Synthesis of 10-Deazapteroic and 11-Deazahomopteroic Acids

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The syntheses of 10-deazapteroic and 11-deazahomopteroic acids are described. These compounds along with their simple 6-phenylalkylpteridinol relatives were found to be inactive as antimalarial agents against the *Plasmodium berghei* or *Plasmodium gallinaceum* strains. 10-Deazapteroic acid was a potent growth inhibitor of *Streptococcus faecium* both in the pteridine and tetrahydropteridine forms.

In a previous communication (3) a rationale was presented for the synthesis of folic acid analogs related to homofolic acid (4) as potential antimalarial agents. Several compounds of the anilinoethylpteridinol series were prepared, none of which were active in the standard antimalarial screen against *Plasmodium berghei*. As a continuation of this investigation we have synthesized four compounds which lack the amine function in the side chain.

The compounds, 2-amino-4-hydroxy-6-(*p*-carboxyphenethyl)pteridine (10-deazapteroic acid) (I), the 6-*p*-carboxyphenylpropyl (11-deazahomopteroic acid) (II), 6-phenylethyl (III) and 6-phenylpropyl (IV) analogs were all inactive as antimalarials when tested in the standard *P. berghei* screen in rats or *Plasmodium gallinaceum* in birds. However, when examined for growth inhibition activity against *Streptococcus faecium* compounds I and II showed moderate inhibition as seen in Table I. Reduction to their tetrahydro derivatives improved the inhibitory potency, particularly in the deazapteroic case (I). The tetrahydrodeazapteroic acid compared favorably with tetrahydrohomopteroic acid as an inhibitor of *S. faecium* growth. The lack of activity displayed by the simple phenylalkyl pteridinols (III and IV) was not unexpected; the compounds were included mainly for comparison purposes. Baker and Ho (5) had previously shown III to be a poor inhibitor of folic reductase.

TABLE I

Growth Inhibition of *Streptococcus faecium* (ATCC 8043)

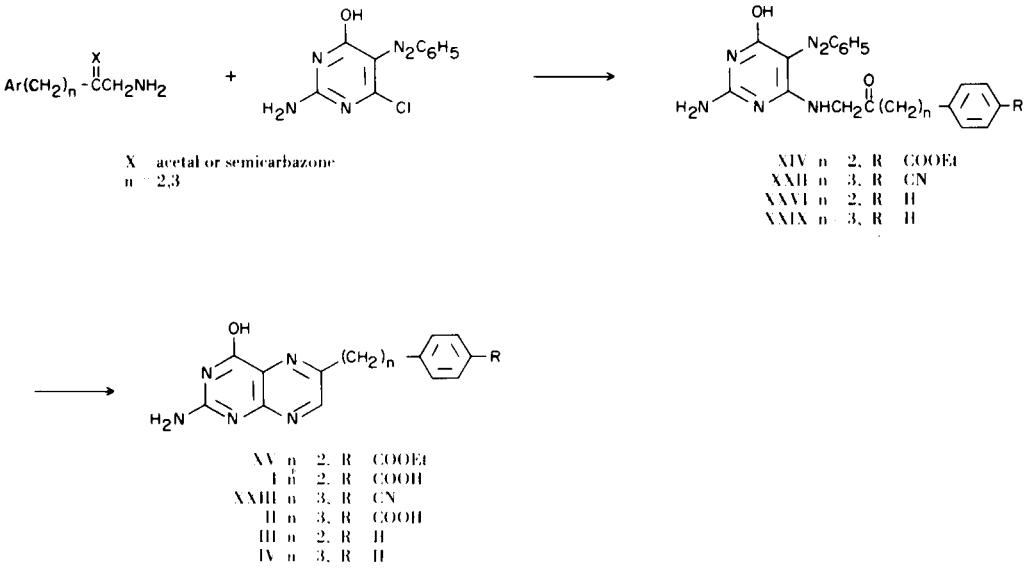
Compound	mμg./ml. Required for 50% Inhibition (a) Before Hydrogenation	After Hydrogenation (b)
I	100	6
II	200	80
III	>20,000	>20,000
IV	8,000	>20,000
XXIII	>20,000	>20,000
Homopteroic acid	400	0.3

(a) Folate present at 1 mμg./ml. (b) Hydrogenated over platinum oxide catalyst. Ultraviolet spectrum changed to that corresponding to a 5,6,7,8-tetrahydropteridine.

