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Hydrazinopyrimidines

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A variety of hydrazino and dihydrazino-5-nitropyrimidines and their derivatives have been prepared by displacement reactions or reaction sequences from 2,4- or 4,6-dichloro-5-nitropyrimidine. These include 2,4- and 4,6-dihydrazino, 2-dimethylamino-4-hydrazino, 2-hydrazino-4-dimethylamino, 2-morpholino-4-hydrazino, and 2-hydrazino-4-amino-5-nitropyrimidines. 2,4-Dihydrazino-5-nitropyrimidine on condensation with selected aldehydes yielded a series of dihydrazones. Of these, *p*-methoxybenzaldehyde (5-nitropyrimidyl-2,4-dihydrazone) showed a reproducible but slight activity in Sarcoma-180 tests.

As part of a continuing interest (1-5) in cancer chemotherapy studies with pyrimidines, we have prepared a series of hydrazino and dihydrazino-5-nitropyrimidines and their aldehyde hydrazones by displacement reactions of 2,4- and 4,6-dichloro-5-nitropyrimidine. A new facet of pyrimidine chemistry has been established in the course of these studies which we wish to describe here. This is the selective replacement of the 4-dimethylamino group by hydrazino in the reaction of 2,4-bis-(dimethylamino)-5-nitropyrimidine with hydrazine hydrate and the irreplaceability of this group in 2-hydrazino-4-dimethylamino-5-nitropyrimidine on reaction with anhydrous hydrazine.

When 2,4-dichloro-5-nitropyrimidine, prepared as described previously (6), was treated with dimethylamine in anhydrous ether, 2,4-bis-dimethylamino-5-nitropyrimidine was produced. Treatment of this material with hydrazine hydrate resulted in the displacement of one of the dimethylamino groups by hydrazino to give a product, m.p. 221°C. The structural assignment for this compound as 2-dimethylamino-4-hydrazino-5-nitropyrimidine, instead of the 2-hydrazino-4-dimethylamino isomer, was based on the following independent synthesis which resulted in the formation of a hydrazine with identical physical and absorption characteristics. *asym*-Dimethylguanidine sulfate and maleic acid were converted into 2-dimethylamino-4-hydroxypyrimidine as previously described (7) with later modifications (8). Nitration of this material yielded the 5-nitro derivative (8) which was converted into 2-dimethylamino-4-chloro-5-nitropyrimidine by treatment with phosphorus oxychloride (8). 2-Dimethylamino-4-hydrazino-5-nitropyrimidine, m.p. 221°, was then prepared by displacement of the chlorine atom by a hydrazino group using hydrazine hydrate.

2,4-Dichloro-5-nitropyrimidine when treated with morpholine, piperidine, or diethylamine in ethanol yielded 2,4-dimorpholino-, 2,4-dipiperidino-, and 2,4-bis-diethylamino-5-nitropyrimidine respectively. 2,4-Dimorpholino-5-nitropyrimidine was treated with hydrazine to yield 2-morpholino-4-hydrazino-5-nitropyrimidine. The structural assignment for this compound was made on the assumption that this displacement would occur at the 4-position as evidenced above in the displacement involving the bis-dimethylamino derivative with hydrazine. Since the analytical data for this compound was only in fair agreement with the monohydrate, benzaldehyde (2-morpholino-5-nitropyrimidyl-4-hydrazone) was prepared as a derivative for which acceptable analytical results were obtained. 2,4-Dipiperidino-5-nitropyrimidine when heated with hydrazine hydrate afforded only trace amounts of the 4-hydrazino derivative while 2,4-bis-diethylamino-5-nitropyrimidine did not undergo detectable displacement by hydrazine.

The preparation of 2-chloro-4-methylaminopyrimidine has been reported previously (9), therefore 2,4-dichloro-5-nitropyrimidine was treated under identical conditions with dimethylamine to yield 2-chloro-4-dimethylamino-5-nitropyrimidine. This compound when treated with anhydrous hydrazine in ether yielded 2-hydrazino-4-dimethylamino-5-nitropyrimidine m.p. 182°. 2,4-Dihydrazino-5-nitropyrimidine was prepared from 2,4-dichloro-5-nitropyrimidine by treatment with anhydrous hydrazine in ether. A number of selected dihydrazones were prepared for evaluation of their tumor retardation characteristics and are listed in Table I. Of these, *p*-methoxybenzaldehyde (5-nitropyrimidyl-2,4-dihydrazone) showed activity at the borderline level in Sarcoma-180 screening tests. The data on three tests were rated at 125 and 500 mg./kg. and - at 125, 250, and 500 mg./kg. in other tests. The significance of these test data has been explained in previous papers in this series.

