Synthesis of 5,10-Dideazaminopterin

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The synthesis of 5,10-dideazaaminopterin by two independent routes is described. Condensation of the piperidine enamine of 4-*p*-carbomethoxyphenylbutyraldehyde (**4**) with ethoxymethylenemalononitrile followed by treatment of the resultant arylethylenaminomalononitrile (**5**) with methanolic ammonia produced 2-amino-3-cyano-5-*p*-carbomethoxyphenethylpyridine (**6**). Cyclization of the aminocyanopyridine with guanidine afforded 4-amino-4-deoxy-5,10-dideazapteroic acid (**8**). Coupling of the pteroate intermediate with glutamate yielded the target 5,10-dideazaaminopterin (**10**).

Alternatively, reduction of 2,4-diamino-6-formyl-5-deazapteridine (**11**) with sodium borohydride gave the 6-hydroxymethyl compound **12**. Conversion to the bromide was followed by alkylation of dimethyl homoterephthalate to afford methyl 4-amino-4-deoxy-10-carbomethoxy-5,10-dideazapteroate (**14**). Decarboxylation with ester cleavage (sodium cyanide in dimethyl sulfoxide at 180°) also gave the diaminopteroic acid (**8**).

5,10-dideazaaminopterin (**10**) was an effective growth inhibitorof folate dependent bacteria, *S. faecium* and *L. casei*.

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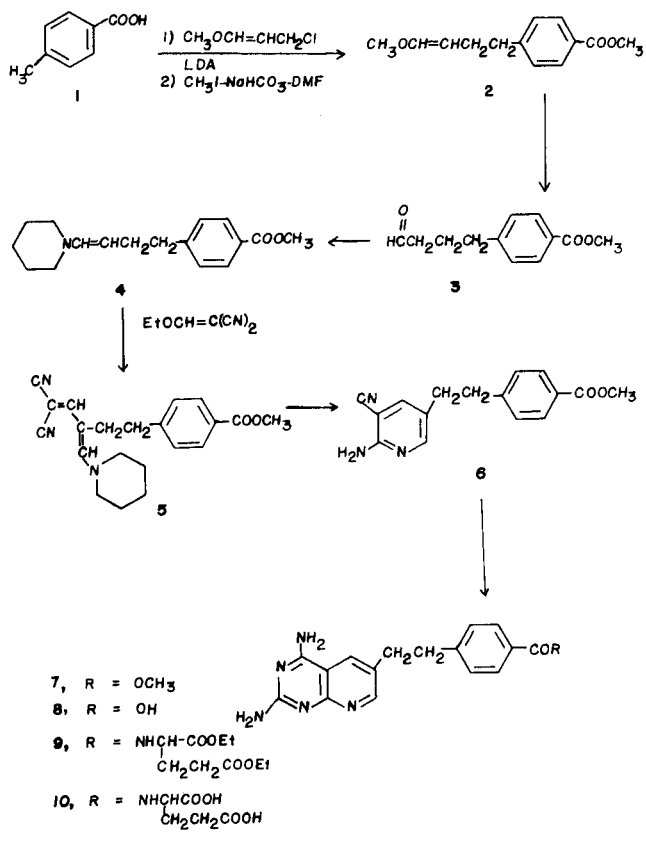
As part of a continuing program in the development of analogs of the clinically useful drug, methotrexate, we have recently focused on the 10-deazafolate series of compounds. We have initially reported the synthesis and biological properties of 10-deazaaminopterin and its 10-alkyl derivatives [1-5]. More recently we described the preparation of 8,10-deazaaminopterin and its antifolate properties [6-8]. In this manuscript we report the synthesis of 5,10-dideazaaminopterin (**10**) and its activity against folate dependent bacteria.