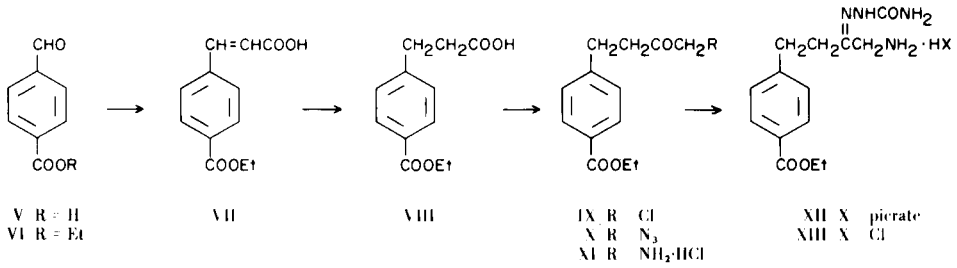
Synthesis of the pteridines was carried out by the general procedure of Boon and Leigh (6) and previously utilized for similar 6-substituted pteridines (3,4). The method (Scheme I) involved condensation of an appropriately substituted aminomethyl ketone (carbonyl blocked) with 2-amino-4-hydroxy-5-phenylazo-6-chloropyrimidine. After acid hydrolysis of the blocking group the pyrimidinylamino ketone was reductively cyclized to a 7,8-dihydropteridine which was oxidized *in situ* with dilute hydrogen peroxide to the pteridine.

The *p*-carbethoxyphenylamino ketone semicarbazone (XIII), necessary for the synthesis of I, was prepared by the route outlined in Scheme II. Condensation of 4-carbethoxybenzaldehyde (VI) with malonic acid afforded 4-carbethoxycinnamic acid (VII), which was hydrogenated over rhodium/carbon to yield the hydrocinnamic acid (VIII). Reaction of the acid chloride of VIII with diazomethane and hydrogen chloride followed by treatment of the resulting chloromethyl ketone (IX) with sodium azide in aqueous methanol gave the azido ketone (X). The azide was hydrogenated over 100% palladium in the presence of an equivalent of hydrogen chloride to afford the aminomethyl ketone (XI) in a 58% yield as the hydrochloride salt. Treatment of XI with semicarbazide hydrochloride in aqueous alcohol gave the semicarbazone which was isolated (85% yield) as the picrate salt (XII). The picrate was easily exchanged for chloride (XIII) by stirring with Dowex 2 (chloride) resin in aqueous methanol.

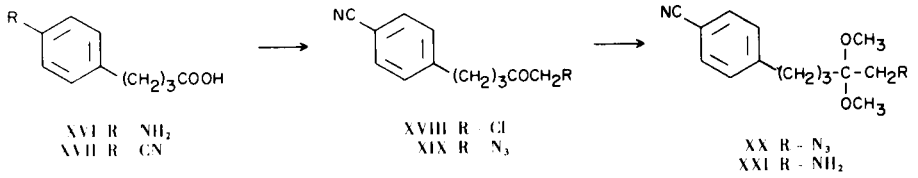
SCHEME I



SCHEME II



SCHEME III



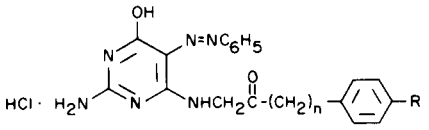
After condensation of XIII with the phenylazochloropyrimidine and subsequent reductive cyclization according to the method described above, the 6-(*p*-carbethoxyphenethyl)pteridine (XV) was obtained in a 65% yield from XIII. Saponification of the ester by 8% sodium hydroxide with crystallization of the sodium salt from the hydrolysis medium afforded 10-deazapteroic acid (I).

