Intermediates in the Formation of Pyrimido[5,4-*d*]-*v*-triazines and Related Substances (1)

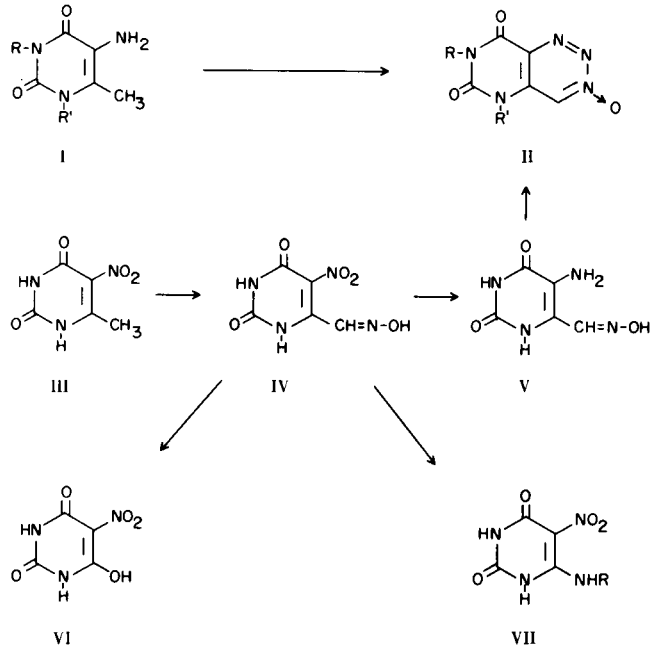
Joe C. Davis (2a), Henry H. Ballard (2b) and Jesse W. Jones (2c)

Department of Chemistry, Texas College

Papesch and Dodson (3) identified pyrimido[5,4-*d*]-*v*-triazine (II) as the product resulting from the action of nitrous acid on certain 5-amino-6-methyluracils (I). Pyrimidine derivatives not previously reported were suggested as possible reaction intermediates. These postulated pyrimidine intermediates were of interest as they are required in a related synthetic problem being studied in this laboratory. It was therefore desirable to undertake a study of the reaction pathway to a pyrimido[5,4-*d*]-*v*-triazine from 5-amino-6-methylpyrimidines.

Pyrimido[5,4-*d*]-*v*-triazine-6,8(5*H*,7*H*)-dione-3-oxide (IV, R=R′=H) was selected for study. The action of sodium nitrite on 5-amino-6-methyluracil (I) in acetic acid gave II (R=R′=H) which analyzed as reported by Behrend (4) and others (3,5). Careful monitoring of the reaction did not provide isolatable intermediates in the reaction path. Procedures were then investigated for introducing a nitrogen function in the 6-methyl group of certain pyrimidines. Attempts to nitrosate 6-methyluracil were not successful following the procedure of Cheng., *et al.* (6) for the formation of 2-hydroxy-4-pyrimidinecarboxaldehyde oxime from the corresponding 6-methylpyrimidine. However, 5-nitro-6-methyluracil (III) in acetic acid reacted with nitrous acid to give 2,4-dioxo-5-nitro-6-pyrimidinecarboxaldehyde oxime (IV). Compound IV was isolated as an orange-yellow crystalline solid in 65% yield. The reduction of IV in methanol with Raney nickel gave a crude product which contained some 2,4-dioxo-5-amino-6-pyrimidinecarboxaldehyde oxime (V). Also V was isolated in 5% yield by the action of sodium dithionite on IV in an aqueous media at 70-75°. Yields of V up to 50% were obtained when this reaction was carried out in a basic solution. The diazotization of V in acetic acid with sodium nitrite at room temperature gave a tan colored solid. The product was subsequently analyzed and proved to be identical in all respects to II (R,R′=H).

