# Pyrimidines X. A Facile Synthesis of 3-Alkyl-5-nitrouracils (1a)

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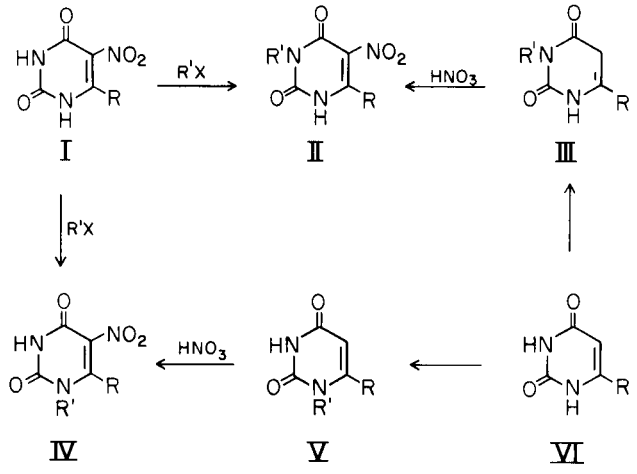
During our recent investigations on the synthesis of 8-azapurines (2) and on the conversion of 6-methyl-5-nitrouracils to pyrimido[5,4-*d*][1,2,3]triazines, pyrazolo-[4,3-*d*]pyrimidines and diazoniumbarbituric acids (3) we developed a facile method for the preparation of 3-alkyl-5-nitrouracils which were needed as starting materials. While 5-nitrouracil (Ia) can be selectively methylated with dimethyl sulfate in aqueous sodium hydroxide to 1-methyl-5-nitrouracil (IVa) in good yield (4), the alternate isomer, 3-methyl-5-nitrouracil (IIa, R′ = $CH_3$) has not been available by direct methylation (5). Direct alkylation of compounds I to afford II seem generally to be unknown (5).




a Series, R=H X=halogen
b Series, R=$CH_3$

An examination of the p*K*a values for the isomeric compound II and IV (Table I) shows that the protons residing on N-1 are more acidic than those at N-3 and, further, established the dissociation sequence of Ia to be in the order of N-1 followed by N-3 (6). From these data it is concluded that selective alkylation of 5-nitrouracil at N-1 was due to its existence predominantly as the *monoanion* with only N-1 ionized. It follows that in the *dianionic* form of I, position N-3, which is more basic, probably would also be more nucleophilic than N-1. This difference in nucleophilicity of the 1- and 3-positions in the dianion should allow for predominant or selective monoalkylations of I at position N-3 when one equivalent of alkylating agent is employed.

The experiments to test this hypothesis were performed under conditions which allow for complete dianion formation. Most alkylations were run in DMF solution because this solvent is known to enhance bimolecular alkylation reactions. 3,6-Dimethyl-5-nitrouracil (IIIb) was synthesized in aqueous solution. In order to achieve homogeniety in the reactions performed in DMF, a quaternary ammonium hydroxide such as tetrabutylammonium hydroxide was employed as the base. Under these conditions the direct synthesis of 3-methyl-5-nitrouracil (IIa, R′ = $CH_3$), 3-benzyl-5-nitrouracil (IIa, R′ = $CH_2C_6H_5$), 3,6-dimethyl-5-nitrouracil (IIb, R′ = $CH_3$) and 3-benzyl-6-methyl-5-nitrouracil (IIb, R′ = $CH_2C_6H_5$) was achieved in good yields starting from the appropriate, commercially-available 5-nitrouracil (Ia) and 6-methyl-5-nitrouracil (Ib).

Previous methods for the synthesis of compounds of type II are laborious, usually achieved by nitration of the 3-substituted-uracils (IIIa and IIIb). The latter are available in low yield by the limited alkylation of VI to mixtures of III and V along with 1,3-dialkyluracils followed by fractionation of the complex reaction mixtures. The selective N-3 alkylation described herein of dianions of I in DMF and water should be quite general for the preparation of N-3-alkylated-5-nitrouracils. Other solvents such as dimethylsulfoxide or hexamethylphosphorotriamide should give similar results. The only by-products detected by paper and thin layer chromatography in these reactions were minor amounts of 1,3-disubstituted-5-nitrouracils (11) along with some starting material.

The drastically altered relative basicities and nucleophilicities of the ring nitrogens in 5-nitrouracils (I) as compared to the parent uracils (VI) are best explained by the fact that in the monoanion of I a negative charge *only* at N-1 can be delocalized by mesomerism with the 5-nitro group. (Elongation of this mesomeric system to include N-3 is blocked by the 2-oxo group). The inductive effect of the 5-nitro group will be in the same order of magnitude for positions N-1 and N-3. With the *dianions* of 5-nitrouracils (I), it is evident that the basicity or nucleophilicity of N-1 is lowered by a combined inductive and

TABLE I

$pK_a$ Values of 5-Nitrouracils

| 5-Nitrouracils | | $pK_a$ for Ionization at | | References |
|---|---|---|---|---|
| Compound No. | R′ | N-1 | N-3 | |
| Ia | | 5.47 ± 0.03 | 11.52 ± 0.04 | (a,b,c) |
| Ib | | 6.38 ± 0.03 | | (a) |
| IIa | $CH_3$ | 5.65 ± 0.02 | | (a) |
| IIb | $CH_3$ | 6.78 ± 0.04 | | (a) |
| IVa | $CH_3$ | | 7.34 ± 0.04 | (a,d) |
| IVb | $CH_3$ | | 7.40 ± 0.02 | (a) |
| IIb | benzyl | 6.47 ± 0.05 | | (e) |

