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SYNTHESIS OF 5-(9-ADENYL)-4-ETHYL-3-METHYL-5(H)-FURANONE

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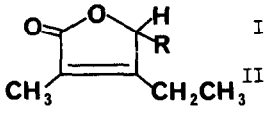
The biological importance of unsaturated lactones is well known. We wish to report the synthesis of the title compound, a new type of adenine derivative which substitutes an α,β-unsaturated γ-lactone for the 9-ribofuranosyl moiety of adenosine. The synthesis proceeded from the known 5-hydroxy-4-ethyl-3-methyl-5(H)-furanone, I (1), which upon treatment with HBr-HOAc yielded the syrupy bromo lactone II. Its nmr spectrum (CCl_4) shows a one proton singlet at δ6.79 for H_5 and a three proton singlet at 1.08 for the 3-methyl. The allylic methylene at 4 appears as a quartet at δ2.57 coupled (J=7.5 Hz) with the methyl triplet at 1.21. In the ir (CCl_4), the carbonyl and double bond appear at 1788 and 1677 cm^{-1}, respectively.

The bromo lactone was condensed with adenine in the presence of K_2CO_3 in DMF (2). The major product was the desired lactone III (mp 199-200°; M^+ 259; $\lambda^{N\ HCL}_{max}$ 256 nm, ε 14,900; $\lambda^{pH\ 7-9}_{max}$ 257 nm, ε 14,600). The uv spectrum in 0.1N NaOH shows decomposition (λ_{max} 262 nm, ε 19,300). The nmr spectrum (TFA) exhibits singlets at δ8.32 and 8.22 for the adenine H_2, and $H_{8'}$, respectively. These are superimposed on a broad absorption band due to NH protons. The 5-proton and 3-methyl appear as singlets at δ7.25 and 1.93, and the methyl of the 4-ethyl as a triplet at 0.84 (J=7.5 Hz). The methylene now appears as a broad multiplet, partially obscured by the 3-methyl peak, centered at δ2.45 (nmdr). The ir spectrum (KBr) shows the carbonyl at 1773 cm^{-1}. From the reaction mixture was isolated a minor component which is an isomer (M^+ 259) of III. Its structure is presently under investigation.

The adenyl lactone III was prepared by another route. The bromo lactone II was condensed



I, R = OH III, R = 9-adenyl

II, R = Br IV, R = 9-(N^6-benzoyl)adenyl

with chloromercuri-6-benzamidopurine in refluxing toluene to give 5-(6-benzamidopurin-9-yl)-4-ethyl-3-methyl-5(H)-furanone (IV) (mp 99-118° softening, 124° eff.; M^+ 363; $\lambda_{max}^{50\% \text{ EtOH}}$ 280 nm, ε 23,500). Its nmr spectrum (pyridine-d_5) shows the five benzenoid protons as multiplets at δ8.40 and 7.53, and $H_{2'}$, $H_{8'}$, H_5 and 3-methyl as singlets at 9.03, 8.88, 7.25 and 1.92, respectively. The ethyl group again appears with the methyl as a triplet at δ0.92 (J=7.5 Hz) and the methylene as a broad multiplet at 2.28 (nmdr). Debenzoylation of IV with methanolic picric acid afforded the adenyl lactone III as the picrate (80%, mp 273-279° d). The picrate was converted with ion exchange resin to the free base, which was shown to be identical with III by ir, uv and tlc.

Attention is drawn to the nmr spectra of the 5-furanone derivatives III and IV which show two interesting examples of magnetic non-equivalence of the methylene protons. Instead of the 1:3:3:1 quartet seen with the bromo lactone II, six peaks of two pseudo quartets were observed, the others being obscured by the 3-methyl absorption. This type of geminal resonance is attributable to non-equivalent protons. In both cases, each of the methylene protons was coupled to the methyl protons to the same extent ($J_{AX}=J_{BX}=7.5$ Hz). Irradiation of the methyl triplet reduced the methylene multiplet to an AB quartet (III: $\nu_A - \nu_B = 32$ Hz, $J_{gem}=15$ Hz; IV: $\nu_A - \nu_B = 45$ Hz, $J_{gem}=16$ Hz). According to Whitesides *et al.* (3) and Lewin *et al.* (4) conformational preference with respect to a chiral center and magnetic anisotropy associated with an aromatic ring may both contribute to non-equivalence. Both these factors appear to contribute to the magnitude of the chemical shift difference between the two methylene protons in the purine derivatives III and IV.

Other derivatives analogous to III are currently being prepared. More detailed results and biological testing will be reported.

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