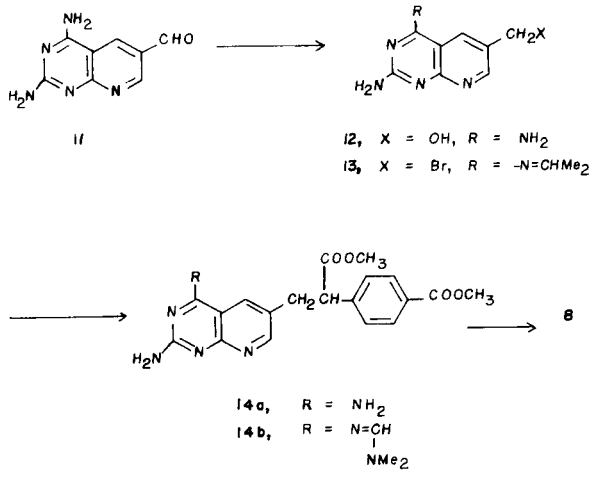
Two independent methods were investigated for the synthesis of 5,10-dideazaaminopterin (**10**) and are outlined in Schemes I and II. The first route was based on our previously reported [9] model sequence for synthesis of 2,4-diamino-6-alkyl-5-deazapterins. The process features condensation of an enamine with ethoxymethylenemalononitrile followed by ring closure of the enaminoylidine malononitrile to a 2-amino-3-cyanopyridine substituted at C-5 by the requisite side chain [10]. Cyclization with guanidine affords the 2,4-diamino-6-substituted-pyrido[2,3-*d*]pyrimidine. The piperidine enamine of 4-*p*-carbomethoxyphenylbutyraldehyde (**3**) was therefore considered as a primary intermediate for conduct of the synthesis *via* the malononitrile route.

Alkylation of the dianion of *p*-toluic acid (**1**) by 3-methoxyallyl chloride with subsequent esterification of the intermediate acid *via* treatment with methyl iodide-sodium bicarbonate in dimethylformamide gave 1-methoxy-4-*p*-car-

Scheme I



Scheme II



bomethoxyphenyl-1-butene (**2**) in a 26% yield [5]. Hydrolysis of the enol ether in 1*N* hydrochloric acid-tetrahydrofuran afforded the aldehyde ester **3**, which could be converted to the enamine **4** in high yield by treatment with piperidine in benzene containing a large excess of anhydrous potassium carbonate. An equimolar mixture of the enamine **4** and ethoxymethylenemalononitrile in acetonitrile was allowed to stand at room temperature for 4 days. During this time the piperidinodienylidinomalononitrile product **5** crystallized from solution. Processing and chromatography of the mother liquors afforded additional material for a total yield of only 13%. Piperidinomethylenemalononitrile was found to be a major byproduct in this preparation. As in the model series [9] we were unable to make improvements in the yield despite variations in time, temperature, reactant ratio, solvent, *etc.*

Treatment of **5** with methanolic ammonium hydroxide at room temperature for 3 days effected displacement of piperidine and ring closure to 2-amino-3-cyano-5-*p*-carbomethoxyphenethylpyridine (**6**) in 87% yield. It was convenient to follow the course of this conversion by monitoring the change of the longwave ultraviolet maximum at 380 nm in **5** to a maximum of 336 nm in **6**. When **6** was heated with an excess of guanidine carbonate at 100° for 3 days in 2-methoxyethanol the 4-amino-4-deoxy-5,10-dideazapteroic acid (**8**) was obtained in quantitative yield. The expected ester **7** was apparently hydrolyzed *in situ* to the acid **8**.

An alternate route for synthesis of the diaminopteroic acid **8** is also shown in Scheme II. The aldehyde **11** [11] was reduced with sodium borohydride in methanol to the hydroxymethyl compound **12** in 40% yield. The alcohol was converted to the bromide by treatment with excess triphenylphosphine dibromide in dimethylformamide [12]. The acidic medium catalyzed reaction of the diamino system with dimethylformamide to yield the mixed dimethylformimino derivatives **13**. The bromide was then used to alkylate the anion of dimethyl homoterephthalate to yield the dimethyl ester of 4-amino-4-deoxy-10-carboxy-5,10-dideazapteroic acid (**14a**) as a mixture with formimino derivative **14b**. When **14a-b** was warmed with an excess of sodium cyanide in dimethyl sulfoxide [7,8,13] at 180-190° smooth cleavage of the esters with concurrent decarboxylation at C-10 took place to afford the diaminopteroic acid **8**.

