Pyrido[2,3-*d*]pyrimidines and Pyrido[2,3-*d*; 5-*d'*]dipyrimidines as Potential Chemotherapeutic Agents. VIII

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Reactions of 5-dimethylaminomethylene-6-imino-1,3-dimethyluracil hydrochloride (**1**) with active methylene compounds **2** and **4** yielded bi- and tricyclic heterocyclic compounds **3** and **5**. All the prepared compounds were screened for chemotherapeutical activities but none were active.

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Pyrimidine and purine derivatives occupy a central position among those molecules which make life possible as they are the building blocks of DNA and RNA. These ring systems are common sources to develop new potential therapeutic agents. A number of pyrido[2,3-*d*]pyrimidines are known to have antibacterial [2], antitumor [3] and anticonvulsant [4] activities. The antibacterial and antitumor activities of pyrido[2,3-*d*]pyrimidines are most likely due to an inhibition of dihydrofolate reductase [5]. Taking this into account, we prepared some pyrido[2,3-*d*]pyrimidines **3** and pyrido[2,3-*d*:6,5-*d'*]dipyrimidines **5** and evaluated their chemotherapeutical activities. 6-Amino-uracil derivatives have been used as versatile intermediates for the synthesis of fused pyrimidines such as purines [6], pteridines [7], pyrrolo[2,3-*d*]pyrimidines [8], thiazolo[3,4-*d*]pyrimidines [9], pyrido[2,3-*d*]pyrimidines [10], pyrido[2,3-*d*:6,5-*d'*]dipyrimidines [11] and other heterocycles. Recently Hirota *et al.* have reported the synthesis of 6-imino-1,3-dimethyl-5-dimethylaminomethyleneuracil hydrochloride from **1**, 6-amino-1,3-dimethyluracil, by the Vilsmeier reaction. This is a versatile intermediate for the synthesis of different types of polycyclic heterocyclic compounds [12].

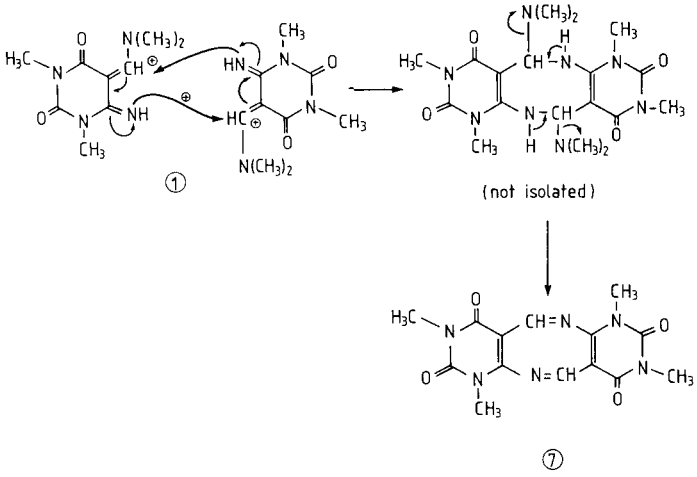

Figure 1

Stirring a mixture of **1** and **2** in the presence of triethylamine in ethanol in an ice bath for 20 minutes or 2 hours at room temperature yielded **3a-c**. However, it failed to give the desired products **3'a-c** from **2'a-c**. The same colourless reaction product **7** with m/z 330 and mp 325.5° was obtained under both conditions. Compound **7** was also formed by stirring a mixture of **1** and triethylamine in ethanol under the conditions used earlier, whereas **6** failed to give this product under similar reaction conditions. This indicates that in the process of self condensation **6** is not the intermediate. The ^{1}H nmr spectrum of the new compound showed two methine signals at δ 9.08 and 8.76 and four distinctly separated methyl group signals at δ 3.58, 3.49, 3.25 and 3.16 due to the non-planar structure of the diazocine moiety. Based on the spectroscopic data and elemental analyses the structure was assigned as 1,3,7,9-tetramethyl[1,5]diazocino[2,3-*d*:6,7-*e*]dipyrimidine-2,4,8,10-tetrone. The probable mechanism of the self condensation is depicted below.

p-Nitrobenzyl cyanide smoothly underwent cyclization with **1** yielding 7-amino-6-(*p*-nitrophenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione due to enhanced reactivity of the CH_2 group by the nitro substituent. Under similar conditions benzyl cyanide and halobenzyl cyanide did not give the cyclic product. In the reaction of **1** with dibenzoylmethane (**2'a**), steric hindrance seems to play a major role in not yielding **3'a**.

