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## Synthesis and Biologic Evaluation of 7-Hydroxymethotrexate, 7-Methylaminopterin, and 7-Methylmethotrexate†

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Chemistry. Although apparently not metabolized in man, the important antitumor folate antagonist methotrexate (MTX, 4-amino-4-deoxy-$N^{10}$-methylpteroylglutamic acid) undergoes biotransformation in several species, notably the rabbit.[1,2] The biotransformation proves to be an oxidative process mediated by aldehyde oxidase (EC 1.2.3.1).[3] On the strength of degradative, chromatographic, and spectral evidence, the product of both the *in vivo* and *in vitro* oxidation of MTX has been assigned the structure, 7-OH-MTX (1).[4]

In this report we describe the synthesis of 7-OH-MTX, which constitutes a confirmation of the structure of MTX metabolite. In addition, we report the preparation of 4-amino-4-deoxy-7-methylpteroylglutamic acid (7-methylaminopterin or 7-Me-AM) (2) and 7-Me-MTX (3). Some preliminary observations regarding the biochemical behavior of these new compounds are included.

7-OH-MTX (1) has been synthesized by the straightforward condensation of 2,4-diamino-7-hydroxy-6-pteridine(α-bromo)acetic acid (6)[5] with *p*-methylaminobenzoylglutamic acid (7).[6]

However, the 7-methyl compounds 2 and 3 were prepared by 2 routes. In the first, 2,4,5,6-tetraaminopyrimidine was allowed to react simultaneously with 3,4-dibromo-2-butanone and *p*-aminobenzoylglutamic acid (9) or 7 in the presence of KI and $I_2$. Since the yields were low, the following approach was adopted. In the second method, the desired intermediate, 2,4-diamino-6-bromomethyl-7-methylpteridine was prepared by the selective reduction of 2,4-diamino-6,7-bis(bromomethyl)pteridine (8) with KI. To prepare 8, 2,4,5,6-tetraaminopyrimidine was condensed with dibromodiacetyl.[7] Finally, reaction of the monobromo compound (not isolated) with either 9 or 7 afforded 7-Me-AM (2) and 7-Me-MTX (3), respectively. Degradative oxidation of both 2 and 3 gave 2,4-diamino-7-methylpteridine-6-carboxylic acid which has been identified with an authentic specimen.[8]

The nmr spectra of 2 and 3 are entirely in accord with the assigned structures. Thus, the only significant difference between the spectra of 2 and 3 and those of their parent compounds AM and MTX is that the low field ($\tau$1.20 and 1.35, respectively) singlet absorptions attributable to the 7-H in AM and MTX have been replaced by singlet absorptions at $\tau$7.38 and 7.44 as a result of the substitution of the 7-hydrogen atoms by 7-methyl groups in 2 and 3.

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Table I. Inhibition of Dihydrofolate Reductase

| Compound | $I_{50}$, n*M* |
|---|---|
| MTX | 23 |
| 7-OH-MTX | 4000 |
| 7-Me-AM | 39 |
| 7-Me-MTX | 26 |

Biological Evaluation. As inhibitors of dihydrofolate reductase (EC 1.5.1.3) of rat liver, the concentrations ($I_{50}$) for 50% inhibition of enzyme activity by these compounds are presented in Table I.

Because of their favorable $I_{50}$, 7-Me-AM and 7-Me-MTX were also screened against mouse L1210 leukemia in comparison with MTX (Table II). 7-Me-AM shows only marginal activity while 7-Me-MTX is inactive when tested under the experimental conditions summarized in the table. The cause of this unexpected inactivity is presently under investigation. It may be the result of failure of the 7-methyl compounds to penetrate into tumor cells or the rapid elimination of these drugs from the body, to mention but two of the many possibilities.