The homolog, 11-deazahomopteroic acid (II), was prepared utilizing a cyano moiety as the source for the *p*-carboxyl group as shown in Scheme III. Commercially available 4-(*p*-nitrophenyl)butyric acid was reduced to the amino acid (XVI) which was diazotized and treated with cuprous cyanide to give the cyanophenylbutyric acid (XVII) in a 56% yield. Conversion of XVII to the chloromethyl ketone (XVIII) and azido ketone (XIX) was readily accomplished. Catalytic reduction of the azide in the presence of the nitrile was untenable so the carbonyl was blocked as the ketal (XX) and the azide selectively reduced with sodium borohydride in boiling 2-propanol. The amino ketal (XXI) was coupled with the phenylazochloropyrimidine, etc., to afford the 6-(*p*-cyanophenylpropyl)pteridine (XXIII). Hydrolysis with 10% sodium hydroxide yielded the acid (II).

The simple phenylalkylpteridines (III and IV) Scheme

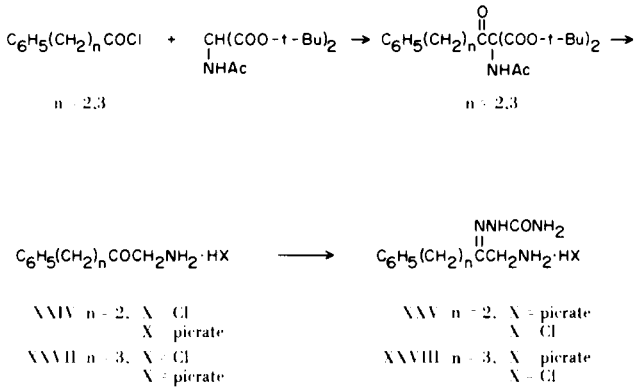
TABLE II

2-Amino-4-hydroxy-5-phenylazo-6-pyrimidinylamino Ketones



No.	n	R	Yield (%)	M.p., °C	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIV	2	COOEt	84	167-170	$C_{23}H_{24}N_6O_4 \cdot HCl \cdot H_2O$	54.8	5.42	16.7	54.6	5.45	16.3
XXII	3	CN	53	142-143	$C_{22}H_{21}N_7O_2 \cdot HCl$	58.5	4.91	21.7	58.3	5.11	21.3
XXVI	2	H	76	212-215	$C_{20}H_{20}N_6O_2 \cdot HCl$	58.4	5.15	20.4	58.1	5.05	20.1
XXIX	3	H	87	122-124	$C_{21}H_{22}N_6O_2 \cdot HCl$	59.1	5.43	19.7	58.9	5.66	19.8

SCHEME IV



IV were synthesized by the general route above. However, the aminomethyl ketone intermediates (XXIV and XXVII) were prepared by a one-step method involving condensation of phenylpropionyl and phenylbutyryl chlorides with di-*t*-butyl acetamidomalonate (7). Acidic decomposition and hydrolysis of the resulting keto diester afforded the amino ketones (isolated as the picrate salts) in 30% and 24% yields, respectively. Blocking of the carbonyl groups as semicarbazones was enacted before conversion to the pteridines.

EXPERIMENTAL

4-Carbethoxycinnamic Acid (VII).

4-Formylbenzoic acid (V) was esterified in the usual manner with ethanol and sulfuric acid to afford 4-carbethoxybenzaldehyde (VI) in a 64% yield, b.p. 92-97°/1.0 mm. The ester (18.3 g., 0.103 mole), 11.0 g. (0.106 mole) of malonic acid, 2.2 ml. of piperidine and 180 ml. of pyridine were heated 3 hours on the steam bath. The solvent was evaporated and the residue shaken with 200 ml. of water. The *p*H was adjusted to 6-7 with acetic acid and the precipitate was collected. The still damp solid was recrystallized from 500 ml. of ethanol to yield 15.1 g. (67%) of white crystals, m.p. 229-230°. An analytical sample, m.p. 234-235°, was similarly obtained from another run. Löw (8) reported m.p. 220°; we observed that the m.p. varies from 220-235° depending on the rate of heating.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.4; H, 5.49. Found: C, 65.4; H, 5.44.

3-(*p*-Carbethoxyphenyl)propionic Acid (VIII).

