The Reaction of Adenine with Epichlorohydrin

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Received June 6, 1975

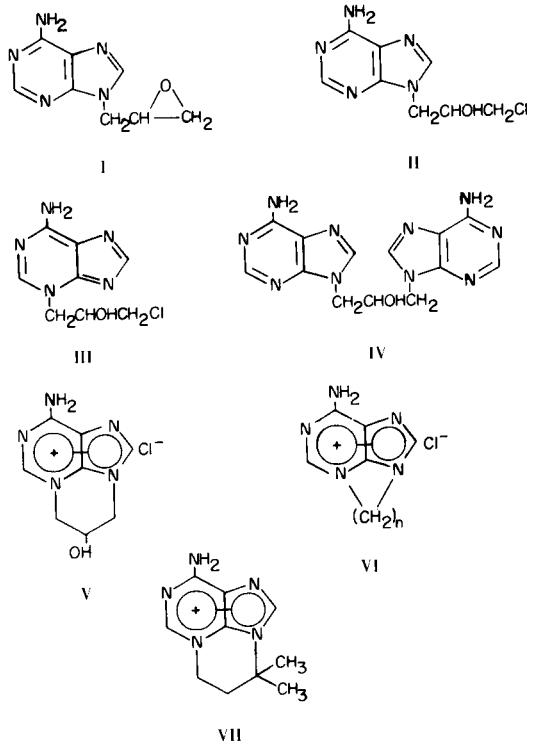
The synthesis of monomers containing purine and nucleotide moieties has attracted considerable attention because of the application of their polymers in biochemical investigations. Recently Takemoto (1) has reported the synthesis of the monomer, 9-(2,3-epoxypropyl)adenine, (I) by ring closure of 9-(3-chloro-2-hydroxypropyl)adenine, (II). The chlorohydrin II was synthesized in 50% yield by the reaction of adenine with epichlorohydrin in hot acetic acid. This highly selective 9-alkylation of adenine was surprising since alkylation of adenine under neutral or mild acid conditions might be expected to favour 3-alkylation, alkaline conditions being needed to effect predominantly 9-alkylation (2).

In our hands the reaction described by Takemoto produced two isomers, the 9-alkylated adenine, II in 5% yield and the 3-alkylated adenine III in 25% yield. The 2-positional isomers could be readily differentiated by thin layer chromatography and their structures were assigned by ultra violet spectroscopy. Compound II showed a λ max at 261 mμ as would be expected for 9-alkylated adenine (3) and compound III showed a λ max at 273 mμ, consistent with the 3-alkylated adenine (3) structure.

The reaction of adenine with epichlorohydrin was also investigated under basic conditions. Treatment of the sodium salt of adenine with one mole of epichlorohydrin gave a mixture of products, from which only the 2:1 product, IV could be isolated. A 43% yield of IV was obtained when the sodium salt of adenine was treated with only ½ mole of epichlorohydrin. The ultra violet spectrum of IV showed a λ max at 260 mμ characteristic of a 9-substituted adenine. When a 10 molar excess of epichlorohydrin was used with the sodium salt of adenine, the expected 9-substituted compound, II was formed in 25% yield.

The 3-substituted adenine, III when refluxed in ethanol or heated in dimethylformamide gave the tricyclic compound, V in good yield. Similar tricyclic compounds VI and VII have been described by Carroway (4) and Leonard (5). The ultra violet spectrum of the tricyclic compound exhibited a λ max at 271 mμ at both *p*H 1 and *p*H 7. Measurements at *p*H 10 were not possible owing to the decomposition of V at that *p*H. The 9-substituted adenine, II was not cyclized under these conditions but when heated at 250° also produced the tricyclic compound V.

The use of the chlorohydrins II and III as synthetic intermediates and as precursors of monomers for the construction of adenine containing polymers is now being studied.



EXPERIMENTAL (6)

3- And 9-(2-Hydroxy-3-chloropropyl)adenine (III and II).

(I) Reaction Under Acid Conditions.

A solution of adenine (21 g., 0.156 mole) and epichlorohydrin (22 g., 0.223 mole) in acetic acid (120 ml.) was heated on a steam bath for 4 hours. The solvent was evaporated and the resultant gum was recrystallized from water (100 ml.) to give the 9-substituted adenine II, 1.40 g. (5%), m.p. > 300°; nmr (DMSO-d_6): τ 1.8 and 1.9 (2s, 2, adenine CH), 2.7 (s, 2, NH_2), 4.25 (v.b., 1, OH), 5.5-5.95 (m, 3, propyl $C_{1,2}$-H), 6.2-6.5 (m, 2, propyl C_3,-H); uv: λ max (ε) 261 mμ (9,530) *p*H 7; Mass spectrum: 227 (M),

192 (M-Cl), 178 (M-CH_2Cl); tlc: Rf 0.3.

