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SOME NOVEL REACTIONS OF 1,3-DIMETHYLURACILS[1]

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Abstract — Treatment of 6-chloro-1,3-dimethyluracil (1) with diazomethane and tertiary amines gave the dimeric compound (2) as the sole product and 1 with secondary amines deduced to the 6-amino dimeric compounds (6). The structural assignment of the dimers is based on physical and chemical evidences.

As part of our programme of studies on novel heterocyclic systems, we have recently reported photochemical syntheses of fused tricyclic[2] and tetracyclic[3] compounds from 1,3-dialkyluracil derivatives. We wish to report here some novel reactions of 6-chloro-1,3-dimethyluracil (1). When 1 was treated with diazomethane in a mixture of ether and tetrahydrofuran for two weeks at room temperature, a crystalline compound(2)(mp 217°, 18~26%) was obtained as the only isolable product. [$C_{12}H_{13}ClN_4O_4$,[4] m/e 314 and 312 (M^+), ^{1}H-nmr ($CDCl_3$), δ3.28 (3H, singlet, NCH_3), 3.43 (6H, singlet, 2 x NCH_3), 3.70 (3H, singlet, NCH_3), 5.73 (1H, singlet, =CH)].

Catalytic hydrogenation (10% Pd/C) of 2 at room temperature gave a dechlorinated product 3. [mp *280° (98%)*, $C_{12}H_{14}N_4O_4$, *m/e 278* (M^+), ^{1}*H-nmr* ($CDCl_3$), NCH_3 *singlets at* δ*3.28, 3.36, 3.40 and* 3.50; singlets for vinylic protons at δ5.63 and 7.40]. The presence of two isolated vinylic proton signals and four NCH_3 singlets in the ^{1}H-nmr spectrum clearly indicated that this product is the dimeric compound (3) as shown in Fig. 1; hence the chlorinated derivative can be assigned the structure 2. When 2 was hydrogenated over Raney nickel under pressure, the tetrahydro derivative (4) was obtained [mp 148° 150°, $C_{12}H_{18}N_4O_4$, m/e 280 (M^+-2), ^{1}H-nmr ($CDCl_3$), δ3.00(3H, singlet NCH_3), 3.10 (3H, singlet, NCH_3), 3.18 (3H, singlet, NCH_3), 3.20 (3H, singlet, NCH_3), 2.80∿3.20 (5H, multiplet, $N\underline{CH_2}\underline{CH}$ CH $\underline{CH_2}CO$-), 4.28(1H, broad, proton at C-6')].

The same product 4 was also obtained from 3 by hydrogenation under the same conditons.

The structure 4 was proved by the unusual low field shift of the proton at C-6' in ^{1}H-nmr spectrum. This paramagnetic shift is caused by the close proximity of the C-6' proton and C-4 carbonyl group.

It is reasonable to assume that dimerization of 1 by elimination of HCl from two molecules may have been caused by the basic nature of diazomethane. This view was supported by isolation of the same product 2 after treatment of 1 with tertiary amines (e.g., DABCO, DBU or Et_3N). Thus, treatment of 6-chlorouracil with tertiary amines has turned out to be a simple method for the preparation of 5,6'-bisuracils.