(a) Private communication from Prof. Dr. W. Pfleiderer and Dr. H. Braun, University of Konstanz, Germany. The $pK_a$ values were estimated under identical conditions by potentiometric titration at 20°. The position of dissociation for Ia and Ib was established by u.v. spectroscopy. (H. Braun in Diplomarbeit, Technische Hochschule, Stuttgart). (b) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 9, 199 (1952). (c) D. J. Brown, *J. Chem. Soc.*, 3647 (1959). (d) D. J. Brown, E. Hoerger and S. F. Mason, *ibid.*, 211 (1955). (e) Determined as previously described (10) by spectrophotometric methods at 23.5 ± 0.5°.

TABLE II

3-Alkyl-5-nitrouracils Synthesized by Direct Alkylation

| Starting Material | Alkylating Agent | Yield and Product (a) | M.p. and (Solvent of Recrystallization) |
|---|---|---|---|
| Ia | $CH_3I$ | 47% IIa ($R' = CH_3$) | 266-267° dec. ($H_2O$) (b) |
| Ia | $C_6H_5CH_2Cl$ | 39% IIa ($R' = CH_2C_6H_5$) | 230-232° ($H_2O$) (c) |
| Ib | $CH_3I$ | 53% IIb ($R' = CH_3$) | 231-233° ($H_2O$) (d) |
| Ib | $C_6H_5CH_2Cl$ | 65% IIb (e) ($R' = CH_2C_6H_5$) | 267-268° (ethanol) |

(a) No attempts were made to improve the yields. All structures were proved by u.v. and n.m.r. spectroscopy. (b) Lit. m.p. 263-265°, D. J. Brown, *J. Chem. Soc.*, 211 (1955). (c) Lit. m.p. 236-237°, M. Prystas and J. Gut, *Collect. Czech. Chem. Commun.*, 28, 2501 (1963). (d) Lit. m.p. 229-233°, P. Henkel, *Ann. Chem.*, 378, 182 (1910). (e) $C_{12}H_{11}N_3O_4$ (261.2). Calcd: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.42; H, 4.28; N, 15.71.

resonance effect, whereas the basicity or nucleophilicity at position N-3 can only be affected by an inductive effect of the 5-nitro substituent. A 5-nitro group in uracils thus gives rise to the sequential dissociation in the order N-1 followed by N-3. It follows also that in the dianionic form of I (because of the mesomeric delocalization of the charge at N-1 by the 5-nitro substituent) N-3 is the more nucleophilic and is therefore alkylated preferentially.

## EXPERIMENTAL

General Procedure.

A solution of 5-nitrouracil (I, 0.1 mole) in 25% tetrabutylammonium hydroxide (0.2 mole) in methanol and 150 ml. DMF was evaporated to a sirup and redissolved in 150 ml. DMF. The alkylating agent (0.1 mole, see Table II) was added at room temperature. The reaction was exothermic and the solution was stirred for one hour. DMF was removed under reduced pressure and the residue was neutralized with acetic acid and purified by recrystallization.

3,6-Dimethyl-5-nitrouracil (IIb).

The synthesis of this compound was also achieved in strong aqueous alkali. 6-Methyl-5-nitrouracil (Ib, 3.4 g., 0.02 mole) was dissolved in 45 ml. of 10% sodium hydroxide. Dimethylsulfate (5 ml.) was added slowly to the stirred solution until crystallization occurred. After 4 hours at room temperature the crystalline precipitate (which is the hydrated sodium salt of IIb) was collected by filtration. The precipitate was dissolved in hot water and crystallized from solution by acidification to *p*H ~ 2 with hydrochloric acid. The yield of IIb was 1.9 g. (53%) m.p. 231-233°.

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(6) It should be noted that previous studies on uracil (7) and on 5-halogeno- (8,9) and 5-methyluracils (9) showed that their monoanions exist in solution as an equilibrium mixture of tautomers resulting from ionization at N-1 and at N-3. The ultraviolet

absorption spectrum of the monoanionic species of 5-nitrouracil (10) however is practically identical with that for 3-methyl-5-nitrouracil (*p*H 8.5; λ max mμ at 342, 253, 238; λ min mμ at 287, ~247, 218) and dissimilar to that for 1-methyl-5-nitrouracil (*p*H 9.4; λ max mμ = 323, 240 shoulder; λ min mμ 269). These data establish the fact [as indicated by Wierzchowski *et al.* (9)] that the 5-nitrouracil monoanion exists predominantly if not exclusively as a single tautomer resulting from ionization at N-1 and not at N-3. The $pK_a$ of 11.52 of 5-nitrouracil (Table I) refers therefore to dissociation of N-3 to the dianion (see also footnote a of Table I).

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(11) When Bredereck's (4) conditions were employed for the synthesis of 1-methyl-5-nitrouracil (see text) the presence in the reaction mixture of some 1,3-dimethyl-5-nitrouracil is also demonstrable by chromatography.

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