A mixture of 1.0 g. of VII, 100 mg. of 5% rhodium-on-carbon and 25 ml. of ethanol was stirred under an atmosphere of hydrogen for 2 hours. The catalyst was removed and the solvent was evaporated *in vacuo*. The crystalline residue was twice recrystallized from cyclohexane to give an analytical sample, m.p. 108.5-110.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.9; H, 6.35. Found: C, 65.1; H, 6.39.

1-Chloro-4-(*p*-carbethoxyphenyl)-2-butanone (IX).

A solution of 1.11 g. (0.005 mole) of VIII in 5 ml. of thionyl chloride was refluxed for 1 hour and evaporated *in vacuo*. The resulting acid chloride was dissolved in 8 ml. of ether and added dropwise to 20 ml. of ethereal diazomethane (0.013 mole, from 2.0 g. of nitrosomethyl urea) at 0-5°. After 1 hour the solution was gassed with dry hydrogen chloride for 30 minutes at 0-5°, allowed to stand another hour and then evaporated *in vacuo*. The residue was redissolved in 25 ml. of ether, filtered and the filtrate evaporated to leave 1.11 g. (87%) of white crystals. The material was recrystallized (Norit) from cyclohexane to afford 0.70 g. (55%) of white crystals, m.p. 72-73°.

Anal. Calcd. for $C_{13}H_{15}ClO_3$: C, 61.2; H, 5.93; Found: C, 61.6; H, 6.00.

1-Azido-4-(*p*-carbethoxyphenyl)-2-butanone (X).

A mixture of 0.70 g. of chloro ketone (IX), 1.3 g. of sodium azide and 20 ml. of 80% methanol was stirred at 35° for 1 hour. The solvent was removed *in vacuo* and the crystalline residue diluted with water. The solid was collected, washed with water and dried to leave 0.69 g. (96%). A portion was recrystallized from cyclohexane to yield an analytical sample, m.p. 67-69°; λ (Nujol) 4.75 (N_3), 5.80 (C=O of ester and ketone).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.8; H, 5.79; N, 16.1. Found: C, 60.0; H, 5.82; N, 16.0.

1-Amino-4-(*p*-carbethoxyphenyl)-2-butanone Hydrochloride (XI).

A mixture of 8.3 g. of azido ketone (X), 3.0 g. of palladium black, 5.5 ml. of 6 *N* hydrochloric acid and 140 ml. of ethanol was stirred under one atmosphere of hydrogen for 7 hours. The catalyst was removed and the filtrate evaporated *in vacuo*. The residue was stirred with ether and the white crystals were collected, washed with ethanol and dried to leave 5.02 g. (58%). An analytical sample, m.p. 148-150°, was obtained from ethanol; λ (Nujol) 3.90 (NH_3^+), 5.79 (ketone C=O), 5.88 (ester C=O), 7.79 (benzoate C–O).

Anal. Calcd. for $C_{13}H_{17}NO_3$·HCl: C, 57.4; H, 6.67; N, 5.16. Found: C, 57.6; H, 6.77; N, 5.52.

1-Amino-4-(*p*-carbethoxyphenyl)-2-butanone Semicarbazone Picrate (XII).

A mixture of 5.0 g. of the amino ketone hydrochloride (XI), 3.0 g. of semicarbazide hydrochloride and 67 ml. of 67% ethanol was stirred 3 hours. The resulting solution was treated with 4.3 g. of picric acid in 250 ml. of hot water to precipitate the picrate, which was collected, washed with water and dried to afford 9.1 g. The infrared spectrum showed about 70% conversion. Retreatment with 2.0 g. of semicarbazide in 300 ml. of hot 50% ethanol finally yielded 8.2 g. (85%) of picrate. No ketone remained in the infrared. A portion was recrystallized from 95% ethanol, m.p. 185-188°; λ (Nujol) 5.88 (ester C=O), 5.97 (semicarbazone C=O).

Anal. Calcd. for $C_{20}H_{23}N_7O_{10}$·1/2 H_2O: C, 45.3; H, 4.57; N, 18.5. Found: C, 45.3; H, 4.56; N, 18.6.

1-Amino-4-(*p*-carbethoxyphenyl)-2-butanone Semicarbazone Hydrochloride (XIII).

