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CONVERSION OF ADENOSINE TO A PENTACYCLIC STRUCTURE BY A 4-NITROQUINOLINE-1-OXIDE METABOLITE MODEL.

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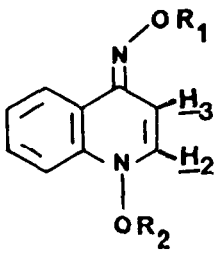
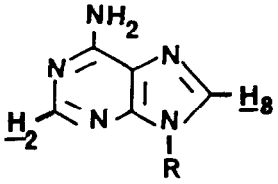
Summary : A new pentacyclic compound 2A has been obtained from the reaction of adenosine 1 with 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline 3, a model for the ultimate metabolite of the carcinogen 4-nitroquinoline-1-oxide. 9-propyladenine 5 gives an analogous pentacyclic product 6A whose crystal structure has been determined.

There has been much recent interest in bifunctional molecules which bind to nucleic acid bases to form cyclic adducts[1a,b,c,d]. This arises both from a search for specific probes for nucleic acids studies[2] and from elucidations of chemical modifications induced by bifunctional mutagenic or carcinogenic substances[3]. The generation of $1,N^6$-etheno adenosines (ε-adenosines) by α-halosubstituted carbonyls is perhaps the best known example [1c].

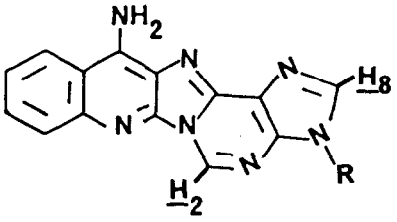
We report here the conversion of adenosine 1 into the pentacyclic derivative 2 as a result of treatment with 1-acetoxy-4-(acetoxyimino)-1,4-dihydroquinoline 3. The diacetoxy compound 3 is an activated form of 4-hydroxyaminoquinoline-1-oxide 4 which is considered as the proximate species metabolically generated from the potent carcinogen 4-nitroquinoline-1-oxide (4-NQO)[4].



3: R_1=R2=Ac
4: R_1=R_2=H
7: R_1=Ac ; R_2=H
8: R_1=H ; R_2=Ac

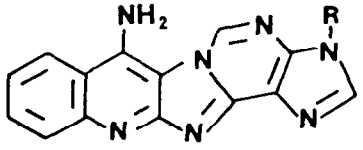


1: R=ribose
5: R=n-propyl



A

2: R=ribose
6: R=n-propyl



B

Adenosine 1 (1 equiv.) was added to the diacetoxy[5a,b] compound 3 dissolved in trifluoroethanol and the solution was maintained in the dark at 20°C for 24h. Isolation was effected by evaporation of the solvent under vacuum and chromatography on silica gel using ethyl acetate-ethanol (9:1) as eluent. A series of crystallisations from ethyl acetate-methanol (6:4) and methanol-water (6:4) gave a colorless solid 2 mp > 300°C (decomp.) in 20% yield[6]. When adenosine 1 was replaced by 9-propyladenine 5 an analogous reaction took place to yield a crystalline product 6. The NMR spectrum[9] of these products 2 and 6 and their mass spectral fragmentation patterns[9] were similar and in agreement with either of the structures A or B. The 270MHz ^{1}H NMR spectra show in particular only one NH_2 group and the absence of the H-2 and H-3 quinoline signals. We could differentiate between the adenine H-2 (δ = 9.38ppm) and H-8 (δ = 8.27ppm) peaks in 6 by synthesis of the deuterium labelled analogue of 6 from 3 and [^{2}H-8]-propyladenine made by heating 9-propyladenine 5 in D_2O under reflux for 5h. Ultimately the structure 6A was determined unambiguously by X-ray diffraction[10] as Fig. 1. The pentacyclic ring system is planar (but with some minor deviations). The packing of the structure shows infinite stacks with centrosymetric counterparts. The distance between the planes is alternatively 3.36 and 3.32 Å. Two centrosymetric stacks are linked by hydrogen bonds (Fig. 2).

Since 2 and 6 have comparable spectral characteristics[11] and provenance it is reasonable to assign a similar structure 2A to the adenosine adduct.

The formation of a pentacyclic structure can be interpreted on the basis of a Michael type addition of adenine N-1 onto the C-2 atom of the α-β-unsaturated oximinoester 3 followed by N-1 acetate elimination. Attack of the resultant hydroxylamino acetate located on quinoline C-4 by adenine N-6 leads to cyclisation to 6A. Comparable reactivities can be found in the chemistry of both mono acetates 7[12] and 8[13].