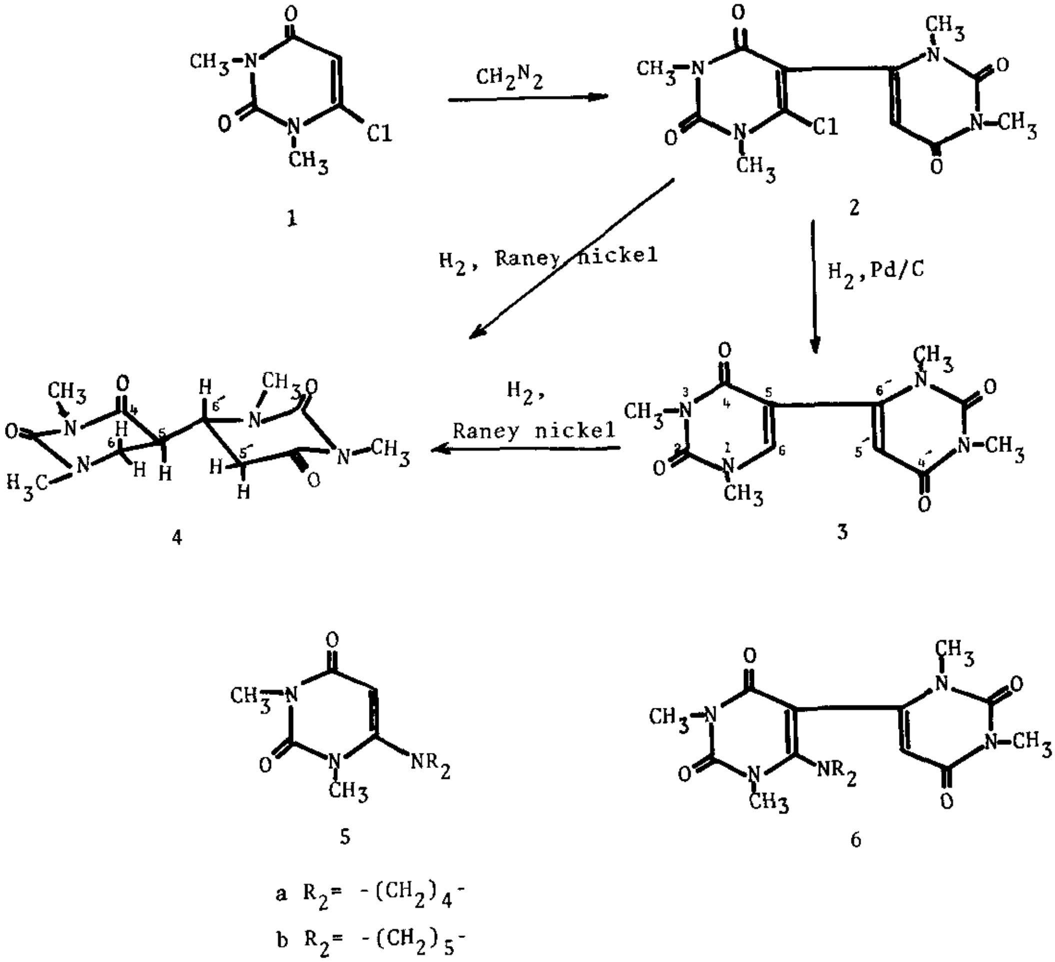

Fig.1

Certain secondary amines (pyrrolidine, piperidine) upon reaction with 1 were found to give, in addition to 6-substituted uracils (5), the corresponding dimeric derivatives 6. [6a, mp 205° (dec), $C_{16}H_{20}N_5O_4$, m/e 347(M^+), ^{1}H-nmr ($CDCl_3$), δ1.7-2.1(4H, multiplet, CCH_2CH_2C), 2.8-3.3 (4H, multiplet, $-CH_2NCH_2-$), 3.33 (3H, singlet, NCH_3), 3.38 (6H, singlet, 2 x NCH_3), 3.42 (3H, singlet, NCH_3), 5.50 (1H, singlet =CH); 6b, mp 156° (dec), $C_{17}H_{22}N_5O_4$, m/e 361 (M^+), ^{1}H-nmr ($CDCl_3$), δ1.4-2.0 (6H, multiplet, $-(CH_2)_3-$), 3.0-3.3 (4H, multiplet, $-CH_2NCH_2-$), 3.32 (3H, singlet, NCH_3), 3.35 (6H, singlet, 2 x NCH_3), 3.88 (3H, singlet, NCH_3), 5.20 (1H, singlet, =CH)]. Compounds 6a and 6b could also be prepared in quantitative yield by treatment of 2 with the corresponding amines. The latter preparation, therefore, provides the proof for the structures 6 for these products.

References and Footnotes

1. Presented in part at 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 5-7, 1978.
2. T. Itoh, H. Ogura and K. A. Watanabe, Tetrahedron Letters, **1977**, 2595.
3. T. Itoh, H. Ogura, N. Kawahara and K. A. Watanabe, Heterocycles, **12**, 1175 (1979).
4. Satisfactory elemental analyses compatible with the structural assignments were obtained for all compounds with melting point described herein. Melting points are uncorrected.

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