Synthesis of Certain Substituted Pyrimidines as Potential Schistosomicidal Agents

M. M. El-Kerdawy, A. A. El-Emam* and H. I. El-Subbagh

Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt

E. Abushanab

Department of Medicinal Chemistry, College of Pharmacy, URI, Kingstone, RI 02881, USA

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A convenient route is reported for the synthesis of seven new pyrimidine derivatives namely: 2-bromomethyl-4,6-dimethoxypyrimidine (**3**), 2-dibromomethyl-4,6-dimethoxypyrimidine (**4**), 2-acetoxymethyl-4,6-dimethoxypyrimidine (**5**), 2-hydroxymethyl-4,6-dimethoxypyrimidine (**6**), 4,6-dimethoxypyrimidine-2-carboxaldehyde (**7**), 2-acetoxymethyl-6-methoxy-3,4-dihydropyrimidin-4-one (**8**) and 2-hydroxymethyl-3,4-dihydro-6-methoxypyrimidin-4-one (**9**).

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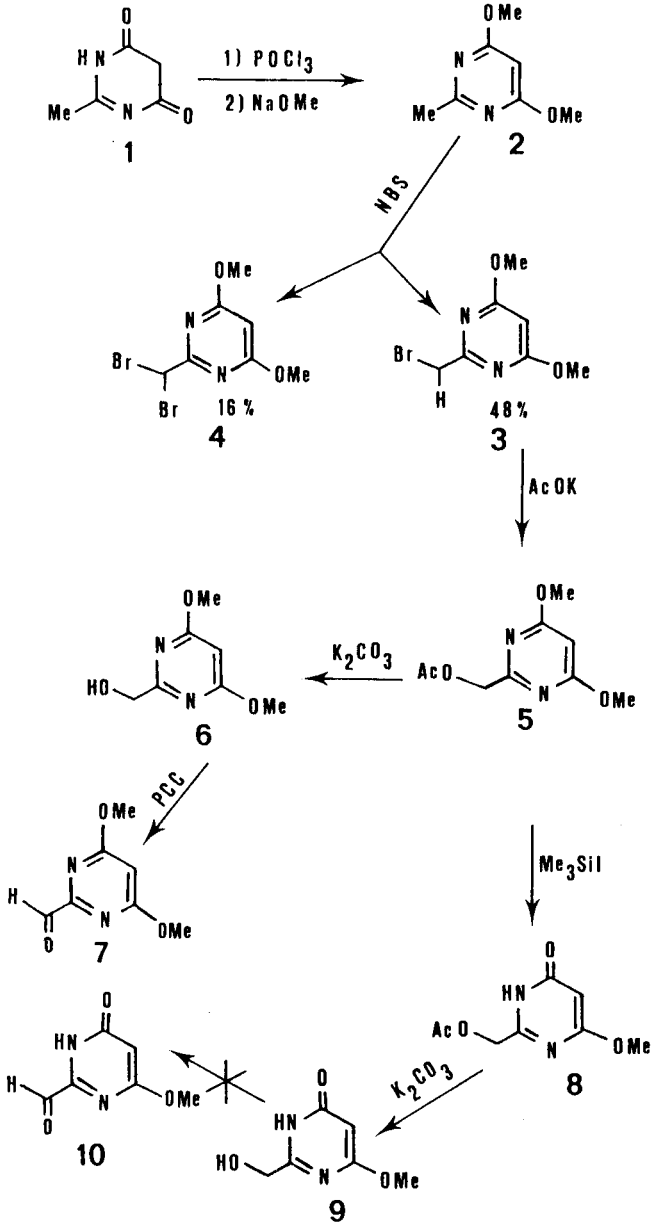
Introduction.

A rational approach for the development of a new schistosomicidal agent might be derived from finding differences between the biochemistry of the host versus the parasite [1]. It was recently reported that there is a difference in pyrimidine metabolism between schistosomes and mammalian cells [2,3]. In mammals, orotatephosphoribosyltransferase (OPRTase) and orotidylate decarboxylase (ODCase) exist as a multi enzyme complex and the major orotate metabolism is uridine monophosphate (UMP) which is essential for pyrimidine biosynthesis [4]. In contrast, in yeast these two enzymes exist as separate entities and the major product of orotate metabolism is orotidine-5'-monophosphate (OMP) [5]. The study of orotate metabolism in *schistosoma mansoni* showed marked differences from the pattern seen in mouse liver but resembled that of the yeast. These results suggested that OPRTase and ODCase may exist as a separate enzyme in *s. mansoni* rather a multi enzyme complex as in mammalian cells [5]. These differences in orotate metabolism which are essential for DNA biosynthesis may provide selective toxicity for a chemotherapeutic agent against schistosomes as compared to the host.