### Experimental Section

Nmr spectra were determined in DMSO-$d_6$ (TMS) with a Varian Model A-60 spectrometer at 60 MHz. Uv spectra were recorded on a Cary Model 14 spectrophotometer. Column chromatography was performed on DEAE-cellulose (Calbiochem, 1.02 mequiv per g) and tlc on cellulose-coated plates (Mann Research Laboratories). Paper chromatography was conducted in a descending manner on Schleicher and Scheull paper (470-A-C) and the chromatograms were viewed under long wavelength uv. Solvent systems used were A: *n*-BuOH–AcOH–$H_2O$ ((5:2:3), B: 5% aqueous $Na_2HPO_4$, C: 5% $NH_4OH$–3% aqueous $NH_4Cl$. Elemental analyses were performed by Dr. William Alford, National Institutes of Health, Bethesda, Md., and, where indicated only by the symbols of elements, were within ±0.4% of the theoretical values.

Ethyl 2,4-Diamino-7-hydroxypteridine-6-acetate (4). A modification of the method of Renfrew, *et al.*,[9] was employed. A suspension of 2,4,5,6-tetraaminopyrimidine sulfate (10.0 g, 42 mmoles) in glacial AcOH (800 ml) was heated to 90° and diethyl sodiooxaloacetate (10.0 g, 48 mmoles) was added with rapid stirring. The mixt was refluxed for 90 min. After cooling to room temp the pale yellow solid was collected by filtn, washed thoroughly with $H_2O$ followed by EtOH, and dried *in vacuo*: 9.5 g (85%).

2,4-Diamino-7-hydroxypteridine-6-acetic acid (5) was prepared by hydrolysis of 4 as described by Renfrew, *et al.*[9]

2,4-Diamino-7-hydroxypteridine-6-(α-bromo)acetic acid (6) was prepared from 5 according to the method of Tschesche, *et al.*[5]

*N*-(*p*-{[(2,4-Diamino-7-hydroxy-6-pteridinyl)methyl]methylamino}benzoyl)-L-glutamic Acid (7-OH-MTX) (1). Condensation of 6 (2.15 g, 6.8 mmoles) with *p*-methylaminobenzoylglutamic acid hydrobromide 7 (3.0 g, 8.3 mmoles) in dry ethylene glycol (130 ml) in the presence of anhyd NaOAc (3.6 g) according to the procedure of Tschesche, *et al.*,[5] afforded 2.05 g (61%) of crude 1.

A sample of the crude product (1.0 g) was suspended in $H_2O$ (20 ml) and $NH_4OH$ soln (28%) was added dropwise, with stirring, until a clear soln resulted. The soln (pH 7.8) was applied to a column (5 × 35 cm) of DEAE-cellulose which had been equilibrated previously with 0.01 *M* $NH_4HCO_3$. The column was eluted in a stepwise fashion by applying a series of $NH_4HCO_3$ buffers of progressively increasing molar strength (1000 × 0.10 *M*, 1000 × 0.15 *M*, 2000 × 0.20 *M*, 2000 × 0.25 *M*, 2000 × 0.30 *M*). Fractions of 10 ml were collected and the elution of successive components was monitored by uv absorption. Fractions containing 7-OH-MTX (0.25–0.30 *M*) were combined, filtd, and evapd at below 50° *in vacuo* while protected from light. The amorphous

Table II. Effect of Treatment with Methotrexate Derivatives on the Survival Time of Mice Bearing Leukemia L1210[a]

| | 7-Me-MTX | | | | 7-Me-AM | | | MTX | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Days | Dose,[b] mg/kg | MST,[c] day | Range, day | Average body weight[d] | MST, day | Range, day | Average body weight | MST, day | Range, day | Average body weight |
| 1 | 1600 | 9 | 9-10 | 2 | | | | | | |
| | 960 | 9.5 | 9-10 | 2 | | | | | | |
| | 500 | | | | 4 | 3-4 | | 15 | 6-15 | -5 |
| | 300 | | | | 13 | 4-19 | -4 | 14.5 | 13-15 | -4 |
| | 180 | | | | 11 | 10-14 | 0 | 14 | 12-15 | 1 |
| 1-9 | 500 | 12 | 10-13 | 0 | | | | | | |
| | 300 | 11 | 10-12 | 2 | 5 | 4-6 | -4 | | | |
| | 180 | 10 | 10-11 | 2 | 8 | 7-8 | -5 | | | |
| | 108 | 10 | 9-12 | 2 | 10 | 9-11 | -8 | | | |
| | 65 | | | | 13 | 10-15 | -4 | | | |
| | 39 | | | | 13 | 11-14 | -2 | | | |
| | 14 | | | | | | | 6 | 5-6 | -3 |
| | 9 | | | | | | | 12 | 7-13 | -7 |
| | 5 | | | | | | | 14.5 | 10-15 | -4 |
| | 3 | | | | | | | 22.5 | 20-26 | 0 |
| | 1.5 | | | | | | | 20 | 19-21 | 0 |

