Reactions of 4,5-Diaminouracils

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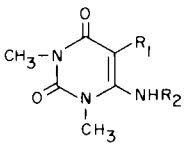
Reactions of 4,5-diaminopyrimidines with various phthalic derivatives, depending on the conditions employed, led to pyrimidines with a 5-*N*-substituted phthalamic acid (III), 5-*N*-substituted phthalimide (II) and 4,5-bis-*N*-substituted phthalimide (VI).

Acetic anhydride normally acetylates 5-aminopryimidines in the cold, but 4-aminopyrimidines only on heating. However the preferential acylation of the 5-amino group in 4,5-diaminopyridimidines to give the monoacyl derivatives is due to the higher nucleophilic character of the 5-amino group (2). Condensation of 4,5-diaminopyrimidines with oxalic acid gives 5-*N*-substituted oxamic acids which are intermediates in the usual synthesis of certain pteridines (3). A recent report (4) on the reactions of 4,5-diaminopyrimidines with succinic acid reveals the formation of 5-*N*-substituted succinamic acids as intermediates which on further heating lead to the corresponding 8-carboxyethyl substituted purines. Here, the mode of cyclization involves the condensation of the diamino pyrimidines with only one carboxyl of succinic acid leading to a five-member ring closure.

We now wish to report a different mode of condensation which a 4,5-diaminopyrimidine with a dicarboxylic acid may undergo; that is cyclization involving only one amino group of the pyrimidine and the two carboxyl groups of the dicarboxylic acid molecule. It was observed that when a mixture of 1,3-dimethyl-4,5-diaminouracil (Ia) (5) and phthalic acid was stirred at 180° for 5 minutes, 1,3-dimethyl-4-amino-5-(*N*-phthalimido)uracil (IIa) was obtained in 78% yield, m.p. > 350°. Its mass spectrum revealed a parent m/e 300. Its nmr spectrum (in DMSO - TMS) showed singlets at δ 3.12 (CH_3, 3H) 3.35 (CH_3, 3H) and 7.75 (aromatic, 4H); broad singlet at 7.2 (NH_2, 2H) which exchanges with deuterium oxide. Acylation of IIa gave the monoacetylated product IIb, m.p. 293-296°.

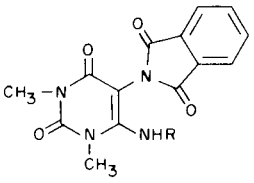
Reaction of Ia with phthalic anhydride at room temperature led to the intermediate III but at higher temperature gave IIa. Compound III melted at 190-200°, immediately recrystallized and remelted at 340-350°. The formation of IIa rather than the tricyclic IV and/or the tetracyclic V (may be obtained from IV by intramolecular interaction and dehydration) may be accounted for on



Ia, R = NH_2, R_2 = H

b, R_1 = NH_2, R_2 = CH_3

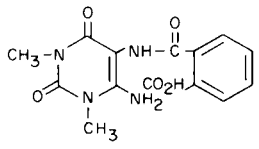
c, R_1 = Br, R_2 = H



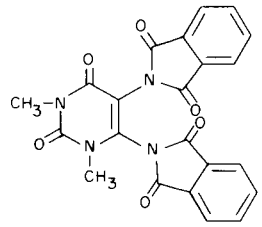
IIa, R = H

b, R = $C(=O)-CH_3$

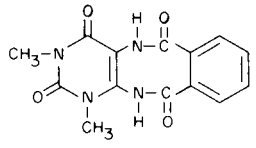
c, R = CH_3



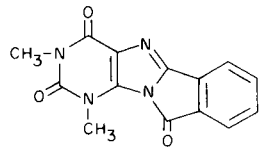
III



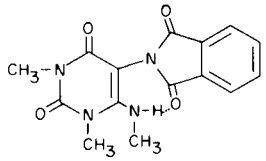
VI



IV



V



VII

the basis of ring strain.

Perhaps a more convenient synthesis of IIa is to heat a mixture of Ia and phthaloyl chloride at 80° for 2 hours. However, if the temperature is raised to 160°, 1,3-dimethyl-4,5-bis(*N*-phthalamido)uracil (VI), m.p. 322-326°, is obtained. This was shown to be a diaddition product by its elemental analysis and its nmr spectrum which indicated singlets at δ 3.30 (CH_3, 3H), 3.36 (CH_3, 3H), 7.8 (aromatic, 4H) and 7.88 (aromatic, 4H).

To further demonstrate that *N*-substitution first occurs on the 5-amino group, 1,3-dimethyl-4-methylamino-5-aminouracil (IIb) (6) was prepared and treated under the same conditions with phthaloyl chloride at 80° for 2 hours. The product isolated was shown to be (IIc) m.p. 279-280°. Its nmr spectrum exhibited a doublet at δ 2.68 (CH_3, 3H), singlets at 3.15 (CH_3, 3H), 3.40 (CH_3, 3H) and 7.92 (aromatic, 4H), and broad singlet at 6.85 (NH, 1H). It is interesting to note that upon addition of D_2), the signal due to NH disappears and the doublet due to NHMe turns to singlet. This may be due to intramolecular hydrogen bonding as indicated in structure VII.

To remove any remaining doubt concerning the structure of IIa, it was further synthesized in very low yield by the treatment of 1,3-dimethyl-4-amino-5-bromouracil (Ic) (7) and potassium phtahlimide in ethyldiglycol at 130° for 4 hours. The physical data collected from this reaction product and IIa were identical.