Results and Discussion.

2-Methyl-4,6-dimethoxypyrimidine (**2**), required as a starting material, was prepared from 2-methyl-3,4,5,6-tetrahydropyrimidine-4,6-dione (**1**) by reaction with phosphorus oxychloride [6] followed by methoxylation with sodium methoxide [7]. Bromination of compound **2** using *N*-bromosuccinimide and benzoyl peroxide in carbon tetrachloride afforded 2-bromomethyl-4,6-dimethoxypyrimidine (**3**) as a major product (48%) and 2-dibromomethyl-4,6-dimethoxypyrimidine (**4**) as a minor product (16%). Compound **3** was converted to the 2-acetoxymethyl derivative **5** using anhydrous potassium acetate in ethanol. Attempts to get the diester of the dibromo derivative **4** were unsuccessful. It was reported that iodotrimethylsilane can



selectively cleave the ether linkage of alkoxypyrimidines [8]. Application of this method to compound **5** resulted in the formation of the monodemethylated derivative **8**. Attempts to cleave both ether linkages using more harsh conditions such as 20% hydrochloric acid led to monodemethylation in addition to the cleavage of the ester linkage and isolation of compound **9**. Hydrolysis of the acetate ester in compounds **5** and **8** was successfully achieved by stirring with potassium carbonate in methanol at ambient temperature giving rise to compounds **6** and **9** respectively. Trials to oxidize the hydroxymethyl group in compound **5** using chromium trioxide/sulfuric acid as a mild oxidizing agent resulted in the formation of tarry material. Oxidation of the hydroxymethyl group in compound **5** was achieved in poor yield by the action of pyridinium chlorochromate (PCC) in methylene chloride [9-13] to afford compound **7**. On the other hand, compound **9** failed to afford compound **10** under the same conditions, this may be attributed to its poor solubility in methylene chloride. The structures of the new compounds **3-9** were assigned on the basis of elemental analysis and ^{1}H-nmr data (Table I).

Table I

^{1}H-NMR Data of Compounds **3-9**

Compound No.	^{1}H-NMR (Deuteriochloroform), δ (ppm)
3	3.95 (6H, s, OCH_3), 4.38 (2H, s, CH_2), 5.85 (1H, s, Ar-H)
4	3.95 (6H, s, OCH_3), 5.88 (1H, s, CH), 6.40 (1H, s, Ar-H)
5	2.10 (3H, s, $COCH_3$), 3.82 (6H, s, OCH_3), 5.02 (2H, s, CH_2), 5.80 (1H, s, Ar-H)
6	3.50-3.70 (1H, m, OH), 3.90 (6H, s, OCH_3), 4.50-4.70 (2H, d, CH_2), 5.80 (1H, s, Ar-H)
7	3.95 (6H, s, OCH_3), 6.05 (1H, s, Ar-H), 9.75 (1H, s, CHO)
8	2.20 (3H, s, $COCH_3$), 3.80 (3H, s, OCH_3), 4.95 (2H, s, CH_2), 5.50 (1H, s, Ar-H), 12.0 (1H, br s, NH)
9	3.70 (3H, s, OCH_3), 4.10-4.30 (2H, d, CH_2), 5.30 (1H, s, Ar-H), 5.50-5.80 (1H, m, OH), 11.70 (1H, br s, NH)

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and uncorrected. The ^{1}H-nmr spectra were recorded on a Varian EM-390 90 MHz spectrometer in deuteriochloroform using TMS as the internal standard. Microanalyses were performed by M-H-W laboratories, Phoenix, Arizona, USA. Silica gel (60-230 mesh) was employed for column chromatographic separation. Compound **1** was prepared by the method cited in lit [6]. Melting points, yield percentages, molecular formulae and microanalytical data of compounds **3-9** are listed in Table II.