[a] $BDF_1$ mice inoculated ip with $10^5$/0.25 ml leukemia L1210 ascites cells. MST of the control group: 10 days (9-11 days). Weight gained: 2 g. [b] Treatment ip. [c] MST = median survival time of 6 mice per group. [d] Average body weight change in grams on day 8 after tumor inoculation.

light yellow residue was dissolved in $H_2O$ (50 ml) and the soln was reevapd. The latter process was repeated. $H_2O$ (25 ml) was added and the soln was centrifuged at 3000 rpm for 5 min. The yellow supernatant was adjusted to pH 5 by the addn of glacial AcOH. The flocculent yellow ppt which sepd was collected by centrifugation, washed with $H_2O$ (2 × 5 ml) and $Me_2CO$ (5 ml) and dried *in vacuo* over $P_2O_5$ at room temp for 48 hr: 0.57 g; uv max (0.1 *N* NaOH) 223 nm (log ε 4.56), 259 (4.09), 307 (4.32), 337 (sh) (4.12); (pH 7.4) 259 (4.08), 303 (4.30), 340 (sh) (4.08); (0.1 *N* HCl) 218 (4.49), 300 (4.28), 334 (sh) (4.08); nmr (DMSO-$d_6$) τ 2.30 (d, 2, $C_2'$-H, $C_6'$-H), 3.6 (d, 2, $C_3'$-H, $C_5'$-H), 6.82 (s, 3, N-$CH_3$), 7.6-8.2 (m, 4, $CH_2 \cdot CH_2$). *Anal.* ($C_{20}H_{22}N_8O_6 \cdot 1.75H_2O$) C, H, N.

The product exhibited $R_f$ values identical with those of the metabolite of MTX when compared by paper chromatography in solvent systems A, B, and C.

2,4-Diamino-6,7-bis(bromomethyl)pteridine Hydrobromide (8). 2,4,5,6-Tetraaminopyridine sulfate (10.0 g, 42 mmoles) was added to a soln of $BaCl_2 \cdot 2H_2O$ (10.3 g, 42 mmoles) in $H_2O$ (250 ml) and the resultant suspension was heated, with stirring, to 90° then allowed to cool to 40°. The ppt of $BaSO_4$ was removed by filtn and the colorless filtrate was concd under reduced pressure to 110 ml. HBr soln (48%, 40 ml) was added with stirring followed immediately by a soln of dibromodiacetyl (10.3 g, 42 mmoles) in EtOH (85 ml). After standing for 5 hr at room temp the yellow cryst product was collected by filtn, washed with cold $H_2O$ (2 × 10 ml), and dried *in vacuo* over $P_2O_5$ for 48 hr: 15.2 g (84%); uv max (0.1 *N* HCl) 256 nm (log ε 4.21) 346 (4.11). *Anal.* ($C_8H_8Br_2N_6 \cdot HBr$) C, H, N, Br.

*N*-(*p*-{[(2,4-Diamino-7-methyl-6-pteridinyl)methyl]amino}-benzoyl)-L-glutamic Acid (7-Me-AM) (2). Method A. A soln of 8 (5.0 g, 11.7 mmoles) in DMF (150 ml) was cooled to 10° and HBr soln (48%, 120 ml) was added slowly with stirring. The resultant pale yellow soln was warmed to 40° and a soln of KI (1.94 g, 11.7 mmoles) in $H_2O$ (7 ml) was added dropwise over 1 hr with rapid stirring. After a further hr at room temp the mixt was cooled to 15° and a soln of $Na_2S_2O_4$ (0.75 g) in $H_2O$ (5 ml) was added to dispel the liberated $I_2$. The mixt was adjusted to pH 3 by addn of a soln of $NaOAc \cdot 3H_2O$ (64 g) in $H_2O$ (90 ml), then *p*-aminobenzoylglutamic acid (9) (6.2 g, 23.3 mmoles) was added with rapid stirring. After standing 24 hr at room temp the deposited yellow cryst solid was collected by filtn, washed with $H_2O$ (2 × 50 ml) and $Me_2CO$ (2 × 20 ml), and dried *in vacuo* over $P_2O_5$ at room temp for 48 hr. The crude product weighed 4.8 g (86%).

