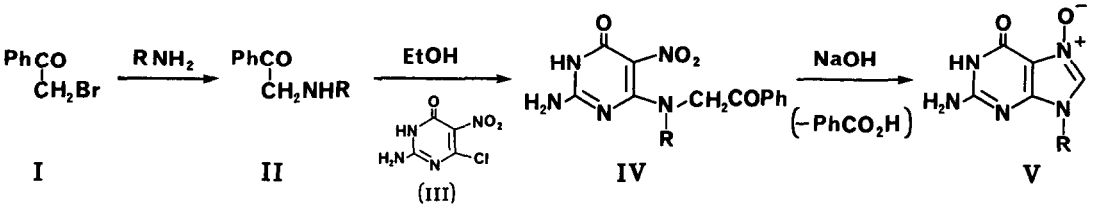
The recent, independent isolations of guanine 7-oxide (VI) from the culture broths of certain *Streptomyces* species by three research groups[1-3] and its observed antitumor,[1-3] antimicrobial,[3] and antiviral[4] activities prompted us to devise a synthetic method of preparation of this antibiotic. Among the four possible heterocyclic *N*-oxides of guanine (VII), the 7-oxide VI is the only one that has not been previously synthesized.[5] Prior to the present study, direct oxidation of VII with peroxytrifluoroacetic acid was known to give the 3-oxide,[5b] not the 7-oxide VI once claimed.[6] This led us to investigate the following stepwise synthesis of VI.

The starting phenacylamine hydrochlorides IIa·HCl,[7] IId·HCl,[8] and IIf·HCl[9] were prepared from phenacyl bromide (I) and appropriate amines according to the literature procedures. Similar alkylations of propylamine, allylamine, and *p*-methoxybenzylamine with I in a mixture of ether and benzene at 5–15°C for 0.5–1 h gave, after treatment with HCl, the hydrochlorides IIb·HCl [45% yield; mp 193–204°C (dec.)],[10] IIc·HCl [35%; mp 183–185°C (dec.)],[11a] and IIe·HCl [37%; mp 214–216°C (dec.)]. Condensations of IIa–f (2 molar eq.), generated from the above hydrochlorides, with 2-amino-6-chloro-5-nitro-4(3*H*)-pyrimidinone (III)[12] in aq. EtOH produced the 6-(dialkylamino)pyrimidines IVa [reflux, 20 min; 86% yield; mp 206–215°C (dec.)], IVb [room temp., 24 h; 68%; mp 198–202°C (dec.)], IVc [reflux, 20 min; 66%; mp 198–202°C (dec.)], IVd [room temp., 12 h; 81%; mp 140–145°C (dec.)], IVe [room temp., 24 h; 77%; mp 128–138°C (dec.)], and IVf [room temp., 24 h; 71%; mp 149–156°C (dec.)].

Treatment of IVa with 2 *N* aq. NaOH at room temperature for 1 h furnished 9-methylguanine 7-oxide (Va) [98% yield; mp > 300°C (lit.[13] mp > 300°C); NMR (1 *N* D_2SO_4) δ:[14] 3.79 (3H, d, $J = 0.4$ Hz, N(9)-Me), 9.03 (1H, q, $J = 0.4$ Hz, C(8)-H)]