EXPERIMENTAL

General.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected; infrared spectra were obtained on a Perkin-Elmer infracord spectrophotometer using the potassium bromide method; ultraviolet spectra on a CF4 "OPTICA" Spectrophotometer in a *p*H 1 solution; nmr spectra on a Varian Model H-60 spectrometer using hexadeuterodimethylsulfoxide as solvent and tetramethylsilane as an internal reference; analyses were performed by the Microanalysis Laboratory, Hebrew University, Jerusalem, Israel.

1,3-Dimethyl-4-5-(*N*-phthalimido)uracil (IIa).

A mixture of 650 mg. of Ia and 2 g. of phthalic acid was heated to 180° and kept at this temperature for 10 minutes. It was then cooled and crystallized from methanol to give 0.9 g. (78%) of IIa, m.p. >350°; uv: λ max 224 mμ (ε 36,700), 264 (ε 18,200); ir: ν max 3500, 1725, 1610, 1500, 1360, 880, 762, 750, 739, 710; nmr: δ 3.12 (s, 3), 3.35 (s, 3), 7.75 (s, 4), 7.2 (s, 2); mass spectrum; m/e 300.

Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.66. Found: C, 56.05; H, 3.86; N, 18.70.

Acetylation of IIa (IIb).

A mixture of 300 mg. of IIa, 4 ml. of acetic anhydride and 3 ml. of pyridine was refluxed for 2 hours. It was then cooled, diluted with ether and filtered. The product obtained was crystallized twice with ethanol-tetrahydrofuran to give pure IIb, m.p. 293-296°; uv: λ max 224 mμ (ε 27900) and 277 (ε 9140); ir: ν max 3450, 1720, 1650, 1360, 885, 716; nmr; δ 1.93 (s, 3), 3.30 (s, 3), 3.34 (s, 3), 7.93 (s, 4) and 10.46 (s, 1) exchanged with deuterium oxide.

Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.37. Found: C, 56.32; H, 3.91; N, 16.46.

Reaction of Ia with Phthalic Anhydride.

A. A solution of 1.48 g. of phthalic anydride and 1.74 g. of Ia in 200 ml. of dioxane was stirred at room temperature overnight. It was then diluted with ether and filtered to give 2.14 g. (67%) of III which was crystallized from methanol, m.p. 199-200° (this immediately recrystallized and remelted at 355-360°); uv, λ max 202 mμ (ε 35300) and 265 (ε 16800); ir: ν max 3450-2600, 1700, 1620, 1510, 1318, 1270, 757; nmr: 3.14 (s, 3), 3.33 (s, 3), 8.65 (s, 1 exchanges with deuterium oxide), 6.69 (s, 2, exchanges with deuterium oxide), 7.65 (m, 5).

Anal. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.80; H, 4.43; N, 17.60. Found: C, 52.90; H, 4.73; N, 17.37.

A sample of III kept stirring at 210° for 10 minutes led to a quantitative yield of IIa, m.p. > 350° which indicated identical uv, ir and nmr as the substance isolated above.

Reaction of Ia with Phthaloyl Chloride.

A mixture of 1 g. of Ia and 5 ml. of phthaloyl chloride was heated at 80° for 8 hours and then was cooled, filtered and washed with dichloromethane. The crude product was crystallized from methanol to give 1.5 g. (85%) of IIa, m.p. >350°. B. A mixture of 1 g. of Ia and 5 ml. of phthaloyl chloride was heated at 160° for 1 hours. It was then cooled, filtered and washed with 50% methanol-ether. The crude product was crystallized from methanol-tetrahydrofuran to give 1.4 g. (55%) of 1.3-dimethyl-4,5-bis(*N*-phthalimido)uracil (VI), m.p. 322-326°; uv: λ max 227 mμ (ε 15600), 284 (4800); ir: ν max 1715, 1660, 1370, 1350, 1300, 878, 761, 705; nmr δ 3.30 (s, 3), 3.36 (s, 3), 7.8 (s, 4H) and 7.88 (s, 4H).

Anal. Calcd. for $C_{22}H_{14}N_4O_6$: C, 61.40; H, 3.28; N, 13.02. Found: C, 61.41; H, 3.17; N, 13.01.

1,3-Dimethyl-4-methylamino-5-(*N*-phthalimido)uracil (IIc).

A mixture of 400 mg. of Ib and 4 ml. of phthaloyl chloride was stirred at 80° for 2 hours. It was cooled, diluted with dichloromethane and filtered. The crude product was crystallized twice from methanol to give 165 mg. of IIc, m.p. 279-280°; nmr: δ 2,68 (d, 3), 3.15 (s, 3), 3.40 (s, 3), 7.92 (s, 4), 6.85 (s, 1); ir: ν max 3610, 1700, 1640, 1560, 885, 756, and 720; uv: λ max 220 (ε 38500) and 267 (ε 23500).

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.27; H, 4.38; N, 17.90.

Reaction of 1,3-Dimethyl-4-amino-5-bromouracil (Ic) with Potassium Phthalimide.

A solution of 1.2 g. of Ic and 0.95 g. of potassium phthalimide in 50 ml. of ethyldiglycol was heated at 120° for 4 hours. It was then cooled, diluted with ether and filtered to give a crude mixture. The fraction soluble in 3:1 methanol-dichloromethane was taken up. It was chromatographed over neutral alumina active grade III. The fraction obtained by elution with tetrahydrofuran was purified a few times by preparative thin layer chromatography. The fraction isolated indicated identical ir, uv and nmr spectra with IIa.

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