Barbituric acid derivatives **4** were also employed as active methylenes. A mixture of **1** with different barbituric acid derivatives separately in DMF at reflux temperature for 1-2 hours yielding pyrido[2,3-*d*:6,5-*d'*]dipyrimidines **5a-f** in 35-80% yield.

All the compounds, which were prepared, were screened for potential antibacterial, antifungal and antiviral activities according to methods described earlier [14], but none of the test chemicals exhibited significant activity.

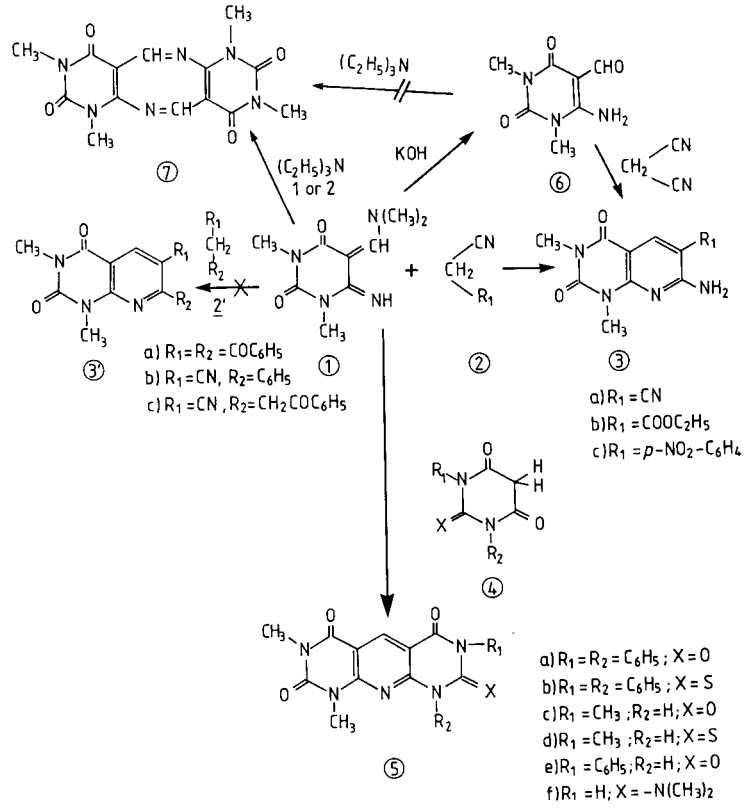

Figure 2

EXPERIMENTAL

All melting points are uncorrected. Proton magnetic resonance spectra (nmr) were recorded on a Perkin Elmer spectrometer 283 instrument, using TMS as the internal reference. Mass spectra (ms) were recorded with a MS 312 Finnigan. Thin layer chromatography (tlc) was performed on silica gel plates with fluorescent indicator and spots were visualized with light at 254 nm. The elemental analyses were performed at C.D.R.I., Lucknow.

6-Imino-1,3-dimethyl-5-[(dimethylamino)methylene]-5,6-dihydrouracil Hydrochloride (**1**).

This compound was prepared from 1,3-dimethyl-6-aminouracil and phosphoryl chloride by the reported procedure [12] in 90% yield, mp 208-210°.

7-Amino-6-cyano-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3a**).

A suspension of **1** (1.23 g, 5 mmoles) and malononitrile (0.34 g, 5 mmoles) in ethanol (20 ml) was treated dropwise with triethylamine (0.6 g, 6 mmoles) at 0-5°. The mixture was stirred for 2 hours and the resulting precipitate was filtered, washed with water and crystallized from acetic acid, 80%, mp 354°, lit [12] >300°. The title compound was also obtained by condensation of **6** with malononitrile in acetic acid.

7-Amino-6-carbethoxy-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**3b**).