2-Chloro-4-amino-5-nitropyrimidine was prepared by ammonolysis of 2,4-dichloro-5-nitropyrimidine. This synthesis along with the proof for the structural assignment have been reported earlier (10). 2-Morpholino-, and 2-piperidino-4-amino-5-nitropyrimidine were synthesized by allowing 2-chloro-4-amino-5-nitropyrimidine to react with morpholine and piper-

Table I

Bis Hydrazones (a) of 2,4-Dihydrazino-5-nitropyrimidine

Aldehyde Used (b)	Formula	C Analysis Calcd.	C Analysis Found	H Analysis Calcd.	H Analysis Found	N Analysis Calcd.	N Analysis Found
(B)	$C_{18}H_{15}N_7O_2$	59.83	59.72	4.15	4.27	27.14	26.92
p-Methyl (B)	$C_{20}H_{19}N_7O_2$	-	-	-	-	25.18	25.38
o-Methoxy (B)	$C_{20}H_{19}N_7O_4$	57.00	56.63	4.54	4.61	23.27	23.75
m-Chloro (B)	$C_{18}H_{13}N_7O_2Cl_2$	50.24	50.42	3.04	3.26	22.79	22.75
p-Methoxy (B)	$C_{20}H_{19}N_7O_4$	57.00	56.83	4.54	4.80	23.27	23.28
p-Dimethylamino (B)	$C_{22}H_{25}N_9O_2 \cdot H_2O$	-	-	-	-	27.09	26.89
2-Methoxy (N)	$C_{28}H_{23}N_7O_4$	-	-	-	-	18.80	18.90

(a) The following procedure was used in preparing the derivatives. To a solution of 0.01 mole of the dihydrazine in dilute hydrochloric acid is added 0.02 mole of the aldehyde in a small amount of ethanol. The hydrazone which precipitated immediately was filtered, washed with ethanol and ether and then dried. The yields were quantitative. The products were recrystallized from either acetic acid or dimethylformamide. These derivatives undergo gradual decomposition above 225°. (b) B, benzaldehyde; N, naphthaldehyde.

idine respectively. Hydrazine hydrate was used to convert the 2-chloro derivative into the corresponding hydrazine, 2-hydrazino-4-amino-5-nitro pyrimidine. Sodium azide converted the 2-chloro derivative into the corresponding 2-azido-4-amino-5-nitropyrimidine which was synthesized alternately by treatment of the hydrochloride of the 2-hydrazino derivative with aqueous sodium nitrite.

When 4,6-dichloro-5-nitropyrimidine, described previously (11), was treated with morpholine in ethanol, 4,6-dimorpholino-5-nitropyrimidine was produced. Treatment with anhydrous hydrazine in ether yielded 4,6-dihydrazino-5-nitropyrimidine.

EXPERIMENTAL

5-Nitrouracil, obtained from commercial sources, was converted into 2,4-dichloro-5-nitropyrimidine by treatment with phosphorus oxychloride (6). 4,6-Dihydroxypyrimidine, obtained from commercial sources, was nitrated to give the 5-nitro derivative which was converted into 4,6-dichloro-5-nitropyrimidine by treatment with phosphorus oxychloride (11). Details of other preparations follow. Melting points are corrected and were determined with a Mel-Temp apparatus.

2,4-Bis-dimethylamino-5-nitropyrimidine.

A solution of 2 g. (0.0103 mole) of 2,4-dichloro-5-nitropyrimidine in 5 ml. of ether was introduced gradually with stirring beneath the surface of a solution containing 3 g. of anhydrous dimethylamine in 20 ml. of ether. A solid precipitated during the addition. The solution was evaporated with a gentle current of air and the resulting product washed with ether and then with water. Recrystallization from ethanol afforded 2.16 g., 96%, of the product, m.p. 83-84°.

Anal. Calcd. for $C_8H_{13}N_5O_2$: N, 33.16. Found: N, 32.94.

2-Dimethylamino-4-hydrazino-5-nitropyrimidine.