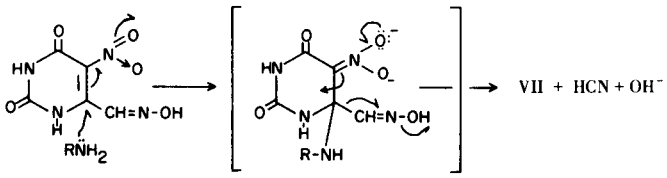
REACTION SCHEME



It was noted that a volatile base was evolved during the initial attempts to reduce IV in base at elevated temperatures. Compound IV was then heated at reflux temperatures in aqueous 5% potassium hydroxide. The precipitate which separated in the hot solution was isolated from dilute acetic acid as a neutral species which analyzed for $C_4H_3N_3O_5$. The physical data of the precipitate proved to be identical to that of 5-nitrobarbituric acid (VI). Ring deactivation by the 5-nitro group appeared to be required since V was unaffected under like reaction conditions.

When a mixture of IV and methylamine in aqueous solution was refluxed for several hours, a product was isolated which could readily be purified by recrystallization from water. The product was homogenous on paper chromatograms and analyzed for $C_5H_6N_4O_4$. Other primary amines gave products (VII, R=ethyl, β-hydroxethyl, propyl, and butyl) with comparable data. Subsequent to the identification of VI, a similar nucleophilic substitution reaction was indicated. Indeed, the physical properties of the 5-nitro-6-alkylaminouracils (VII, R = methyl and β-hydroxyethyl) as reported by Creswell and Wood (7) were identical to the products isolated in the above described reaction. Though novel to pyrimidine chemistry, this reaction gave products in lower yields than published procedures (7).

A possible mechanism for the replacement of an aldoxime by amines is:



This reaction is analogous in some respects to the action of base on *o*-nitrobenzaldehyde oxime (8,9). The product of such reaction in the presence of dilute base was *o*-nitrobenzonitrile whereas, in strong base *o*-nitrobenzamide results. One significant difference is noted, however. The intermediate nitrile, if formed, is readily replaced by an amine under the conditions of the reaction rather than being hydrolyzed to the corresponding amide. There was no evidence of the latter in the reaction mixtures examined.

EXPERIMENTAL (10)

2,4-Dioxo-5-nitro-6-pyrimidinecarboxyaldehyde Oxime (IV).

5-Nitro-6-methyluracil (III) (60 g.) was dissolved in 800 ml. of hot water-acetic acid solution (50%, v/v). To this solution at 70° was added an aqueous solution of sodium nitrite (60 g. in 100 ml. of water) in one continuous portion. The reaction mixture was stirred in a loosely covered container for 0.5 hours at 70-75°. An orange-yellow precipitate separated while stirring. The mixture was allowed to cool to room temperature for several hours and was then filtered, washed with water and dried *in vacuo* at 85° to yield 45.5 g. of high purity product. A small sample recrystallized from water for analysis. Compound IV decomposed explosively and melted at 218-220°; R_f, A, 0.29: B, 0.69; λ max nm (ϵ x 10^{-3}):(*p*H 1.7)246 (11.8), 296 (7.8); (*p*H 11)289 (12.2), 350 (shoulder) (3.4).

Anal. Calcd. for $C_5H_4N_4O_5$: C, 30.00; H, 2.00; N, 28.00. Found: C, 30.45; H, 2.33; N, 27.62.

2,4-Dioxo-5-amino-6-pyrimidinecarboxaldehyde Oxime (V).

Procedure 1.

2,4-Dioxo-5-nitro-6-pyrimidinecarboxaldehyde oxime (IV) (20 g.) was dissolved in 200 ml. of 10% potassium hydroxide below 40°. To the stirred solution was added 30 g. of sodium dithionite in small portions at 35-40° which required approximately 10 minutes. The mixture was allowed to stir for 1 hour at 35-40° and then the solution was adjusted to *p*H 5 with acetic acid to yield after drying in air, 8.5 g. of crude product. Compound V was recrystallized from methanol and dried *in vacuo* at 85°. The recrystallized product slowly decomposed when heated above 300°; R_f, A, 0.18, B, 0.42; λ max nm (ϵ x 10^{-3}): (*p*H 1.7)296 (6.0), 340 (shoulder) (3.4); (*p*H 11)340 (9.2).

Anal. Calcd. for $C_5H_6N_4O_3$. C, 35.29; H, 3.53; N, 32.92. Found: C, 35.15; H, 3.6; N, 32.8.