The acid **8** was coupled with diethyl L-glutamate *via* the mixed anhydride method (isobutyl chloroformate-triethylamine) to give the glutamate ester **9**. Hydrolysis of **9** in 1*N* sodium hydroxide-2-methoxyethanol at room temperature afforded 5,10-dideazaaminopterin (**10**).

In Table I compound **10** is compared with 10-deazaaminopterin, 8,10-dideazaaminopterin and methotrexate for inhibition of exogenous folate dependent bacteria *Streptococcus faecium* and *Lactobacillus casei*. The compound was a strong inhibitor of bacterial growth, but was less effective than the other deazapterin analogs or methotrexate. Enzyme inhibition was similar to the comparative analogs.

Table 1

Bacterial Growth and Enzyme Inhibition by 5,10-Dideazaaminopterin

	Concentration, ng/ml for 50% growth inhibition [a]				Concentration *M*, for 50% inhibition [b]	
	S. faecium		*L. casei*			
Compound	ATCC8043	MTX resistant	ATCC7469	MTX resistant	Dihydrofolate reductase	Thymidylate synthase
10	0.23	6300	0.020	>2000	1.2×10^{-8}	2.3×10^{-4}
methotrexate	0.17	4100	0.004	$>5 \times 10^{5}$	9.3×10^{-9}	1.3×10^{-4}
10-deazaaminopterin	0.20	>2000	0.01	>2000	2.0×10^{-8}	2.3×10^{-4}
8,10-dideazaaminopterin	0.04	1200	0.005	>2000	1.0×10^{-8}	1.1×10^{-4}

[a] Folate concentration = 1 ng/ml. [b] Enzymes derived from *L. casei*.

EXPERIMENTAL

1-Methoxy-4-*p*-carbomethoxyphenyl-1-butene (**2**).

To 775 ml of dry tetrahydrofuran at 0-5° under nitrogen was slowly added 475 ml (0.66 mole) of 1.4 *M* butyllithium in hexane. Then at 0-5° was added 90 ml (0.64 mole) of freshly distilled diisopropylamine over 15 minutes. After another 10 minutes a solution of 43 g (0.32 mole) of *p*-toluic acid in 180 ml of tetrahydrofuran was added over 30 minutes. The deep red solution was kept at ambient temperature under nitrogen for 18 hours. The solution was chilled to 0-5° and treated dropwise under nitrogen with 290 ml of ice cold 1 *M* 3-methoxyallyl chloride [5,14] in ether, which caused quenching of the red color. The yellow mixture was evaporated *in vacuo* and partitioned between 500 ml of water and 300 ml of ether. The aqueous solution was washed with another 200 ml of ether, chilled and acidified with acetic acid until precipitation was complete. The product acid was extracted into two 200-ml portions of dichloromethane. The extract was washed with 100 ml of water, dried over magnesium sulfate, and evaporated to leave 56 g of amber oil. A mixture of the oil (56 g), sodium bicarbonate (50 g), methyl iodide (85 g) and 150 ml of dimethyl formamide was stirred at room temperature for 3 days. The mixture was diluted with 600 ml of water and extracted successively with 400 ml and two 150 ml portions of pentane. The pentane extract was washed with 50 ml of water, dried over magnesium sulfate and evaporated to leave 36 g of amber oil. The oil was distilled *in vacuo* to give 5 g of methyl *p*-toluate at 40-45°/0.2 mm and 18 g (26%) of product at 110-120°/0.2 mm; nmr (deuteriochloroform): 2.33 (2H, m, -CH_2Ar), 2.80 (2H, m, CH_2), 3.46 (3H, s, -OCH_3), 3.91 (3H, s, $COOCH_3$), 4.80 (1H, m, 2-CH=), 6.30 (1H, d, 1-CH=), 7.26 (2H, d, 3',5'-H's), 8.00 (2H, d, 2',6'-H's). Analysis (glc) showed 2 peaks in a 4:1 ratio, both showed m/e 220 (M^+) indicating a mixture of *cis-trans* isomers.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32. Found: C, 70.7; H, 7.19.