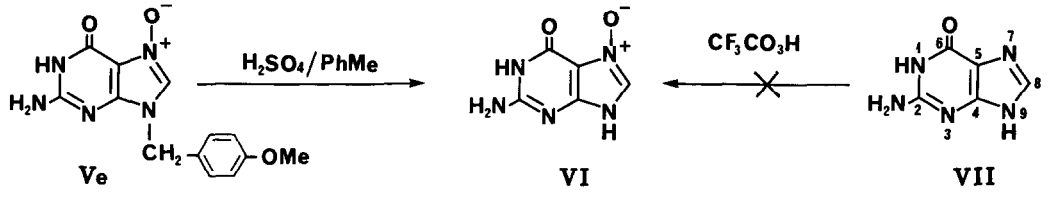
and benzoic acid (99% yield), which were identified by direct comparison with authentic samples. Similar cyclizations of IVb–f gave the 7-oxides Vb (87% yield; mp > 300°C),[11b] Vc (90%; mp > 300°C),[11c] Vd (84%; mp > 300°C), Ve (61%; mp > 300°C),[11d] and Vf (70%; mp > 300°C). The 7-oxide structures of Vb–f were supported by the similarity to Va in the mode of formation and in the UV spectra[15] and by the presence of a one-proton singlet [C(8)-H] in the NMR spectra in 1 *N* D_2SO_4 (*e.g.*, Vd: δ 9.02; Ve: δ 8.96).[14] Such cyclizations of the nitro derivatives IVa–f through nucleophilic attack by a carbanion on the NO_2 nitrogen atom have precedents in the literature.[13,16]

On the other hand, a parallel sequence of reactions starting with the *N*-unsubstituted phenacylamine (II: R = H) did not work at the cyclization step. This failure is probably due to destabilization of the phenacyl carbanion by the adjacent NH group. However, removal of the substituent at the 9-position



a: R = Me b: R = $MeCH_2CH_2$ c: R = CH_2=$CHCH_2$

d: R = $PhCH_2$ e: R = MeO–⟨⟩–CH_2 f: R = ⟨⟩



of a V-type compound without rupture of the N(7)-O bond should give the target molecule VI. Treatment of Ve with 10 molar eq. of conc. H_2SO_4 at 25°C for 1.5 h in the presence of toluene actually provided VI (mp > 300°C)[11d] in 89% yield. The identity of this sample with natural VI[11d] was confirmed by direct comparison of the UV (H_2O at pH 1, 7, and 13), IR (Nujol), and ^1H NMR (1 *N* D_2SO_4) spectra as well as the chromatographic behavior. The above deblocking procedure was based on the recently reported specific debenzylation of 3-benzyladenine[17] and 7-alkyl-3-benzyladenines[18] that proceeds through benzyl carbenium ion formation and trapping of the cation by transbenzylation with toluene. However, application of the same procedure to Vd or Vc failed to give the desired product VI.

As regards the problem of the tautomeric structures of guanine 7-oxide in the solid state, the N(7)-oxide structure VI has been preferred by Kern *et al.*,[1] whereas the N(7)-OH structure has been proposed by Kitahara *et al.*[2b] In solution, the two forms may coexist at equilibrium.[3] The strong absorption band at 234 nm (ε 19600) observed in the UV spectrum of VI in H_2O at pH 7 resembles that observed for the 7-oxides V. This fact, together with the previous deduction that the strong absorption in the 215–240 nm range for purine *N*-oxides is considered to be due to >N→O or the enol anion >N–O$^-$,[19] suggests that the neutral species has a considerable proportion of the N(7)-oxide tautomer in H_2O.

The first synthesis of the antitumor antibiotic guanine 7-oxide (VI) has thus been accomplished via the above 4-step route starting from I and III and proceeding through the intermediates IVe and Ve. It is interesting to note that the *N*-oxides Vd and Ve have been found to possess some *in vitro* activities against L5178Y leukemia.

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10. Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds isolated.
11. The elemental analysis suggested that this sample contains the following amount of water of crystallization: (a) 1/4 molar eq.; (b) 1/2 molar eq.; (c) 3/5 molar eq.; (d) 1/3 molar eq.
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14. In ppm downfield from internal sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4.
15. For example, Va: λ_{max} [H_2O (pH 1)] 255 nm (ε 11100), 281 (7200); λ_{max} [H_2O (pH 7)] 236 (21100), 270 (8100); λ_{max} [H_2O (pH 13)] 231 (20000), 280 (8500); Vd: λ_{max} [H_2O (pH 1)] 258 (11900), 282 (8000); λ_{max} [H_2O (pH 7)] 237 (21400), 270 (9300); λ_{max} [H_2O (pH 13)] 232 (19600), 281 (9600).
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