2-(Bromomethyl and dibromomethyl)-4,6-dimethoxypyrimidines **3** and **4**.

A suspension of 2-methyl-4,6-dimethoxypyrimidine (**2**) (0.155 g, 1.0 mmole), *N*-bromosuccinimide (0.195 g, 1.1 mmoles) and benzoyl peroxide (5 mg), in carbon tetrachloride (15 ml) was stirred under nitrogen in presence of light at ambient temperature for 14 hours. The solution was then filtered and evaporated to dryness. The remaining crude product was eluted from a silica gel column using light petroleum to yield compounds **3** and **4**.

2-Acetoxymethyl-4,6-dimethoxypyrimidine (**5**).

A mixture of compound **3** (47 mg, 0.2 mmole) and anhydrous potassium acetate (80 mg, 0.8 mmole) in ethanol (5 ml) was heated under reflux for 4 hours. The reaction mixture was then quench-

Table II

Characterization Data of Compounds **3-9**

Compound No.	Mp °C	Yield %	Molecular Formulae	Calcd./Found (%) C	H	N
3	38-39	48	$C_7H_9BrN_2O_2$	36.07 36.24	3.89 3.97	12.04 11.91
4	120-122	16	$C_7H_8Br_2N_2O_2$	26.94 27.14	2.58 2.73	8.98 9.06
5 [a]		88	$C_9H_{12}N_2O_4$	50.93 50.78	5.70 5.61	13.20 13.12
6	60-62	40	$C_7H_{10}N_2O_3$	49.40 49.52	5.92 5.72	16.46 16.54
7	70-72	8	$C_7H_8N_2O_3$	49.99 50.06	4.79 4.83	16.66 16.72
8	96-98	39	$C_6H_{10}N_2O_4$	48.48 48.17	5.08 5.33	14.13 13.85
9	168-170	16	$C_6H_8N_2O_3$	46.15 46.17	5.16 5.11	17.94 17.76

[a] Compound **5** is liquid at ambient temperature.

ed with water and extracted with chloroform, the organic layer was dried over magnesium sulphate and the solvent was evaporated. The remaining crude product **5** was purified by elution from a silica gel column using chloroform.

2-Hydroxymethyl-4,6-dimethoxypyrimidine (**6**).

A mixture of compound **5** (0.42 g, 2.0 mmoles) and anhydrous potassium carbonate (0.28 g, 2.0 mmoles) in methanol (20 ml) was stirred at ambient temperature for 12 hours. The solvent was then removed *in vacuo* and the residue was dissolved in chloroform, dried and evaporated. The obtained crude product (**6**) was then crystallized from methanol.

4,6-Dimethoxypyrimidine-2-carboxaldehyde (**7**).

A solution of compound **6** (105 mg, 0.6 mmole) and pyridinium chlorochromate (195 mg, 0.9 mmole) in methylene chloride (10 ml) was stirred under nitrogen at ambient temperature for 75 minutes. The solvent was then evaporated. Compound **7** was obtained by elution of the remaining residue from silica gel column using *n*-hexane:ethyl acetate (6:1).

2-Acetoxymethyl-6-methoxy-3,4-dihydropyrimidin-4-one (**8**).

A solution of compound **6** (42 mg, 0.2 mmole) and iodotrimethylsilane (84 mg, 0.42 mmole) in chloroform (5 ml) was stirred at ambient temperature for 12 hours. The reaction mixture was then quenched with water and extracted with chloroform. The chloroformic extract was washed with sodium thiosulphate solution, dried and evaporated. The remaining residue was eluted from a silica gel column using *n*-hexane:chloroform (1:9) to afford compound **8**.

2-Hydroxymethyl-6-methoxy-3,4-dihydropyrimidin-4-one (**9**).

A mixture of compound **5** (0.28 g, 1.3 mmoles) in hydrochloric acid (20%, 5 ml) was heated under reflux for 3 hours. The solution was then cooled, neutralized with 6*N* sodium hydroxide solution (*p*H 6) and freeze-dried. The residue was then extracted with ethyl acetate, the extract was evaporated and the remaining residue was crystallized from methanol to afford compound **9**.

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