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THE NOVEL SYNTHESIS OF A [6 5 6] LINEAR ISOGUANOSINE TYPE TRICYCLIC NUCLEOSIDE USING CARBONYL SULFIDE

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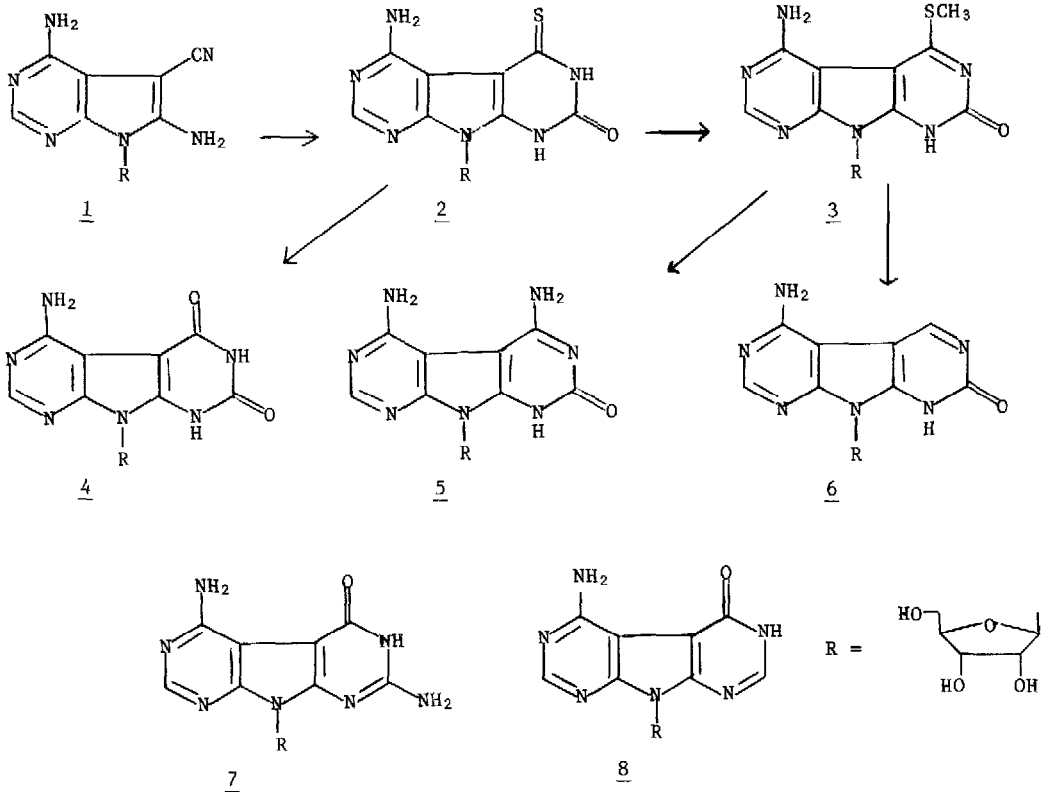
The novel one-step synthesis of a fused pyrimidin-2-one-4-thione derivative from an o-aminonitrile using carbonyl sulfide is described.

The significant antitumor activity observed[2,3] for certain tricyclic nucleosides prepared in our laboratory, e g , 4,5-diamino-8-(β-D-ribofuranosyl)pyrazolo[3',4'-5,4]pyrrolo[2,3-d]-pyrimidine[4] and 6-amino-4-methyl-8-(β-D-ribofuranosyl)(4H,8H)pyrrolo[4,3,2-de]pyrimido[4,5-c]-pyridazine[5] prompted us to continue our research efforts in the tricyclic nucleoside area. We have recently synthesized a new class of tricyclic nucleosides in which the aglycon has a [6 5 6] "linear" geometry with the ribosyl moiety residing on the five membered ring. However, we were unable to prepare, in this series, the adenosine-isoguanosine analog 4,5-diamino-9-(β-D-ribofuranosyl)pyrimido[5,4-f]pyrrolo[2,3-d]pyrimidin-7-one (5) using the standard approaches.

Our initial attempts to synthesize 5 directly by ring annulation[6] of 6-aminotoyocamycin[7] (1) with ethyl chloroformate, followed by treatment with ammonia, were unsuccessful. Also, a fusion of 1 with urea[6] resulted in a black reaction mixture from which no identifiable products could be isolated. We then decided to convert the 5-cyano group of 1 into a more reactive form[8] such as an amidine or alkyl imino ether group which should function more effectively in a ring-closing reaction However, these attempts to form the above derivatives were unproductive since the cyano group was found to be essentially resistant toward attack by nucleophiles. These results further confirmed our earlier findings[7] that in this ring system, a 4- and/or 6-amino group serves to deactivate a cyano group located at the 5-position. The synthesis of isoguanosine, per se, has been accomplished[9] by cyclization of 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-thiocarboxamide with diethylcarbonate in ethanolic sodium ethoxide solution to give 6-thioxanthosine (5% yield based on the 2',3'-O-isopropylidene, 5-amino-4-cyanoimidazole

ribonucleoside) The 6-thioxanthosine was then methylated and treated with ammonia to afford isoguanosine Attempts to use this procedure for the synthesis of 4-amino-9-(β-D-ribofuranosyl)-pyrimido[5,4-f]pyrrolo[2,3-d]pyrimidin-5-thione-7-one from 6-aminothiosangivamycin[7] (2) only resulted in the isolation[10] of 1