A sample of the crude product (100 mg) was dissolved in $H_2O$ (5 ml) by dropwise addn of $NH_4OH$ soln (28%), and the soln was applied to a column (2.3 × 30 cm) of DEAE-cellulose (bicarbonate form). The column was eluted with a linear gradient of $NH_4HCO_3$ (1000 ml of 0.1 *M* $NH_4HCO_3$ in the mixing flask, 1000 ml of 0.8 *M* $NH_4HCO_3$ in the reservoir; both solns were 0.1 *M* in mercaptoethanol). The development of the column was monitored by uv absorption and fractions containing 7-Me-AM were combined, filtd, and evapd at below 50° *in vacuo* while protected from light. The residue was dissolved in $H_2O$ (10 ml) and reevapd. $H_2O$ (10 ml) was added and the soln was adjusted to pH 5 by the addn of glacial AcOH. The ppt was collected by centrifugation, washed with $H_2O$ (3 × 5 ml) and $Me_2CO$ (5 ml), and dried *in vacuo* over $P_2O_5$ at room temp for 48 hr: 94.5 mg (94.5%). The purity of the product was checked by tlc in systems A, B, and C. It migrated as a single spot which appeared as a dark purple quench when viewed under uv: uv max (0.1 *N* NaOH) 258 nm (log ε 4.45), 282 (4.46), 361 (4.40); (0.1 *N* HCl) 244 (4.29), 288 (4.25), 333 (4.11); nmr (DMSO-$d_6$) τ 2.23 (d, 2, $C_2'$-H, $C_6'$-H), 3.10 (d, 2, $C_3'$-H, $C_5'$-H), 7.38 (s, 3, 7-$CH_3$), 7.6-8.2 (m, 4, $CH_2CH_2$). *Anal.* ($C_{20}H_{22}N_8O_5 \cdot 1.5H_2O$) C, H, N.

Method B. 2,4,5,6-Tetraaminopyridine sulfate (3.65 g, 15.3 mmoles), *p*-aminobenzoylglutamic acid (1.80 g, 6.8 mmoles) and 3,4-dibromo-2-butanone[10] (3.7 g, 13.8 mmoles) were condensed according to the general procedure of Seeger, *et al.*[11] The crude product was extd with $NH_4HCO_3$ soln (0.5 *M*, 100 ml) and the ext was filtd and evapd to dryness. $H_2O$ (20 ml) was added and the soln was reevapd. The residue was dissolved in $H_2O$ (20 ml) and chromatographed on a column (4.5 × 35 cm) of DEAE-cellulose (bicarbonate form). Elution was achieved with a linear gradient of $NH_4HCO_3$ (2000 ml of 0.01 *M* $NH_4HCO_3$ in the mixing flask, 2000 ml of 0.8 *M* $NH_4HCO_3$ in the reservoir; both solns were 0.1 *M* in mercaptoethanol). Fractions containing 7-Me-AM were combined and the product was isolated as described above, 0.57 g(8%). It exhibited identical chromatographic and spectral properties with the product prepared by method A.