This product was prepared from **1** and ethyl cyanoacetate as described in the preceding experiment, 85%, mp 225°, lit [13], mp 220°.

7-Amino-6(*p*-nitrophenyl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3c**).

A suspension of **1** (1.23 g, 5 mmoles) and *p*-nitrobenzyl cyanide (0.81 g, 5 mmoles) was treated with triethylamine (0.6 g, 6 mmoles) at 0-5°. The reaction mixture was then stirred for 2-3 hours at room temperature and the resulting precipitate was filtered off. It was crystallised from DMSO as a yellow crystalline solid and yielded 0.65 g (40%), mp 333-338°; ms: m/z 327 (M^+), 282 (M^+-NO_2); nmr (DMSO-d_6): δ 3.48 (s, CH_3), 3.30 (s, CH_3), 7.09 (s, NH_2), 7.78 (s, 1H), 8.33-8.23 (m, 2H, *o*-phenyl-H), 7.76-7.66 (m, 2H, *m*-phenyl-H).

Anal. Calcd. for $C_{15}H_{13}N_5O_4$: C, 55.04; H, 3.97; N, 21.40. Found: C, 55.25; H, 4.23; N, 21.68.

1,3-Dimethyl-7,9-diphenylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**5a**).

A mixture of **1** (1.0 g, 4 mmoles) and 1,3-diphenylbarbituric acid (1.13 g, 4 mmoles) in DMF (10 ml) was treated under reflux for 1.5 hours. After cooling, the mixture was diluted with water. The resulting precipitate was filtered off, washed with ethanol and finally crystallized from DMSO yielding 0.8 g (47%), mp >300°; ms: m/z 427 (M^+).

Anal. Calcd. for $C_{23}H_{17}N_5O_4$: C, 64.63; H, 3.98; N, 16.39. Found: C, 64.78; H, 4.12; N, 16.52.

1,3-Dimethyl-7,9-diphenylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(1*H*,3*H*,7*H*)-trione-8(9*H*)-thione (**5b**).

The compound was obtained from **1** (0.9 g, 3.7 mmoles) and 1,3-diphenyl-2-thiobarbituric acid (1.07 g, 3.7 mmoles) as described in the preceding experiment, yielding 0.85 g (53%), after crystallization from DMSO: ethanol; ms: m/z 443 (M^+).

Anal. Calcd. for $C_{23}H_{17}N_5O_3S$: C, 62.30; H, 3.83; N, 15.80. Found: C, 62.52; H, 4.01; N, 16.10.

1,3,7-Trimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**5c**).

Refluxing a mixture of **1** (0.75 g, 3 mmoles) and 3-methylbarbituric acid (0.43 g, 3 mmoles) in DMF (10 ml) yielded 0.35 g of the title compound after crystallization from DMF: ethanol, 38%, mp >300°; ms: m/z 289 (M^+), 261 (M^+-CO), 232 (M^+-CH_3NCO), 204 (232-CO).

Anal. Calcd. for $C_{12}H_{11}N_5O_4$: C, 49.82; H, 3.80; N, 24.22. Found: C, 49.63; H, 3.62; N, 24.52.

1,3,7-Trimethylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(1*H*,3*H*,7*H*)-trione-8(9*H*)-thione (**5d**).

The title compound was obtained from **1** (0.49 g, 2 mmoles) and 3-methyl-2-thiobarbituric acid (0.3 g, 2 mmoles) as described earlier in 30% yield, mp 300°; ms: m/z 305 (M^+), 277 (M^+-CO), 233 (M^+-CH_3NCO), 191 (233-CH_3NCO); nmr (DMSO-d_6): 3.58 (s, CH_3), 3.54 (s, CH_3), 3.50 (s, CH_3), 8.53 (s, 1H).

Anal. Calcd. for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.60; N, 22.95. Found: C, 47.35; H, 3.82; N, 23.25.

1,3-Dimethyl-7-phenylpyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone (**5e**).

A mixture of **1** (1 g, 4 mmoles) and 3-phenylbarbituric acid was refluxed in DMF for 2 hours and the desired product was isolated as described in the preceding experiment, yielding 0.65 g, 45%, after crystallization from DMSO; ms: m/z 351 (M^+).