Procedure 2

Compound IV (10 g.) was suspended in 100 ml. of water and stirred vigorously. To the mixture at 70-75° was added sodium dithionite (15 g.). The solution that resulted was allowed to stir for 1 hour at 70-75°. On cooling at room temperature for 2 hours, an orange-yellow precipitate (0.5 g.) was filtered and dried in air. The product was identical in all respects to V as prepared by procedure 1.

Hydrolysis of 2,4-Dioxo-5-nitro-6-pyrimidinecarboxaldehyde Oxime (IV).

Compound IV (5 g.) was dissolved in 5% aqueous potassium hydroxide (100 ml.) and refluxed for 4 hours. The precipitate that separated in the hot solution was filtered and washed with water. The precipitate was resuspended in hot acetic acid (5%, v/v), triturated, filtered and finally washed with water and dried to yield 2 g. of crystalline product. A comparison of the product with an authentic sample of 5-nitrobarbituric acid by IR and UV spectroscopy and by paper chromatography in solvent systems (A and B) proved them to be identical.

Preparation of 5-Nitro-6-alkylaminouracils (VII).

A mixture of 5 g. of IV and the appropriate amine (excess) in 100 ml. of water was refluxed for 5 hours. The solution was cooled at 15-20° for several hours, the precipitate collected and resuspended in 50 ml. of hot water. The resulting mixture was acidified to *p*H 5 with acetic acid to yield the 5-nitro-6-alkylaminouracil. Recrystallization was accomplished using water-methanol as solvent.

5-Nitro-6-ethylaminouracil (VII, R=ethyl).

This compound had m.p., 299-301°; λ max nm (ϵ x 10^{-3}): (*p*H 1.7)255 (26.8), 32 (13.0); (*p*H 11)224 (15.4), 330 (16.0).

Anal. Calcd. for $C_6H_8N_4O_4$. N, 28.00. Found: N, 28.3.

5-Nitro-6-*n*-propylaminouracil (VII, R=*n*-propyl).

This compound had m.p. 274-275°; λ max nm (ϵ x 10^{-3}): (*p*H 1.7)226 (28.0), 320 (12.0); (*p*H 11)224 (14.8), 330 (14.6).

Anal. Calcd. for $C_7H_{10}N_4O_4$. C, 39.30; H, 4.68; N, 26.15. Found: C, 39.51; H, 4.72; N, 26.40.

5-Nitro-6-*n*-butylaminouracil (VII, R=*n*-buryl).

This compound had m.p. 260-262°; λ max nm (ϵ x 10^{-3}): (*p*H 1.7)225 (13.2), 320 (11.4); (*p*H 11)224 (13.2), 330 (13.2).

Anal. Calcd. for $C_8H_{12}N_4O_4$. N, 24.55. Found: N, 25.02.

Pyrimido[5,4-*d*]-*v*-triazine-6,8(5H,7H)-dione-3-oxide (II).

Procedure 1.

5-Amino-6-methyluracil (11) (I) (3 g.) was suspended in 50 ml. of galcial acetic acid and cooled to 15-20°. To this suspension was added sodium nitrite (3 g. in 10 ml. of water). The mixture was stirred at 15-20° for 0.5 hour. The precipitate was filtered, washed with water and dried to give 1.3 g. of product. The product (II) isolated was homogenous on paper chromatograms and identical in every respect to the substance previously reported (3,4,5).

Procedure 2.

2,4-Dioxo-5-amino-6-pyrimidinecarboxaldehyde oxime (V) (2 g.) in glacial acetic acid (60 ml.) was treated in one continuous portion with 2 g. of sodium nitrite at 24-30°. The mixture was allowed to stir at this temperature for 2 hours and was then filtered, and washed with cold water. The product was dried in air to yield 2.1 g. which proved to be identical to II prepared by procedure 1.

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(2a) Undergraduate Scholar; (b) Predoctoral Fellow; (c) to whom correspondence should be addressed at the Department of Chemistry, Bishop College, Dallas, Texas 75241.

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(10) All melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. The ultraviolet spectra were determined on a Beckman DB spectrophotometer with a Sargent SRL recorder. Decending chromatography was carried out on Whatman #1 paper employing the solvents: A, *t*-Butanol: 5*N* (aq.) Ammonia (7/3, v/v): B, *t*-Butanol: 5*N*(aq) Acetic acid (7/3, v/v).

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Tyler, Texas 75701