4-*p*-Carbomethoxyphenylbutyraldehyde (**3**).

A mixture of 28 g of the enol ether ester **2**, 60 ml of tetrahydrofuran and 300 ml of 1*N* hydrochloric acid was stirred at 40° for 15 hours. The mixture was extracted with 200 and 100 ml portions of dichloromethane. The extract was washed with 100 ml of saturated sodium bicarbonate, dried over magnesium sulfate and evaporated *in vacuo* to leave 26 g of yellow liquid. The material was purified by preparative liquid chromatography on silica gel with elution by 12% ethyl acetate-88% hexane. Evaporation of solvent afforded 14.1 g (53%) of pure aldehyde; nmr (deuteriochloroform): 1.95-3.0 (6H, m, -$CH_2CH_2CH_2$-), 3.90 (3H, s, $COOCH_3$), 7.25 (2H, d, 3',5'-H's), 8.00 (2H, d, 2',6'-H's), 9.82 (1H, s, CHO). The product was characterized as the 2,4-dinitrophenylhydrazone, mp 122-123°, after recrystallization from ethanol-ethyl acetate.

Anal. Calcd. for $C_{18}H_{18}N_4O_6$: C, 56.0; H, 4.70; N, 14.5. Found: C, 56.2; H, 4.67; N, 14.4.

2-Cyano-4-*p*-carbomethoxyphenethyl-5-piperidino-2,4-pentadienonitrile (**5**).

To 11.0 g (0.053 mole) of the aldehyde **3** was added dropwise, with cooling by a cold water bath, 5.87 ml (0.06 mole) of piperidine, followed by addition of 18 g of powdered anhydrous potassium carbonate. The mixture was stirred at 60° (pre-heated bath) for 40 minutes, cooled and thrice extracted with 30-ml portions of dichloromethane. The extract was rapidly filtered and the solvent removed *in vacuo* to leave 13.1 g (90%) of enamine as a yellow oil; nmr (deuteriochloroform): 1.55 (6H, br s, piperidine-$CH_2CH_2CH_2$-), 2.40 (2H, m, CH_2Ar), 2.80 (6H, m, -CH_2N, 3-CH_2), 3.95 (3H, s, $COOCH_3$), 5.20 (1H, m, 2-CH=), 5.90 (1H, d, 1-CH=), 7.25 (2H, d, 3',5'-H's), 8.00 (2H, d, 2',6'-H's).

The enamine **4** (13.1 g, 0.048 mole) was dissolved in 50 ml of acetonitrile and treated slowly with a solution of 5.4 g (0.044 mole) of ethoxymethylenemalononitrile in 20 ml of acetonitrile with cooling by a cold water bath. The solution was kept at room temperature for 4 days causing deposition of crystals. The solid was collected, washed with acetonitrile and dried to leave 835 mg. The filtrate was evaporated, the residue washed with 75 ml of ether and the insoluble gum was taken up in 40 ml of acetonitrile-ether (3:1). After 2 days a second crop of 380 mg of crystals was obtained. The mother liquor was chromatographed on silica gel (300 g) with elution by ethyl acetate-chloroform (2:3) to give another 810 mg for a total yield of 2.02 g (13%). A portion was recrystallized from ethanol, mp 205-207°; nmr (deuteriochloroform): 1.73 (6H, m, piperidine CH_2), 2.9 (4H, br s, -CH_2CH_2Ar), 3.53 (4H, m, CH_2N-), 6.83 (1H, s, 5-CH=), 6.90 (1H, s, 3-CH=), 7.40 (2H, d, 3',5'-H's), 8.07 (2H, d, 2',6'-H's); uv (ethanol): λ 236 mm (15,041), 380 (51,472); ir (Nujol): 4.55 μ (C≡N), 5.90 (ester, C=O), 7.80 (ArCOOCH_3).