These unsuccessful attempts prompted us to subsequently initiate a novel approach for the synthesis of the desired isoguanosine nucleoside analog 3 We now wish to report the successful synthesis of 3 using a ring closure involving an o-aminonitrile grouping with the novel reagent carbonyl sulfide Treatment of 1 (500 mg, 1.63 mmoles) with a solution of carbonyl sulfide (1.5 ml) in methanolic-sodium hydroxide solution (300 mg, 7 5 mmoles in 18 ml of methanol) in a sealed vessel at 180° for 7 hr furnished a yellow solid. The solid was dissolved in water and the pH of the solution adjusted to 5 by the slow addition of 2 N hydrochloric acid which resulted in the precipitation of a solid (400 mg, 61% yield) The elemental analysis of this solid suggested an empirical formula corresponding to that of the tricyclic compound 2 This product

lacked an absorption band for a cyano group (region near 2200 cm^{-1}) in the ir spectrum and the uv spectrum indicated that ring closure had probably occurred since the product (2) showed a significant bathochromic shift in comparison to the starting material[7] 1 ($\lambda_{Max}^{CH_3OH}$ of 292 nm for 2 and a $\lambda_{Max}^{CH_3OH}$ of 274 nm for 1) Furthermore, this large shift to a longer wavelength in the uv spectrum is also indicative[11] that the thione group is adjacent to the pyrrole ring, i.e at the 5-position of the tricyclic ring rather than the 7-position.

Although we assumed that this product was the "linear" tricyclic nucleoside 2, there was a possibility that ring closure had taken place between the 5-cyano group and the 4-amino group (rather than the 6-amino group) which would yield a "triangular" type tricyclic nucleoside containing a seven-membered ring. However, the annulation of 1 with carbonyl sulfide has been shown[12] to yield a "linear" tricyclic nucleoside on the basis of the following chemical conversions Methyl iodide (10 mole excess) was added to a solution of 2 (150 mg, 0.41 mmoles) in dilute ammonium hydroxide (15 ml of a 0.75% solution) to furnish a 64% yield of the corresponding 5-methylthio derivative 3 (a sharp 3-proton singlet was observed at δ 2 18). Subsequent treatment of 3 (300 mg) with ammonium hydroxide (1 5 ml of a 28% solution) at 130° for 14 hr provided nucleoside material (71% yield) which was subsequently established as the desired adenosine-isoguanosine analog 5 The pmr spectrum of 5 (DMSO-d_6) was compared and found to be similar to the spectrum of the adenosine-guanosine[12] analog 7 The signal for the anomeric proton (H-1') of 5 was observed at δ 5 05 (compared to δ 5 10 for 7) and H-2' appeared at δ 6.23 (compared to δ 6 20 for 7) In contrast to the pmr spectrum, the uv spectra of 5 [$\lambda_{Max}^{pH\ 1}$ = 311 (ε = 11,500), 287 (ε = 13,900), $\lambda_{Max}^{CH_3OH}$ = 294 5 (ε = 17,400), $\lambda_{Max}^{pH\ 11}$ = 307 (ε = 16,700)] was quite different from the uv spectra of the adenosine-guanosine[12] analog 7 [$\lambda_{Max}^{pH\ 1}$ = 303 (ε = 17,100), $\lambda_{Max}^{CH_3OH}$ = 313 (ε = 16,100), 303 (ε = 18,500), $\lambda_{Max}^{pH\ 11}$ = 303 5 (ε = 15,000)]. Oxidative-hydrolysis of 2 using concentrated ammonium hydroxide and 30% hydrogen peroxide provided a 56% yield of the known[12] "linear" tricyclic nucleoside 4-amino-9-(β-D-ribofuranosyl)-pyrimido[5,4-f]pyrrolo[2,3-d]pyrimidin-5-7-dione (4) which established the "linear" nature of the original ring closed product 2. Finally, dethiation of 3 using Raney nickel has provided an -one derivative (6) with an empirical formula identical to the nucleoside 4-amino-9-(β-D-ribofuranosyl)pyrimido[5,4-f]pyrrolo[2,3-d]pyrimidin-5-one[12] (8) However, the spectral data (pmr, uv) for the dethiation product 6 is significantly different from the data observed[12] for 8 Therefore, the nucleoside obtained from the carbonyl sulfide ring closure of 1 must possess

the structure 2 with the thione group located in the 5-position of the tricyclic ring rather than the isomeric structure with the thione group in the 7-position

We would like to propose that the mechanism of the ring-closing reaction with carbonyl sulfide is similar to that proposed[13] for reactions of o-aminonitriles with carbon disulfide. The mechanism would involve the initial formation of a monothiocarbamate salt, cyclization to a m-thiazine derivative through nucleophilic attack on the cyano group selectively, by sulfur ion, followed by a ring-opening and a ring-reclosure sequence. This one-step synthesis of a fused pyrimidin-one-thione derivative should be of considerable utility and we are currently conducting experiments designed to test the generality of this interesting reaction

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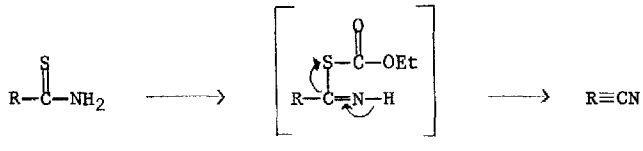

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