

Midwest Research Institute

## 1,3-Dimethyl-5-nitro-6-chlorouracil (I)

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In connection with a study of compounds closely related to toxoflavin and fervenulin (2), a key intermediate, 1,3-dimethyl-5-nitro-6-chlorouracil (I,  $R_1, R_2 = \text{CH}_3$ ), has been prepared by the direct nitration of 1,3-dimethyl-6-chlorouracil.

Because of the extreme reactivity of 5-nitro-6-chlorouracil (3) (I,  $R_1, R_2 = \text{H}$ ), nitration of 6-chlorouracil requires rather carefully controlled conditions. The reaction conditions become increasingly critical when the ring nitrogens are substituted by alkyl groups. This is well illustrated in the preparation of 3-methyl-5-nitro-6-chlorouracil (2c) (I,  $R_1 = \text{H}, R_2 = \text{CH}_3$ ) wherein the reaction temperature must not exceed room temperature.

The importance of the title compound as a useful intermediate has been demonstrated recently by other investigators who utilized it for the synthesis of some interesting purine glycosides (4). Since the preparation of the compound was not reported in that communication but referred to us as the originating source, the detailed preparation of I ( $R_1, R_2 = \text{CH}_3$ ) and that of its reduced derivative, 1,3-dimethyl-5-amino-6-chlorouracil, is hereby reported.

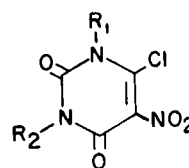
## EXPERIMENTAL (5)

## 1,3-Dimethyl-5-nitro-6-chlorouracil.

To a two-necked flask equipped with a drying tube and a dropping funnel was added 125 ml. of concentrated sulfuric acid. The flask was immersed in an ice-water bath and 42.5 g. of 1,3-dimethyl-6-chlorouracil (6) was added portionwise with stirring. To the resulting solution was added dropwise 42 ml. of fuming nitric acid at such a rate that the reaction temperature throughout the addition was kept at  $10^\circ$ . As soon as the addition was complete, the solution was poured onto 500 g. of ice flakes with vigorous stirring to form a viscous paste. This was promptly stirred with 500 ml. of chloroform for 5 min. The chloroform layer was separated and the ice-water layer was extracted with an additional 200 ml. of chloroform. The chloroform extracts were combined and quickly evaporated at room temperature under reduced pressure to give a pale yellow solid. After drying in a desiccator over calcium chloride the product weighed 38-40 g., m.p.  $65-68^\circ$ . The product was analyzed directly without further purification. For comparison, the product was dissolved in cold benzene and reprecipitated upon the addition of petroleum ether (b.p.  $35-60^\circ$ ) and the melting point of the product was not changed.

*Anal.* Calcd. for  $\text{C}_8\text{H}_9\text{ClN}_3\text{O}_4$ : C, 32.8; H, 2.76; Cl, 16.0; N, 19.2. Found: C, 32.9; H, 2.78; Cl, 15.9; N, 18.9.

It is of interest to note that 1,3-dimethyl-5-nitro-6-chlorouracil was found to be quite soluble in benzene but only slightly soluble in methanol, whereas 3-methyl-5-nitro-6-chlorouracil (2c) was not soluble in benzene but very soluble in methanol.



I

## 1,3-Dimethyl-5-amino-6-chlorouracil.

Ten grams of 1,3-dimethyl-5-nitro-6-chlorouracil was dissolved in 250 ml. of benzene containing three drops of concentrated aqueous ammonia. The resulting mixture was separated from a small amount of insoluble material by filtration and the filtrate was hydrogenated at 60 p.s.i. in the presence of 1.5 g. of 5% platinum on charcoal at room temperature. After about 1 hr. the equivalent amount of hydrogen was absorbed and the reaction mixture was filtered. The filtrate was evaporated to dryness under reduced pressure to give 3.0-4.3 g. of crude product, m.p.  $110-120^\circ$ . Recrystallization from a mixture of ethanol and water gave 2 g. of pure material, m.p.  $120-121^\circ$ .

*Anal.* Calcd. for  $\text{C}_8\text{H}_9\text{ClN}_3\text{O}_2$ : C, 38.0; H, 4.25; N, 2.22. Found: C, 38.3; H, 4.53; N, 21.8.

For comparison, the corresponding 3-methyl-5-amino-6-chlorouracil was similarly prepared, except methanol was used as the solvent, from the known 3-methyl-5-nitro-6-chlorouracil (2c). The compound, after recrystallization from methanol, melted at  $243^\circ$  with decomposition.

*Anal.* Calcd. for  $\text{C}_8\text{H}_9\text{ClN}_3\text{O}_2$ : C, 34.2; H, 3.44; N, 23.9. Found: C, 34.6; H, 3.64; N, 23.6.

## REFERENCES

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- (4) (a) E. Bühler and W. Pfeiderer, *Angew. Chem.*, **76**, 713 (1964); (b) *Tetrahedron Letters*, 3007 (1964).
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