Anal. Calcd. for $C_8H_{10}ClN_5O$: C, 42.1; H, 4.4; N, 30.8. Found: C, 42.1; H, 4.5; N, 30.9.

The aqueous filtrate was evaporated and the resultant gum was triturated with ethanol/ether to give the crude 3-alkylated adenine III, which was recrystallized from aqueous ethanol, (7.5 g., 25%), m.p. 308-310°; nmr (d_6 DMSO): τ 1.8 and 2.2 (2s, 2, adenine CH), 2.05 (s, 2, NH_2), 4.2 (v.b., 1, OH), 5.4-6.0, (m, 3, propyl C_1, C_2-H), 6.25-6.4 (m, 2, propyl C_3-H); uv: λ max (ϵ) 2.73 mμ, (8,960); *p*H 7; Mass spectrum: identical qualitatively with the spectrum of the 9-isomer, tlc: Rf 0.7.

Anal. Calcd. for $C_8H_{10}ClN_5O$: C, 42.1; H, 4.4; N, 30.8. Found: C, 42.6; H, 4.3; N, 30.6.

(II) Reaction Under Basic Conditions.

A mixture of adenine (2.7 g., 0.02 mole) and 50% sodium hydride dispersion (1.0 g., 0.02 mole) in dry dimethyl formamide (30 ml.) were stirred vigourously at room temperature for 1 hour. Epichlorohydrin (18.5 g., 0.2 mole) was added and the mixture was stirred for 16 hours. The resulting suspension was filtered and the filtrate poured into ether (500 ml.). The precipitated gum was recrystallized from warm 2*N* hydrochloric acid to give the 9-alkylated adenine II hydrochloride, which on treatment with a 5% sodium bicarbonate solution gave the free base (1.1 g., 25%).

1,3-Diaden-9-yl-propan-2-ol (IV).

A mixture of adenine (10 g., 0.074 mole) and a 50% sodium hydride dispersion (3.6 g., 0.074 mole) in dry dimethylformamide (120 ml.) was stirred at room temperature for 1 hour. Epichlorohydrin (4.6 g., 0.05 mole) was added and the mixture was stirred for 48 hours. The suspension was filtered and the filtrate poured into ether (800 ml.). The resultant precipitated solid was recrystallized from 2*N* hydrochloric acid to give IV dihydrochloride, monohydrate (6.5 g., 43%) m.p. >300°; uv: λ max (ϵ) 260 mμ (14,700) *p*H 7.

Anal. Calcd. for $C_{13}H_{14}N_{10}O{\cdot}2HCl{\cdot}H_2O$: C, 37.4; H, 4.3; N, 33.5; Cl, 17.0. Found: C, 37.6; H, 4.3; N, 33.5; Cl, 17.0.

Treatment of an aqueous solution of the dihydrochloride with a 5% sodium bicarbonate solution gave the free base, which was recrystallized from water to give the monohydrate, micro prisms, m.p. >310°; nmr (d_6 DMSO): τ 1.85 and 1.90 (2s, 4, adenine CH), 2.75 (s, 4 NH_2) 4.30 (v.b., 1 OH) 5.75 (m, 5, propyl CH and CH_2): Mass spectrum: 326 (M).

Anal. Calcd. for $C_{13}H_{14}N_{10}O\ H_2O$: C, 45.4; H, 4.6; N, 40.7. Found: C, 45.8; H, 4.7; N, 41.1.

10-Amino-5,6-dihydro-5-hydroxy-4*H*-pyrimido[1,2,3-*cd*]purin-3-ium Chloride (V).

The 3-alkylated adenine (1.4 g.) was heated in dry dimethylformamide for 3 hours. The reaction mixture was filtered and the filtrate poured into ether (200 ml.). The brown precipitate was recrystallized from aqueous ethanol to give the tricyclic compound (V). (1.0 g., 70%), m.p. >300°; nmr (d_6 DMSO): τ 0.80 (v.b., 2, NH_2), 1.25 and 1.55 (2s, 2, adenine CH), 3.85 (v.b., 1, OH), 5.3-5.9 (m, 5, propyl CH); uv: λ max (ϵ) 271 mμ (8,400), *p*H 7; Mass spectrum: 191 (M).

Anal. Calcd. for $C_8H_{10}ClN_5O$: C, 42.1; H, 4.4; N, 30.6; Cl, 15.6. Found: C, 42.4; H, 4.6; N, 30.7; Cl, 15.5.

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(6) Melting points are uncorrected. Ultraviolet spectra were determined on aqueous solutions using a Perkin Elmer 137 spectrometer. Mass spectra analyses were performed on a Hitachi Perkin Elmer RMU-6E machine. Nmr spectra were taken on a Varian HA 100D spectrometer. In the experimental section the following symbols were used in the nmr data: s, singlet, m, multiplet and v.b., very broad. Thin layer chromatography was carried out using Merk Kieselgel F_{254} plates with the solvent system acetonitrile/water, 88:12.