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7-DEAZAPURINES IV. NOVEL MOLECULAR REARRANGEMENT AND FACILE NUCLEOPHILIC AROMATIC SUBSTITUTION OF 7-DEAZAPURINES

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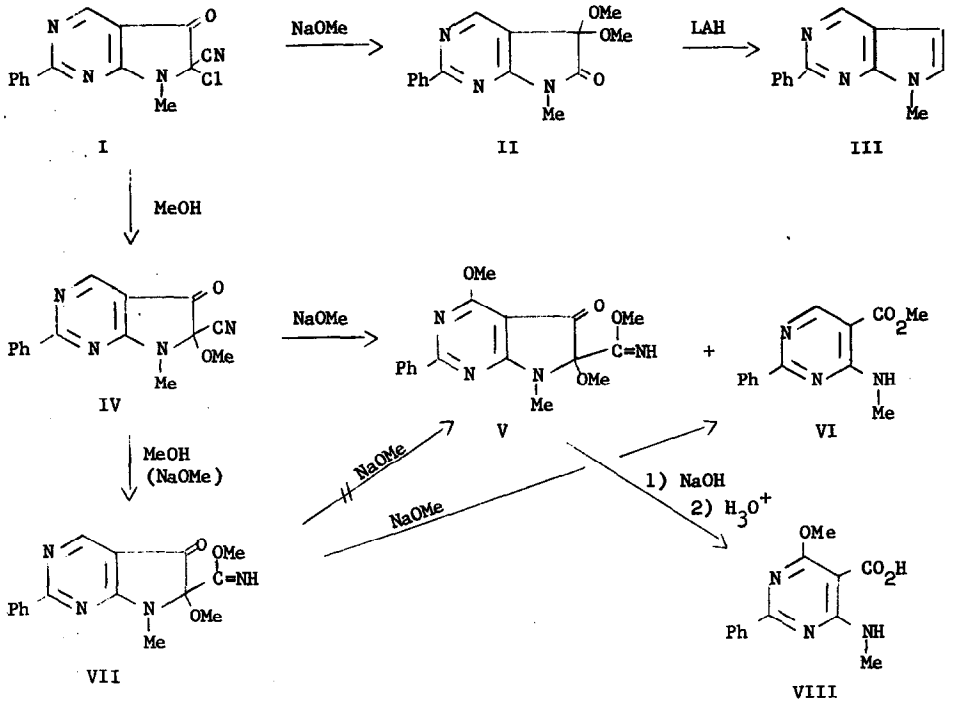
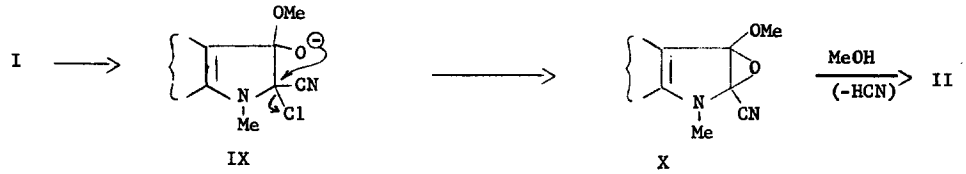
Previously we reported on the preparation of 6-chloro-5,6-dihydro-7-methyl-5-oxo-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carbonitrile (I) and its reaction with methanol to give 5,6-dihydro-6-methoxy-7-methyl-5-oxo-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carbonitrile (IV) (1). In this communication we wish to report on their unusual chemical behavior.



Treatment of I with a base such as sodium methoxide or guanidine in methanol under refluxing conditions for 45 min. afforded a crystalline product, m.p. 141-144°, in 40-70% yield. The structure of the product was established as 7-methyl-2-phenyl-5H-pyrrolo[2,3-d]pyrimidine-5,6-(7H)-dione 5-dimethyl acetal (II) by elemental analyses (2) and by spectral as well as chemical

data. The ir spectrum showed carbonyl absorption at 5.70 μ (3). Preservation of the pyrrolo[2,3-d]pyrimidine ring system was demonstrated by its reduction by $LiAlH_4$ in THF to the previously described 7-methyl-2-phenylpyrrolo[2,3-d]pyrimidine (III) (5)(6). The uv spectrum of II [(95% EtOH) 251 (ε, 28.2 x 10^3) and 286 mμ (ε, 11.7 x 10^3)] was different from those of IV and related 5-oxo derivatives (1). The resemblance of the uv spectrum of II to those of unambiguously prepared 5,7-dihydro-7-alkyl-2-phenyl-6H-pyrrolo[2,3-d]pyrimidin-6-ones (9) coupled with the position of the ir carbonyl absorption (10) suggested that the keto function was in the 6-position (11). This was further supported by the nmr spectrum which showed its C-4 proton signal at δ 8.53 ppm, noticeably shifted from the C-4 proton signal of IV (δ 8.71 ppm) (12 The other nmr signals are δ 8.45 (m, 2H) and 7.52 (m, 3H) (aromatic), 3.60 (s, 6H, 2-OCH_3) and 3.28 ppm (s, 3H, N-CH_3). Major mass spectral peaks are m/e 285 (M^+), 270, 256, 254, 242, 212, 210, 205, and 156.

A possible explanation for the rearrangement involves the formation of intermediate X, formed by nucleophilic attack by methoxide ion on the 5-oxo group as shown below (13). The oxirane nucleus of X is then attacked by methoxide from the less hindered side, with concomitant removal of the cyano group resulting in formation of the oxo group at the 6-position.