One tenth of a gram of 2,4-bis-dimethylamino-5-nitropyrimidine was heated for a few minutes with 2 ml. of hydrazine hydrate (85% in water). The starting pyrimidine melted and then dissolved; the solution turned red, and the product began to crystallize out. On cooling 0.03 g., 30%, of the yellow compound was obtained, m.p. 221° after recrystallization from water. No melting point depression was observed with a sample the preparation for which is described below.

Anal. Calcd. for $C_6H_{10}N_6O_2$: C, 36.36; H, 5.09; N, 42.42. Found: C, 36.64; H, 5.11; N, 42.16.

This compound was also prepared as follows. To 1 ml. of anhydrous hydrazine was added 0.14 g. of 2-dimethylamino-4-chloro-5-nitropyrimidine (7,8). The mixture was heated on a steam bath for 5 minutes and the resulting precipitate filtered, washed with cold water and then recrystallized from water to yield 0.035 g., 25%, of the product, m.p. 221°.

2-Chloro-4-dimethylamino-5-nitropyrimidine.

Three ml. of a 25% aqueous solution of dimethylamine was adjusted to *p*H 8 with acetic acid and then added to a mixture of 1.05 g. of 2,4-dichloro-5-nitropyrimidine in 6 ml. of dioxane. The resulting solution was stirred for 2 hours and then poured into 50 ml. of ice water. The precipitate was filtered and recrystallized from ethanol to yield 0.75 g., 75%, of the product, m.p. 117°.

Anal. Calcd. for $C_6H_7N_4O_2Cl$: N, 27.65. Found: N, 27.53.

2-Hydrazino-4-dimethylamino-5-nitropyrimidine.

A solution of 0.3 g. of 2-chloro-4-dimethylamino-5-nitropyrimidine in 20 ml. of ether was introduced slowly with stirring to a solution containing 1 ml. of anhydrous hydrazine in a small amount of ether. The resulting mixture was allowed to stand for one hour at room temperature after which the precipitate that formed was filtered, washed with ether and then water. Recrystallization from water gave 0.24 g., 80%, of the product, m.p. 182-183°.

Anal. Calcd. for $C_6H_{10}N_6O_2$: N, 42.42. Found: N, 42.17.

2,4-Dimorpholino-5-nitropyrimidine.

Two tenths of a gram of 2,4-dichloro-5-nitropyrimidine in 5 ml. of ethanol was added to a solution of 1.0 g. of morpholine in 5 ml. of ethanol. After the exothermic reaction had subsided, the reaction mixture was cooled and partially evaporated under a gentle current of air to yield 0.29 g., 95% of the crude product. Recrystallization from benzene-petroleum ether afforded the pure product, m.p. 135°.

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80. Found: C, 48.86; H, 5.90.

2,4-Bis-diethylamino-5-nitropyrimidine.

The procedure described above was used, except morpholine was replaced by diethyl amine. The crude product obtained in 63% yield was recrystallized from ethanol, m.p. 52°.

Anal. Calcd. for $C_{12}H_{21}N_5O_2$: N, 26.20. Found: N, 25.92.

2,4-Dipiperidino-5-nitropyrimidine.

The procedure described above was used except that morpholine was replaced by piperidine. The crude product obtained in 80% conversion was recrystallized from ethanol, m.p. 113-114°.

Anal. Calcd. for $C_{14}H_{21}N_5O_2$: N, 24.04. Found: N, 23.90.

2-Morpholino-4-hydrazino-5-nitropyrimidine.

Two tenths of a gram of 2,4-dimorpholino-5-nitropyrimidine was heated for a few minutes at 80° with 1 ml. of hydrazine hydrate (85%

in water). The red colored reaction mixture was cooled, 2 ml. of water added and the crude product collected on a filter. Recrystallization from water afforded the pure product in 40% conversion, m.p. 222°.

Anal. Calcd. for $C_8H_{12}N_6O_3 \cdot H_2O$: C, 37.20; H, 5.46; N, 32.54. Found: C, 36.90; H, 4.84; N, 32.10.

The condensation of this material with benzaldehyde under conditions favorable for hydrazone formation produced the expected hydrazone which was recrystallized from acetic acid.

Anal. Calcd. for $C_{15}H_{16}N_8O_3$: C, 54.88; H, 4.91; N, 25.61. Found: C, 55.16; H, 4.64; N, 25.66.

2,4-Dihydrazino-5-nitropyrimidine.