*N*-*p*-({[(2,4-Diamino-7-methyl-6-pteridinyl)methyl]methylamino}benzoyl)-L-glutamic acid (7-Me-MTX) (3). Method A. The exptl method was the same as that described for 7-Me-AM except that the isolation procedure was modified due to the different solubility characteristics of 7-Me-MTX. The reaction mixt derived from 8 (5.0 g, 11.7 mmoles) and *p*-methylaminobenzoylglutamic acid hydrobromide (10.8 g, 29.9 mmoles) was concd to *ca.* 50 ml *in vacuo* at below 50° on a rotary evaporator. The dark brown viscous residue was taken up in $H_2O$ (400 ml) and filtd, and the soln was adjusted to pH 5 by the addn of 0.5 *N* NaOH with cooling and stirring. After standing 48 hr at 5° the yellow solid which had sepd was collected by filtn, washed copiously with $H_2O$ and $Me_2CO$, and dried *in vacuo* over $P_2O_5$ at room temp for 48 hr. The crude product weighed 3.8 g (66%). A sample (100 mg) of the crude product was purified on DEAE-cellulose according to the procedure detailed for 2 (except that 0.4 *M* $NH_4HCO_3$ soln was used in the reservoir); 91 mg of pure 3 was obtained: uv max (0.1 *N* NaOH) 225 nm (log ε 4.40), 304 (4.41) 360 (3.95); (0.1 *N* HCl) 244 (4.18), 309 (4.21), 332 (sh) (4.09); nmr (DMSO-$d_6$) τ 2.25 (d, 2, $C_2'$-H, $C_6'$-H), 3.15 (d, 2, $C_3'$-H, $C_5'$-H), 6.90 (s, 3, N-$CH_3$), 7.44 (s, 3, 7-$CH_3$), 7.6-8.2 (m, 4, $CH_2CH_2$). *Anal.* ($C_{21}H_{24}N_8O_5 \cdot 1.5H_2O$) C, H, N.

Method B. Condensation of 2,4,5,6-tetraaminopyrimidine sulfate (3.65 g, 15.3 mmoles), *p*-methylaminobenzoylglutamic acid hydrobromide (2.44 g, 6.8 mmoles), and 3,4-dibromo-2-butanone (3.17 g, 13.8 mmoles) according to the procedure of

Seeger, *et al.*,[11] and working up the product according to the method described above (2, method B) yielded 0.52 g (7%) of **3**. It was identical with the product prepared by method A.

**Permanganate Oxidation of 7-Me-AM and 7-Me-MTX.** The 7-methyl compd (50 mg) was dissolved in 0.1 *N* NaOH (10 ml) and the soln was adjusted to pH 8 by the dropwise addn of 0.5 *N* HCl. $KMnO_4$ soln (5%, 1.7 ml) was added with stirring and the mixt was allowed to stand for 5 min at room temp. Excess $KMnO_4$ was destroyed by the addn of a few drops of $H_2O_2$ (30%) and the pptd $MnO_2$ was removed by centrifugation. The ppt was washed with $H_2O$ (2 ml) and the washing and supernatant were combined and chromatographed on a column (1 × 17 cm) of DEAE-cellulose (bicarbonate form) by applying a linear gradient of $NH_4HCO_3$ soln (500 ml of 0.01 *M* $NH_4HCO_3$ in the mixing flask and 500 ml of 0.4 *M* $NH_4HCO_3$ in the reservoir). The pteridine fraction was identified as 2,4-diamino-7-methylpteridine-6-carboxylic acid by chromatographic and spectral comparison with an authentic sample.[5] The recovery was *ca.* 30%. The nonpteridine fractions derived from 2 and 3 possessed spectral characteristics identical with those of *p*-aminobenzoylglutamic acid and *p*-methylaminobenzoylglutamic acid, respectively.

**Acknowledgments.** We thank Dr. Dah Hsi Wang Ho for the enzyme assays. We are grateful to Professor Heinz Rembold for a sample of 2,4-diamino-7-methylpteridine-6-carboxylic acid.