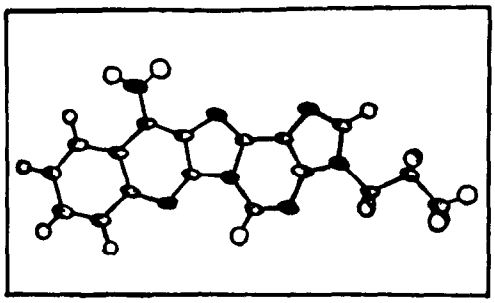


Fig. 1

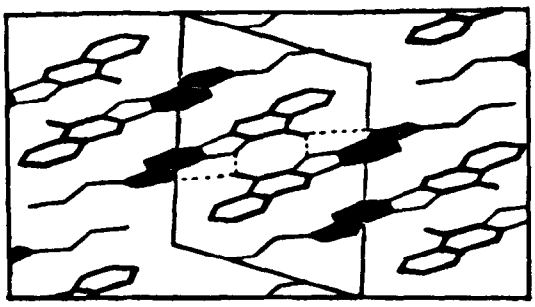


Fig. 2

It thus appears that in a non nucleophilic solvent like trifluoroethanol reaction with adenosine leads to heterocyclisation. This should be compared to the results observed in nucleophilic solvents (water, methanol, ethanol), or in DMSO in the presence of nucleophilic agents like amines or thiols. In such media, 3 is selectivily deacylated to monoacetate 7 and the subsequent reaction products arise from this species. Adducts observed until now from the reaction of the diester 3 with DNA correspond to this latter reaction pathway[14a,b].

We are now looking for evidence of cyclic adduct 2 formation at the polynucleotide level.

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5. a : Y. Kawazoe "Carcinogenesis : "A Comprehensive Survey", (T. Sugimura Ed.), Raven Press (1981), Vol 6. b : Y. Kawazoe, M. Araki, Gann (1967), 58, 485.
6. Nitrosoquinoline[7] (30%) and a complex mixture of quinolinylazoquinoline oxides[8] (30%) are the other by products formed in the reaction.
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8. T. Kosuge, H. Zenda, H. Sawanishi, Chem. and Pharm. Bull. (Japan), (1969), 17, 2389 and preceding papers.
9. 2 : NMR : (DMSO d_6, 270MHz, 60°C) : 9.41 (1H, s, H-2 ade) ; 8.54 (1H, s, H-8 ade) ; 8.37 (1H, d, J=8.5Hz H-5 quin.) ; 7.91 (1H, d, J=8.5Hz H-8 quin.) ; 7.60 (1H, t, H-6 or H-7 quin.) ; 7.44-7.28 (3H, m, H-7 or H-6 quin. and NH_2) ; 6.05 (1H, d, H-1') ; 5.34 (1H, d, OH-2') ; 5.00 (1H, d, OH-3') ; 4.86 (1H, t, OH-5') ; 4.53 (1H, m, H-2') ; 4.16 (1H, m, H-3') ; 3.95 (1H, m, H-4') ; 3.70-3.51 (2H, m, H-5'). M.S. : m/e : 407 (M^+) ; 275 ; 247 ; 157 ; 144 ; 129 ; 103.
6 : NMR (DMSO d_6, 270MHz, 60°C) : 9.38 (1H, s, H-2 ade) ; 8.36 (1H, d, J=8,5Hz H-5 quin.) ; 8.27 (1H, s, H-8 ade) ; 7.91 (1H, d, J=8,5Hz H-8 quin.) ; 7.58 (1H, t, H-6 or H-7 quin.) ; 7.38-7.28 (3H, m, H-7 or H-6 quin. and NH_2) ; 4.24 (2H, t, prop.) ; 1.88 (2H, m, prop.) ; 0.86 (3H, t, prop.). M.S. : m/e : 317 (M^+) ; 289 ; 275 ; 243 ; 169 ; 157 ; 146 ; 141 ; 129 ; 119 ; 103. Fluorescence : (Ethanol) λ_{max} 485nm : ϕ_f 3.10^{-3}. U.V. : (Ethanol) λ_{max} nm (ϵ) : 380 (3088) ; 350 (4117) ; 314 (7500) ; 292 (8602) ; 280 (9411) ; 260 (15441).
10. Crystals for X-ray analysis could be obtained from methanol solution and by vapor diffusion at 4°C : the crystals were triclinic ; space group P1 a = 7.937 (6) , b = 10.166 (7), c = 10.652 (7) A ; α = 117.56 (6), β = 106.25 (6), γ = 81.54 (6) , U = 731.3 A^3 ; Z = 2 ; Dcal = 1.445g/cm^3, μ = 5.72cm^{-1} ; R = 004 for 1355 observed reflexions. The structure was solved by Multan 80 (P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G.M. Germain, J.P. Declerq, M. Woolfson (Multan 80 : A system of computer programms for the automatic solution of crystal structures from X-ray diffraction data (1980), York, England and Louvain La Neuve, Belgium).
11. The only striking difference is at H-8 next to the substituant R as one might expect.
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