Anal. Calcd. for $C_{21}H_{23}N_3O_2$: C, 72.2; H, 6.63; N, 12.0. Found: C, 72.0; H, 6.99; N, 11.9.

2-Amino-3-cyano-5-*p*-carbomethoxyphenethylpyridine (**6**).

To 1.46 g of the dinitrile **5** in 50 ml of methanol was added 2.0 ml of concentrated ammonium hydroxide. The solution was kept at ambient temperature for 3 days at which time the uv spectrum showed the reaction to be complete. The precipitated crystals were collected, washed with methanol and dried to afford 930 mg. The filtrate was concentrated to give another 108 mg for a total yield of 1.048 g (87%); nmr (DMSO-d_6): 2.75 (2H, t, 5-pyr CH_2), 2.90 (2H, t, benzylic CH_2), 3.83 (3H, s, CH_3), 6.67 (2H, s, NH_2), 7.33 (2H, d, 3',5'-H's), 7.73 (1H, s, C-6H), 7.87 (2H, d, 2',6'-H's), 8.00 (1H, s, C-4H); ir (Nujol): 3.05, 3.25 (NH_2), 5.85 (ester C=O), 7.80 (ArCOOCH_3); uv (ethanol): λ 248 nm (26,000), 336 (5,687).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.3; H, 5.38; N, 14.9. Found: C, 68.1; H, 5.52; N, 15.0.

4-Amino-4-deoxy-5,10-dideazapteroic Acid (**8**). Method A.

A mixture of 100 mg (0.35 mmole) of the aminopyridine ester **6** was added to guanidine free base (0.35 mmole) (from 34 mg guanidine hydrochloride and 8 mg sodium) in 5 ml of 2-methoxyethanol. The mixture was heated for 3 days at 100° and the solvent was evaporated *in vacuo*. The residue was dissolved in 5 ml of water and acidified with acetic acid. The precipitate was collected, washed with water and dried to yield 117 mg (100%). The material was dissolved in 1.5*N* ammonium hydroxide, filtered and reprecipitated with acetic acid to afford an analytical sample; nmr (DMSO-d_6): 2.95 (4H, m, -CH_2CH_2-), 7.35 (2H, d, 3',5'-H's), 7.85 (2H, d, 2',6'-H's), 8.27 (1H, s, C-5H), 8.46 (1H, s, C-7H); uv (*p*H 13): λ 245 nm (25,902), 344 (5,803).

Anal. Calcd. for $C_{16}H_{15}N_5O_2 \cdot H_2O$: C, 58.7; H, 5.23; N, 21.4. Found: C, 58.6; H, 5.39; N, 20.9.

We were unable to reproduce the above results in later runs and found it necessary to use a ratio of 4 equivalents guanidine to 1 of amino pyridine. The reaction still required 3 days under those conditions.

Method B.

A solution of 325 mg (0.7 mmole) of the crude **14a-b** mixture in 8 ml of dimethyl sulfoxide was heated to 180° and treated with 182 mg (3.7 mmoles) of sodium cyanide. The solution darkened and gas evolution occurred. Heating at 180-190° was maintained for 2.5 hours. The solvent was removed *in vacuo* and the dark residue treated with 10 ml of water to give nearly a complete solution. After filtration the filtrate was treated with acetic acid to precipitate the product. The material was collected and extracted into hot 50% dimethylformamide. After filtration the filtrate was evaporated *in vacuo* to leave 101 mg (47%) of product whose uv and nmr spectra were equivalent to material prepared by Method A.