A solution containing 3.0 g. of 2,4-dichloro-5-nitropyrimidine in 50 ml. of anhydrous ether was introduced slowly with stirring to a solution of 5 ml. of anhydrous hydrazine in 500 ml. of anhydrous ether. A brown precipitate formed immediately which was filtered, washed with ether and then with cold water and dried to give 2.7 g., 75%, of the crude product. Recrystallization from water yields the pure product, m.p. 270° (d). The sample for analysis was dried at 100° under vacuum for seven days.

Anal. Calcd. for $C_4H_7N_7O_2$: C, 25.95; H, 3.82; N, 52.95. Found: C, 25.81; H, 4.22; N, 52.07.

Dihydrazones of this material were prepared and are listed in Table I. The dibenzoyl derivative was prepared in the conventional manner. The crude product was recrystallized from dimethylformamide and water, m.p. greater than 225°.

Anal. Calcd. for $C_{18}H_{15}N_7O_4$: C, 54.95; H, 3.85; N, 24.95. Found: C, 54.94; H, 3.87; N, 24.26.

2-Morpholino-4-amino-5-nitropyrimidine.

To a solution of 1.6 g. of morpholine in 5 ml. of ethanol was added 0.55 g. of 2-chloro-4-amino-5-nitropyrimidine (10). The resulting mixture was warmed until solution was complete, cooled and then water added to precipitate 0.7 g., 99%, of the product which was recrystallized from ethanol, m.p. 214°.

Anal. Calcd. for $C_8H_{11}N_5O_3$: N, 31.10. Found: N, 31.26.

2-Piperidino-4-amino-5-nitropyrimidine.

This compound was prepared by the procedure described above except that piperidine was used in place of morpholine. The product was recrystallized from ethanol, m.p. 156°.

Anal. Calcd. for $C_9H_{13}N_5O_2$: N, 31.38. Found: N, 31.48.

2-Hydrazino-4-amino-5-nitropyrimidine.

To 3 ml. of hydrazine hydrate (85% in water) was added in small increments 1.7 g. of 2-chloro-4-amino-5-nitropyrimidine. After the exothermic reaction had subsided, the colored reaction mixture was diluted with water, filtered and the resulting product washed with cold water and dried to give 1.65 g., 99%, of a green powder. Recrystallization from water produced the purified product, decomposing gradually above 225°.

Anal. Calcd. for $C_4H_6N_6O_2$: N, 49.40. Found: N, 49.18.

2-Azido-4-amino-5-nitropyrimidine.

A solution containing 1.55 g. of 2-chloro-4-amino-5-nitropyrimidine, 0.58 g. of sodium azide and 4 ml. of absolute ethanol was heated under reflux for four hours. The reaction mixture was filtered while hot, the precipitated salt washed with 2 ml. of absolute ethanol and the resulting filtrate concentrated to give 1.10 g. of the product. Recrystallization from ethanol gave the purified product, m.p. 181-182°.

Anal. Calcd. for $C_4H_5N_7O_2$: N, 54.14. Found: 54.30.

This compound was also prepared as follows. To a solution containing 0.03 g. of 2-hydrazino-4-amino-5-nitropyrimidine in 2 ml. of 5% hydrochloric acid which was cooled to 0° was added dropwise with stirring a solution containing 0.012 g. of sodium nitrite in a small amount of water. The precipitate that formed was collected on a filter, washed with water and recrystallized from ethanol, m.p. 181-182°. With a sample from the preparation described above, no melting point depression was observed.

4,6-Dimorpholino-5-nitropyrimidine.

To 1.5 g. of 4,6-dichloro-5-nitropyrimidine in 20 ml. of ethanol was added a solution containing 2.5 g. of morpholine in 20 ml. of ethanol. After the exothermic reaction had subsided, the reaction mixture was cooled and partially evaporated under a gentle current of air to yield 1.6 g. of the product which was recrystallized from ethanol, m.p. 178-179°.

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: N, 23.72. Found: N, 23.56.

4,6-Dihydrazino-5-nitropyrimidine.

A solution containing 1.0 g. of 4,6-dichloro-5-nitropyrimidine in 25 ml. of anhydrous ether was introduced slowly with stirring to a solution of 2 ml. of anhydrous hydrazine in 300 ml. of anhydrous ether. After the addition the precipitate was filtered, washed with ether and then with cold water to give 0.15 g. of the product which was recrystallized from water, m.p. 206°.

Anal. Calcd. for $C_4H_7N_7O_2$: N, 52.95. Found: N, 52.90.

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