# A Novel Ring Closure and a New Synthesis of 3-Deazaguanine.



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The reaction of methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate with hydroxylamine provided methyl 5(4)-carboxamidoximylmethylimidazole-4(5)-carboxylate which cyclized on reduction to yield 3-deazaguanine.

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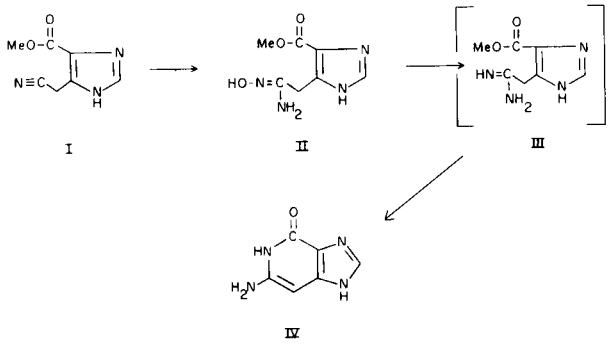
3-Deazaguanine (IV) is a structural analog of guanine in which there is an isosteric replacement of the nitrogen at the 3-position. 3-Deazaguanine (2,3) has exhibited interesting in vitro and in vivo activity (4,5) against leukemia L1210, adenocarcinoma 755 and mammary adenocarcinoma R3230AC and 13762 as well as against a variety of DNA and RNA viruses (6). It has also been reported (7) to inhibit, *in vitro*, purine nucleotide biosynthesis in Ehrlich ascites tumor cells. The interest in the chemotherapeutic activity of 3-deazaguanine has emphasized the need for its larger quantities for further studies. We now describe a convenient synthesis of this compound by a novel ring closure.



I II III



IV

The starting matierial, methyl 5(4)-cyanomethylimidazole-4(5)-carboxylate (I) for this reaction was synthesized as reported (3). The key intermediate, methyl 4(5)-carboxamidoximylmethylimidazole-5(4)-carboxylate (II) was obtained by refluxing a solution of I in ethanol with 4 molar hydroxylamine buffer. Under conditions the methyl ester group of I was found stable whereas the nitrile group reacted readily with hydroxylamine to provide II in 85% yield. The hydrogenation of II in the presence of Raney Nickel catalyst provided IV in 52% yield. The formation of compound IV would be expected due to the cyclization of amidine III formed via the reduction of amidoxime II. The advantage of this procedure is that the synthesis of 3-deazaguanine can be accomplished rapidly in good yield and relatively pure form without the use of a high pressure reaction vessel.

## EXPERIMENTAL

The physical properties were determined with the following instruments: m.p., Thomas Hoover app (uncorrected); ir, Perkin-Elmer Model 257 spectrophotometer (potassium bromide); uv spectra, Cary 15 uv spectrophotometer (*p*H 1 and *p*H 11); nmr, Perkin-Elmer Model R-20A spectrometer (DSS). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Methyl 4(5)-Carboxamidoximylmethylimidazole-5(4)-carboxylate (II).

A mixture of hydroxylamine hydrochloride (14.0 g., ~200 mmoles) and sodium carbonate (10.5 g., 100 mmoles) was stirred at room temperature in water (50 ml.) to provide the hydroxylamine buffer. To this was added methyl 4(5)-cyanomethylimidazole-5(4)-carboxylate (3) (I, 15.0 g., 90.90 mmoles) and ethanol (50 ml.). The reaction mixture was refluxed for 45 minutes. The solvent was evaporated *in vacuo* and the residue was triturated with water (50 ml.). A crystalline product was obtained which was collected by filtration, washed with cold water (20 ml.), cold ethanol (20 ml.) and dried to provide 17.0 g. (85%) of II as light brown crystals. The crude product was chromatographically homogeneous and of sufficient purity for further reaction. For analytical purposes a sample (1 g.) was recrystallized from water using Norite to provide 0.8 g. (80%) of II as needles which after drying (80°, *in vacuo* over phosphorus pentoxide) turned light brown, m.p. 182-183° dec.; nmr (DMSO-$d_6$) $\delta$ 3.67 (s, 2, $CH_2$), 3.8 (s, 3, $CH_3$), 5.4 (s, (br), 2, $NH_2$), 7.7 (s, 1, $H_2$).

*Anal.* Calcd. for $C_7H_{10}N_4O_3$; C, 42.42; H, 5.09; N, 28.27. Found: C, 42.30; H, 4.97; N, 28.47.

3-Deazaguanine (IV).

A sample of activated Raney Nickel was washed well with water and weighed wet (10 g.). It was transferred into a pressure hydrogenation bottle containing a solution of II (10 g., 50.5 mmoles) dissolved in hot water (250 ml.). The mixture was hydrogenated at 40-45° on a Parr apparatus at 45 psi for 20 hours. The reaction mixture was removed from the Parr apparatus and heated to reflux with stirring for 15 minutes. The catalyst was removed by filtration through a Celite pad. The filtrate on concentration (volume *ca.* 50 ml.) and cooling gave white needles of pure 3-deazaguanine (3.5 g.). An additional quantity of 3-deazaguanine was obtained as follows. The mother liquor was adjusted to *p*H 4 by adding diluted hydrochloric acid. The solvent was evaporated to dryness and the residue was triturated with methanol. The crystallin product thus obtained was dissolved in water (*ca.* 10 ml.) and adjusted to *p*H 8 by adding a

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saturated solution of sodium bicarbonate. The crude 3-deazaguanine which separated was filtered and recrystallized from water to yield 500 mg. of pure IV, total yield 4.0 g. (52.8%). The product IV (m.p $>350^{\circ}$) was found identical (uv, tlc mobility and nmr) with an authentic sample (3) of 3-deazaguanine.

## REFERENCES AND NOTES

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