5,10-Dideazaaminopterin (**10**) [15].

A mixture of 162 mg (0.52 mmole) of the diamino acid **8**, 0.14 ml (1.04 mmoles) of triethylamine and 5 ml of dimethylformamide was stirred at 80° for 10 minutes. The nearly complete solution was cooled to room temperature and treated with 0.14 ml (1.04 mmoles) of isobutyl chloroformate. After one hour a mixture of 250 mg (1.04 mmoles) of diethyl L-glutamate, 0.14 ml (1.04 mmoles) of triethylamine and 1 ml of dimethylformamide was added. The mixture was stirred for 48 hours and evaporated to dryness *in vacuo* to leave a brown solid. The residue was washed with 5

ml of water, then stirred with 5 ml of saturated sodium bicarbonate and 5 ml of ether for 30 minutes. The insoluble portion was collected, dissolved in chloroform and chromatographed on 2.5 g of silica gel with elution by 5% methanol in chloroform to give 40 mg of a yellow semi-solid; tlc (silica gel, methanol-chloroform, 1:4) R_f 0.5 by uv detection; ms: m/e 494 (M^+); nmr (DMSO-d_6): 1.20 (6H, t, CH_3), 2.1 (2H, m, -CH_2-), 2.98 (4H, s, 9,10-CH_2CH_2-), 4.25 (4H, q, -OCH_2-), 4.80 (1H, d, -NHC*H*), 7.35 (2H, d, 3',5'-H), 7.82 (2H, d, 2',6'-H), 8.30 (1H, s, C-7H), 8.50 (1H, s, C-5H).

A solution of 35 mg the diester **9** in 1 ml of 2-methoxyethanol-1*N* sodium hydroxide was kept at room temperature for 4 hours and diluted with water. The solution was acidified with acetic acid and evaporated *in vacuo*. The residual gum was treated with a little water to give a pale yellow crystalline precipitate. The material was collected by centrifugation, washed with water and dried to leave 25 mg; ms: m/e for bis trimethylsilyl derivative 582 (M^+); uv (*p*H 13): λ *247 nm (32,874), 346 (6,678); nmr* (DMSO-d_6): 2.00 (1H, m, CH), 2.05 (1H, m, CH), both of glutamate CH_2, 2.34 (2H, m, C*H*$_2$COOH), 3.00 (4H, m, C-9 and C-10 CH_2), 4.40 (1H, m, C*H*NH), 6.76 (2H, b s, 2-NH_2), 7.30 (2H, d, 3',5'-ArH), 7.80 (4H, m, NH_2 and 2',6'-ArH), 8.37 (2H, m, C-5 H and CON*H*), 8.49 (1H, 5, C-7H); (TFA-d): 2.40 (1H, m), and 2.60 (1H, m) both CH of glutamic CH_2, 2.83 (2H, m, C*H*$_2$COOH), 3.21 and 3.31 (each 2H, m, bridge-CH_2CH_2-), 5.08 (1H, m, C*H*NH), 7.35 (2H, d, 3',5'-ArH), 7.82 (2H, d, 2',6'-ArH), 8.65 (1H, s, C-5H), 9.13 (1H, s, C-7H).

Anal. Calcd. for $C_{21}H_{22}N_6O_5 \cdot \frac{1}{3}H_2O$: C, 54.6; H, 5.37; N, 18.2. Found: C, 54.8; H, 5.58; N, 17.9.

2,4-Diamino-6-hydroxymethyl-5-deazapteridine (**12**).