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# Synthesis of 5-Fluoro-6,8-dimethylbenz[*a*]anthracene

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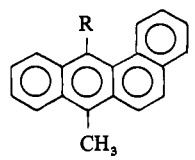
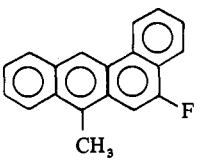
Since 7-methylbenz[*a*]anthracene (**1**) is by far the most potent carcinogen in the monomethylbenz[*a*]anthracene series[1-3] and 5-fluoro-7-methylbenz[*a*]anthracene (**2**) is inactive,[4] the hypothesis has been made that deactivation of a benz[*a*]anthracene is accomplished in the host by some reaction which occurs at the 7 position if unprotected by a Me group.[5] Furthermore, it was suggested that the reaction sequence leading to cancer may occur by attack at the 5 position of **1** since **2** is without carcinogenic activity[4] whereas other fluorinated derivatives of **1** are carcinogenic.‡

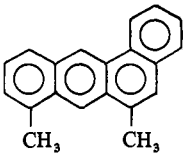


1,R = H
1a, R = $CH_3$

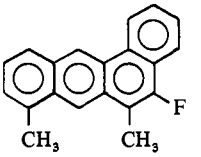


2

Support for the idea that deactivation at the 7 position is important is found in the fact that 6,8-dimethylbenz[*a*]anthracene[5] (**3**) is a potent carcinogen.‡,[6] In this compound deactivation at the 7 position may be blocked by 2 Me groups at 6 and 8. In order to find out if the carcinogenic activity of **3** could be eliminated by substitution of an F at 5, we have synthesized 5-fluoro-6,8-dimethylbenz[*a*]anthracene (**4**). Since **4** is inactive‡ it appears that the 5 position in **3** may be the position at which metabolism leading to cancer occurs, just as it appears to be in the case of **1** (and also in the case of 7,12-dimethylbenz[*a*]anthracene).‡,§



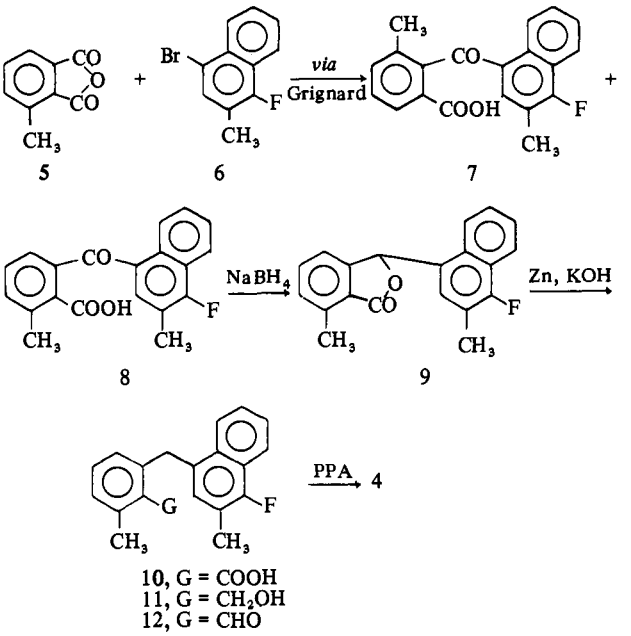
3



4

The synthesis of **4** was accomplished as outlined in Scheme I.

Scheme I



## Experimental Section#

**4-Bromo-1-fluoro-2-methylnaphthalene (6).** 1-Amino-2-methylnaphthalene[5] was converted into 1-formylamino-2-methylnaphtha-

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‡Private communication from Drs. J. A. and E. C. Miller, McArdle Memorial Laboratory, University of Wisconsin, Madison, Wis.

§Private communication from Dr. C. B. Huggins, Ben May Laboratory for Cancer Research, University of Chicago, Ill., who reports also that 4-fluoro-, 8-fluoro-, and 11-fluoro-7,12-dimethylbenz[*a*]anthracenes produced sarcomas in over 50% of L-E rats.

#All mps are uncorrected. The term "worked up in the usual way" means that an ether–PhH extract of the organic products was washed with water, dil acid and/or base as needed, satd NaCl, and dried by filtration through a bed of anhyd $MgSO_4$. The solvent was then distd or evapd in a rotary evaporator. Nmr spectra were recorded on a Varian Associates A-60 nuclear magnetic resonance spectrometer using carbon tetrachloride as a solvent and TMS as an internal reference. Mass spectra were recorded on an Associated Electrical Industries, Ltd. MS 902 mass spectrometer.