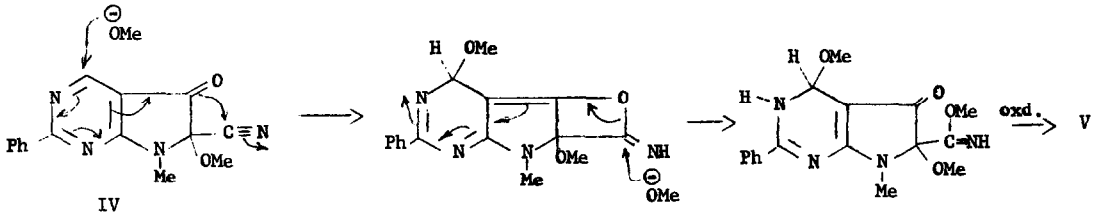


When IV was treated with sodium methoxide, a nucleophilic aromatic substitution occurred on the pyrimidine nucleus. Treatment of IV with an equimolar quantity of sodium methoxide in methanol for 25 min. on a steam bath afforded two products. The major product (m.p. 177-179°), isolated in 35% yield, was identified as 5,6-dihydro-4,6-dimethoxy-7-methyl-5-oxo-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboximidic acid methyl ester (V) on the basis of its elemental analyses ($C_{17}H_{18}N_4O_4$; M^+ m/e 342) and spectral data [ir (KBr) 3.08 (NH), 5.81 (CO), and 5.99 μ (C=N); uv max. (95% EtOH) 227 (ε, 21.6 x 10^3), 286 (ε, 12.0 x 10^3), 295 (ε, 24.5 x 10^3), and 239 mμ (ε, 17.1 x 10^3) (shoulder)]. Preservation of the basic ring system was indicated by the similarity of the uv spectrum of V to that of IV and VII (1). The nmr spectrum of V provided confirmative evidence for the assigned structure; apart from other proton signals, which remained essentially unchanged, there were two additional singlets (3H each) at δ 4.23 (4-OMe) and 3.73 ppm (C(OMe)=NH); the signal at δ 8.71 due to C_4-H in the spectrum of IV was absent.

In the mass spectrum of V, the parent peak at 284 m/e which was derived from M^+ with a loss of m/e 58 (-C(OMe)=NH) supported the iminoether portion of the structure. Chemical evidence for structure V was obtained by its degradation by 10% aq. NaOH solution to 4-methylamino-6-methoxy-2-phenyl-5-pyrimidinecarboxylic acid (VIII) [m.p. 203-205° dec.; ir (KBr) 3.05 (NH) and 5.88 μ (C=O); nmr ($DMSOd_6$) δ 3.13 (d, 3H, NHMe), 4.07 (s, 3H, OMe), 7.55 (m, 3H, aromatic), 8.47 (m, 2H, aromatic) and 8.67 ppm (m, 1H, NH, disappeared on D_2O treatment)], the structure of which was confirmed by an independent unequivocal synthesis. In addition to the formation of V, a selective cleavage of the pyrrole portion of the deazapurine ring system also took place to give 4-methylamino-2-phenyl-5-pyrimidinecarboxylic acid methyl ester (VI) as a minor product.

Interestingly, when IV was treated with only a catalytic amount of sodium methoxide, 5,6-dihydro-6-methoxy-7-methyl-5-oxo-2-phenyl-7H-pyrrolo[2,3-d]pyrimidine-6-carboximidic acid methyl ester (VII) (1) was the main product. Furthermore, attempted conversion of VII into V under conditions similar to those used for the preparation of V afforded VI instead. Apparently, the nucleophilic substitution reaction on the pyrimidine nucleus takes place prior to or simultaneously with the formation of the iminoether. This result suggests an involvement of the cyano group at the 6-position in the process of the substitution reaction. It also suggests that IV may be an intermediate in the formation of VI, although a direct cleavage of the pyrrole nucleus in IV cannot presently be ruled out.

A possible reaction sequence for the unusual nucleophilic aromatic substitution is shown in the following equation.



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REFERENCES

(1) D. H. Kim and A. A. Santilli, Tetrahedron Letters, 2441 (1971).

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

(3) This higher carbonyl frequency than that of normal γ-lactams (5.71-5.88 μ) (4) may be due to the effect of the neighboring pyrimidine nucleus and the α-methoxy groups.

(4) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd. ed., John Wiley & Sons, Inc., New York, N.Y., 1958, p-214.

(5) R. A. Partyka (Bristol-Meyers Co.) U.S. Patent 3,311,628 (1967).

(6) Although the exact nature of the reduction is not apparent, it appears that the ketal is reduced by the presence of the carbonyl group at C_6 (7), followed by further reduction to III (8).

(7) Although acetals and ketals are known to be inert to LAH, there are examples in the literature in which the presence of a reducible carbonyl group at the α-position makes them susceptible to reduction [N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N.Y., 1956, pp 682-683].

(8) This may be analogous to the reported reduction of 3-hydroxyoxindoles by LAH to indoles [J. Bergman, Acta Chem. Scand., 25, 1277 (1971); P. L. Julian and H. C. Printy, J. Amer. Chem. Soc., 71, 3206 (1949)].

(9) These compounds were prepared by a modified method of N. Nesbitt and P. Sykes [J. Chem. Soc., 3057 (1954)].

(10) The ir C=O absorption bands of 5-oxo 7-deazapurines fall in the 5.76-5.80 μ (7) range.

(11) Several attempts to prepare hydrazone derivatives failed.

(12) The isomeric 7-methyl-2-phenyl-5H-pyrrolo[2,3-d]pyrimidine-5,6-(7H)-dione 6-dimethyl acetal is expected to show its 4-H resonance signal at δ 8.7-9.0 ppm. (Our unpublished results).

(13) α-Halogenoketones are known to form oxiranes when treated with NaOMe [C. L. Stevens, W. Malik, and R. Pratt, J. Amer. Chem. Soc., 72, 4758 (1950)]