Anal. Calcd. for $C_{17}H_{13}N_5O_5$: C, 58.12; H, 3.70; N, 19.94. Found: C, 58.23; H, 3.85; N, 20.08.

1,3-Dimethyl-8-dimethylaminopyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6-(1*H*,3*H*,7*H*,9*H*)-trione (**5f**).

This compound was synthesized by refluxing a mixture of **1** (1 g, 4 mmoles) and 2-dimethylamino-4,6-dioxo-3,5-dihydropyrimidine (0.7 g, 4 mmoles) in DMF (8 ml) and isolated as usual, yielding 0.5 g, 40% after crystallization from DMSO, mp >300°; ms: m/z 302 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_6O_3$: C, 51.65; H, 4.63; N, 27.81. Found: C, 51.38; H, 4.54; N, 27.55.

1,3,7,9-Tetramethyl[1,5]diazacino[2,3-*d*:6,7-*e*]dipyrimidine-2,4,8,10-tetrone (**7**).

To a suspension of **1** (1.23 g, 5 mmoles) in ethanol and **2'a-c** (5 mmoles) in ethanol, triethylamine (0.6 g, 6 mmoles) was added slowly under stirring in an ice bath. After completion of the addition, the mixture was stirred at room temperature for 2 hours. The resulted colourless solid was filtered, washed with ethanol and finally crystallized from DMSO, mp 325.5°; ms: m/z 330 (M^+); uv (methanol): λ max nm 305.4, 238 (sh); ir (potassium bromide): ν max cm^{-1} 3060, 2950 (ν CH), 1710 (C=O), 1660 (δ CH); nmr (DMSO-d_6): δ 9.08, 8.76 (s, methine H), 3.58, 3.49, 3.25 and 3.16 (s, 4-CH_3).

Anal. Calcd. for $C_{14}H_{14}N_6O_4$: C, 50.91; H, 4.20; N, 24.45. Found: C, 50.81; H, 4.06; N, 24.05.

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REFERENCES AND NOTES

[1] Present address: Medicinal Chemistry Division, C.D.R.I., Lucknow, India.

[2] Suzuki, *Chem. Pharm. Bull.*, **28**, 761 (1980).

[3] E. M. Gsiusky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1980).

[4] E. Kretzchmar, *Pharmazie*, **35**, 253 (1980).

[5a] R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **80**, 3449 (1958); [5b] G. H. Hitchings and J. J. Burchall, *Advan. Enzymol.*, **27**, 417 (1965).

[6] D. J. Brown, "Fused Pyrimidines", Part II "Purines", J. H. Lister, ed, Wiley-Interscience, New York, 1971, II.

[7] J. Weijland, M. Tischler and E. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945).

[8] Y. Tamura, T. Sakaguchi, T. Kawasaki and Y. Kita, *Heterocycles*, **3**, 1983 (1975).

[9a] Y. Furukawa, O. Miyashita and S. Shima, *Chem. Pharm. Bull.*, **24**, 970 (1976); [9b] R. Niess and H. Eilingsfield, *Ann. Chem.*, 2019 (1974).

[10a] H. Ogura and M. Sakaguchi, *Chem. Pharm. Bull.*, **21**, 2014 (1973); [10b] A. D. Broom, J. L. Shim and G. Anderson, *J. Org. Chem.*, **41**, 1095 (1976); [10c] F. Yoneda, M. Koya and T. Nagamatsu, *Synthesis*, 75 (1983).

[11a] F. Yoneda, K. Senga and S. Nishigaki, *Chem. Pharm. Bull.*, **21**, 260 (1973); [11b] T. Nagamatsu, Y. Sakuma and F. Yoneda, *Synthesis*, 923 (1983).

[12] K. Hirota, Y. Kitade, H. Sajiki and Y. Maki, *Synthesis*, 589 (1984).

[13] K. Hirota, Y. Kitade and S. Senda, *J. Heterocyclic Chem.*, **22**, 345 (1985).

[14] V. J. Ram, D. A. Vanden Berghe and A. J. Vlietinck, *J. Heterocyclic Chem.*, **21**, 1307 (1984).