Tetrahedron Letters,Vol.24,No.41,pp 4491-4492,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

THE REACTION OF GUANOSINE AND 2'-DEOXYGUANOSINE WITH ACROLEIN

G.Galliani*[1] and C.Pantarotto [2]

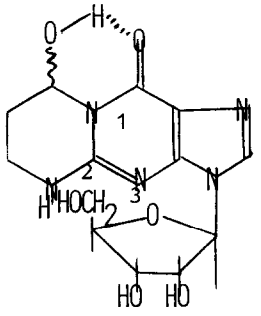
[1] Istituto di Chimica Organica dell'Università, v.Venezian 21, 20133, Milano, Italy
[2] Istituto di Ricerche Farmacologiche M.Negri, v.Eritrea 62, 20157, Milano, Italy

Acrolein reacts with guanosine and 2'-deoxyguanosine in dimethylsulphoxide; the structure of the adducts is described.

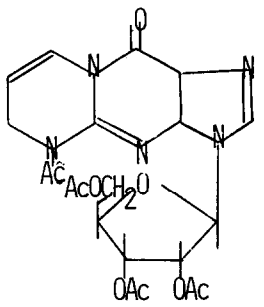
Several reports deal with the reactivity of the purine moiety of guanosine with electrophilic reagents [1]. These reactions are possibly an explanation for the mutagenicity and cancerogenicity of many electrophilic xenobiotics. Here we describe the reaction of guanosine and 2'-deoxyguanosine with acrolein.

Guanosine (2.0 g) was dissolved in dimethylsulphoxide (20 ml) and treated with acrolein (4.0 ml). The solution was kept at room temperature for two days. Benzene (200 ml) was added and the suspension was stirred for two hours. After separating the clear solution, the residue was triturated in ethanol. The precipitate was filtered and crystallized twice from ethanol-water (1:1 v:v). The compound, hereafter referred to as (I) (1.9 g after the crystallizations) was homogeneous in TLC (silica gel, chloroform:methanol 7:3 v:v, R_f= 0.32). Elemental analysis gave: C 44.01%, H 5.19%, N 19.46%. These values are consistent with the formula $C_{13}H_{15}N_5O_6 \cdot H_2O$; one mole of water per mole of (I) was actually lost after standing at 90° overnight. The ^{13}C spectrum of (I) in dimethylsulphoxide showed three peaks in addition to the peculiar spectrum of guanosine [2], at 25.6 δ, 32.2 δ, and 68.6 δ respectively. The off-resonance spectrum showed the peaks at 25.6 and 32.2 δ as triplets, and the peak at 68.6 δ as a doublet. These data are consistent with the presence of a methylene group on a nitrogen atom, a methylene group connected with two carbon atoms, and a methine group such as CH-O or N-CH-O. The ^1H NMR spectrum of (I) was the superimposition of the spectrum of guanosine (after eliminating two protons on nitrogen atoms) with the following signals: a broad signal at 1.6 δ (2 H), a multiplet at 3.7 δ (2 H), a broadened singlet at 5.0 δ (1 H), and a slightly broadened doublet at 8.3 δ (1 H). The anomalous distribution of intensities of the last resonance suggests that this signal, which can be eliminated by shaking with D_2O, is given by two diastereotopic hydroxyl groups rather than by simple spin-spin coupling. All of these data suggest the structure (a) for compound (I). The proton resonance assignments were confirmed by double resonance experiments. The alternative structure, deriving from a Michael-like addition of N 1 to the double C=C bond of acrolein, seems to be ruled out by the proton resonance at 8.3 δ which is typical for a hydroxyl engaged in a intramolecular hydrogen bond, as it is likely only in the case of structure (a). Moreover the resonance at 3.7 δ is consistent with the values reported for N^2-alkylguanines [1c].

The broadening of the ^1H signal can be attributed to the presence of both diastereoisomers of (I)



(a)



(b)

Compound (I) was also treated with acetic anhydride in the presence of anhydrous sodium acetate at 80°C for two hours. After dilution in benzene and evaporation under reduced pressure, the main product could be purified by silica gel chromatography, and was obtained as a yellowish oil which solidified on standing under reduced pressure. Its mass spectrum showed the molecular peak at m/e 489. Its ^{13}C spectrum showed that four acetyl groups had been introduced and that the methylene group at 25.6 δ and the methine group at 68.6 δ had disappeared; the second methylene group had been shifted to 40.0 δ. The formation of a double C=C bond was monitored by the appearance of two doublets in the off-resonance spectrum at 107.2 and 126.1 δ respectively. The ^1H spectrum confirmed the presence of two vinyl protons and the maintenance of the methylene group near the nitrogen atom, whose resonance had been shifted to 4.5 δ by the introduction of an acetyl group on N^2. The tetraacetyl derivative can thus assigned structure (b).

An analogous adduct was formed by treating 2'-deoxyguanosine with acrolein in the same conditions, as it was confirmed by ^{13}C NMR. When guanosine was treated with crotonaldehyde and cinnamaldehyde, no adduct could be observed by TLC after two days. An adduct was observed by TLC in the case of methylvinylketone, but its formation was much slower than in the case of acrolein.

References

1) a) E.J.Eyring and J.Ofengand, Biochemistry, 6, 2500 '1967); B.M.Goldschmidt, T.P. Blazej, and B.L.Van Duuren, Tetrahedron Letters, 1583 (1968); c) R.Shapiro, B.I.Cohen, S.J.Shiuey, and H.Maurer, Biochemistry, 8, 238 (1969); d) R.C.Moschel and N.J.Leonard, J.Org.Chem., 41, 294 (1976); e) P.D.Sattsangi, N.J.Leonard , and C.R.Frihart, J.Org.Chem., 42, 3292 (1977); f) B.M.Goldschmidt, B.L.Van Duuren, and R.C.Goldstein, Tetrahedron Letters, 1177 (1979).

2) L.G.Marzilli, B. deCastro, and C.Solorzano, J.Am.Chem.Soc., 104, 461 (1982).

(Received in UK 22 July 1983)