To a stirred suspension of 850 mg (4.5 mmoles) of the aldehyde **11** in 125 ml of methanol, at room temperature, was added 100 mg (2.5 mmoles) of sodium borohydride portionwise over 5 minutes. The mixture was stirred for 1 hour and some insoluble material (165 mg, mostly **11** by nmr analysis) was removed by filtration. The filtrate was diluted with 25 ml of water and the methanol was removed under reduced pressure. The aqueous residue was filtered and the collected precipitate washed with water and dried to leave 334 mg (40%) of pale yellow solid; uv (*p*H 13): λ 247 nm, 266, 342; nmr (DMSO-d_6): 4.54 (2H, s, -CH_2O-), 5.28 (1H, br s, OH), 6.34 (2H, s, NH_2), 7.67 (2H, br s, NH_2), 8.37 (1H, d, J = 2 Hz, C-7H), 8.67 (1H, d, J = 2 Hz, C-5H).

Anal. Calcd. for $C_8H_9N_5O$: C, 50.2; H, 4.75; N, 36.6. Found: C, 50.2; H, 4.71; N, 36.5.

Treatment of **12** with Triphenylphosphine Dibromide.

To an ice cold solution of 5.49 g (20.9 mmoles) of triphenylphosphine in 52 ml of dry dimethylformamide was added 1.08 ml (20.9 mmoles) of bromine over 2 minutes with stirring. The orange solution was stirred for 10 minutes at 0-5°, then 1.00 g (5.2 mmoles) of the diaminoalcohol **12** was added. The mixture was stirred at ambient temperature for 20 hours followed by the addition of 3 ml of ethanol. After 10 minutes the solvent was removed *in vacuo* and the residue was thoroughly washed with three 50-ml portions of toluene. The material was twice digested with 50 ml portions of warm (50°) tetrahydrofuran, filtered and dried *in vacuo* to leave 2.70 g (94%) of **13** as a dihydrobromide dimethylformimino dimethylformamide solvate; nmr (DMSO-d_6): 2.73, 2.90 (6H, s, HCON*Me*$_2$), 3.30, 3.40 (6H, s, -N=C-N*Me*$_2$), 5.00 (2H, s, -CH_2Br), 8.00 (1H, s, *H*-CO-N*Me*$_2$), 8.87 (1H, s, *H*-C-N*Me*$_2$), 9.50 (1H, s, C-7H), 9.60 (1H, s, C-5H).

Alkylation of Dimethyl Homoterephthalate with the Bromide Mixture.

To a stirred suspension of potassium hydride (from 1.71 g of 24.6% oil suspension, 10.5 mmoles, pentane washed) in 10 ml of dry dimethylformamide at −40° was added a solution of 2.19 g (10.5 mmoles) of dimethyl homoterephthalate in 10 ml of tetrahydrofuran. The mixture was stirred for 30 minutes and a suspension of 1.0 g (1.8 mmoles) of the bromomethyl compound **13** in 20 ml of dimethylformamide was added over 5 minutes. The mixture was sitrred at −40° for 30 minutes, then at ambient temperature for 15 hours. The mixture was neutralized with a little acetic acid and evaporated *in vacuo* to leave a yellow paste. The residue was treated with 50 ml of hot 2-propanol and filtered. The filtrate was evaporated and dried to leave 385 mg (50%) of a yellow powder. The nmr spectra indicated this to be a mixture of the 2,4-diamino-10-carbomethoxy ester **14a** and an *N*-formimino derivative **14b**. A portion was chromatographed by preparative tlc to afford **14b** as a gum; nmr (deuteriochloroform): 3.20 (1H, d, C-9H), 3.30 (6H, s, C-NMe_2), 3.50 (1H, d, C-9H), 3.67 (3H, s, 10-$COOCH_3$), 3.90 (4H, s, 10-H, Ar$COOCH_3$), 7.45 (2H, d, 3',5'-H's), 8.00 (2H, d, 2',6'-H's), 8.20 (1H, s, C-7H), 8.40 (1H, s, C-5H), 8.80 (1H, s, HC=N). The crude mixture of **14a-b** was suitable for decarboxylation to the diamino pteroic acid, **8** (Method B).

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