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7-DEAZAPURINES III. ABNORMAL REACTION OF 6-CYANO-5-HYDROXYPYRROLO[2,3-*d*]PYRIMIDINES WITH THIONYL CHLORIDE

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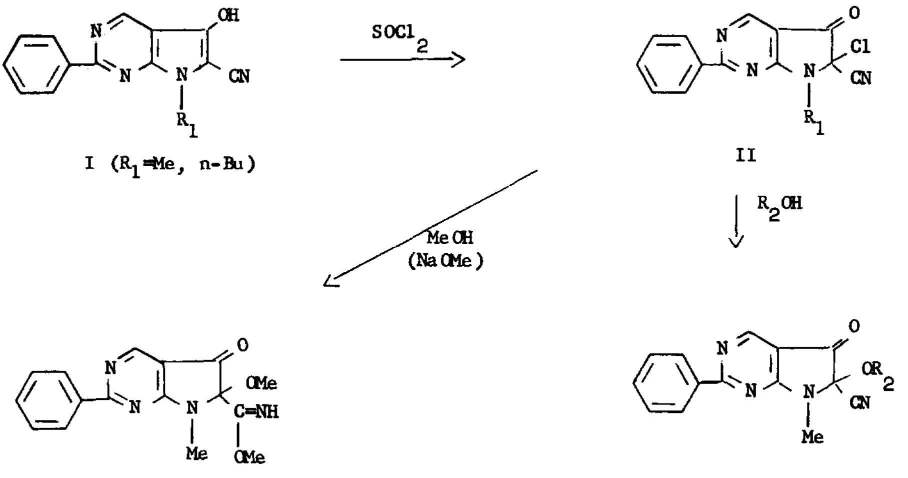
The recent isolation of the 7-deazapurinenucleotides, i.e. tubercidin, toyocamycin, and sangivamycin, which are potent antileukemic agents, has focused considerable interest on the chemistry of the pyrrolo[2,3-*d*]pyrimidines (the 7-deazapurines).

We now wish to report an *abnormal* reaction of 5-hydroxy-7-alkyl—2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (I) (1) with thionyl chloride. When I (R_1=Me) was treated with a large excess of thionyl chloride under refluxing conditions with the expectation of replacing the hydroxy group with a chloro group, II (R_1=Me) was obtained instead, in nearly quantitative yield. The structure of II (R_1=Me), m.p., 183-185°, M^+, *m/e* 284, was established by its elemental analyses (2) and spectral data. In agreement with this structure were the strong ir band at 5.76 μ (C=O), the uv absorption maxima (95% EtOH) at 219 (ε, 19.4 x 10^3),



I (R_1=Me, n-Bu)

II

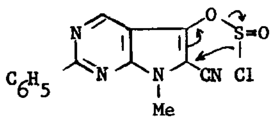
IV

III (R_2=Me, Et, $CHMe_2$)

254 (ϵ, 12.5×10^3), and 296 $m\mu$ (ϵ, 16.2×10^3), and the nmr signals ($CDCl_3$) at δ 8.92 (H,s), 8.55 (2H,m), 7.50 (3H,m), and 3.42 ppm (3H,s).

As expected, the chloro group was readily replaced by nucleophiles; for example, treatment of II (R_1=Me) with boiling methanol for 30 min. replaced the chlorine with a methoxy group to give III (R_2=CH_3) {m.p. 169-171°; ir 5.8 μ; uv max. 217 (ϵ, 38.5×10^3), 262 (ϵ, 23.8×10^3), and 235 $m\mu$ (ϵ, 25.1×10^3) shoulder; nmr δ 8.71 (H,s), 8.50 (2H,m), 7.52 (3H,m), 3.30 (3H,s), and 3.15 ppm (3H,m)] in a quantitative yield. When II (R_1=Me) was allowed to react with methanol at room temperature in the presence of a catlytic amount of sodium methoxide it was converted into IV [m.p. 125-127°; ir 3.09, 5.80, 5.94 μ; uv max. 217 (ϵ 18.6×10^3), 267 (ϵ, 13.3×10^3), 296 (ϵ, 21.1×10^3), and 234 $m\mu$ (ϵ, 14.9×10^3) shoulder; nmr., δ 8.71 (H,s), 8.50 (2H,m), 7.55 (3H,m), 3.73 (3H,s), 3.25 (3H,s), and 3.07 ppm (3H,s); mass spectrum m/e 58 fragmentation, -C(OMe)=NH].

The abnormal reaction of I with thionyl chloride may be due to the strong electrophilic character of C_6 in the intermediate V which is doubly activated by a CN group and an electron-withdrawing 4-aminopyrimidine system. Thus, after an initial formation of V by a normal mode of reaction, the subsequent internal nucleophilic attack takes place at the nucleophilic center of V (C_6), instead of at C_5, with an allylic type rearrangement (SNi′), resulting in formation of II (4,5).



V

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(1) D. H. Kim and A. A. Santilli, J. Heterocyclic Chem. 6, 819 (1969).

(2) All new compounds reported were analyzed satisfactorily for C, H, N, and Cl.

(3) There are a few reports in the literature which describe other types of abnormal reactions of thionyl chloride, for example, a) A. J. Krubsack, T. Higa and W. E. Slack, J. Amer. Chem. Soc. 92, 5258 (1970), b) A. J. Krubsack and T. Higa, Tetrahedron Letters 5149 (1968), c) G. Büchi and G. Lukas, J. Amer. Chem. Soc. 86, 5654 (1964), d) E. C. Taylor, A. McKillop, Y. Shvo, and G. H. Hawks, Tetrahedron 23, 2081 (1967), e) P. K. Freeman, F. A. Raymond, and J. N. Blazevich, J. Org. Chem. 34, 1175 (1969).

(4) The possibility of an S_N2' type mechanism initiated by Cl^- which is generated in the formation of V cannot be ruled out, although it is less likely under the conditions used.

(5) The sulfur monoxide thus expelled is known to disproportionate to sulfur dioxide and sulfur; H. Zeise, Z. Physik. Chem. (B), 51, 120 (1942).