A mixture of 8.0 g. of the picrate (XII), 60 g. of Dowex 2 (chloride) resin and 240 ml. of 75% ethanol was heated until a nearly transparent supernatant liquid was obtained. The mixture was stirred for 15 hours, filtered and the filtrate was treated with another 20 g. of resin for 2 hours. After filtration the solvent was removed *in vacuo* to leave 4.6 g. of crystalline residue, which was stirred with 50 ml. of ethanol. The white crystals were collected, washed with alcohol and dried to leave 3.7 g. (73%). An analytical sample, m.p. 194-196.5°, was obtained from ethanol.

Anal. Calcd. for $C_{14}H_{20}N_4O_3$·HCl: C, 51.2; H, 6.44; N, 17.0. Found: C, 51.2; H, 6.42; N, 16.6.

4-(*p*-Cyanophenyl)butyric Acid (XVII).

4-(*p*-Aminophenyl)butyric acid (XVI) was prepared in 81% yield, m.p. 130-132°, by low pressure hydrogenation of the nitro acid over platinum oxide in 50% methanol; Moffett and Vaughn (9) observed m.p. 130-132°. To 51.8 g. (0.29 mole) of XVI was added 315 ml. of water and 48.3 ml. (0.58 mole) of concentrated hydrochloric acid. The mixture was cooled to −1° and a solution of 19.9 g. (0.29 mole) of sodium nitrite was added over 30 minutes, with temperature control at −1 to +2°. This diazonium reagent was then added at 70-75° over 10 minutes with vigorous stirring to cuprous cyanide freshly prepared from 72.5 g. of cupric sulfate and 86 g. of potassium cyanide in 150 ml. of water. After another 15 minutes the mixture was cooled and extracted twice with 300 ml. portions of ether. The ether was dried over magnesium sulfate and evaporated to leave 26.8 g. of light orange crystals. The aqueous cyanide solution was adjusted to *p*H 6-7 and extracted with 200 ml. of ether to give another 9.6 g. of red solid. The latter was extracted with two 1-liter portions of hot cyclohexane. After 20 hours 3.7 g. of off-white crystals deposited for a total of 30.5 (56%). An analytical sample, m.p. 84-85°, was obtained from cyclohexane; λ (Nujol) 4.5 μ (CN), 5.85 (COOH).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.8; H, 5.86; N, 7.40. Found: C, 70.1; H, 5.84; N, 7.46.

1-Chloro-5-(*p*-cyanophenyl)-2-pentanone (XVIII).

A solution of 14.8 g. (0.07 mole) of the acid chloride (from XVII and thionyl chloride) in 120 ml. of ether was added to 0.18 mole of diazomethane in 270 ml. of ether. The remainder of the reaction was conducted as for IX above, except that a crystalline diazo ketone separated. This required the addition of dichloromethane to maintain solution during the treatment with dry hydrogen chloride. A yield of 10.4 g. (66%) of yellow crystals was obtained. Recrystallization from ether afforded white crystals, m.p. 71-72.5°.

Anal. Calcd. for $C_{12}H_{12}ClNO$: C, 65.0; H, 5.43; N, 6.29. Found: C, 64.9; H, 5.58; N, 6.28.

1-Azido-5-(*p*-cyanophenyl)-2-pentanone (XIX).

A mixture of 10.4 g. of XVIII, 22.0 g. of sodium azide and 300 ml. of 80% methanol was stirred 3.5 hours. The solvent was evaporated *in vacuo* and the aqueous residue partioned between dichloromethane and water. Removal of the solvent afforded 10.7 g. (100%) of the azido ketone as a syrup; λ (film) 4.50 (C≡N), 4.75 (N_3), 5.80 (C=O).

1-Amino-2,2-dimethoxy-5-(*p*-cyanophenyl)pentane (XXI).

A mixture of 10.7 g. of azido ketone (XIX), 1.5 g. of *p*-toluenesulfonic acid, 53.0 ml. of trimethyl orthoformate and 107 ml. of methanol was refluxed for 3.5 hours. The solvent was removed *in vacuo* and the residue was dissolved in 50 ml. of dichloromethane. The solution was added with stirring to 25 ml. of saturated sodium bicarbonate. After separation the aqueous portion was twice extracted with 25-ml. portions of dichloromethane. The dichloromethane was dried over magnesium sulfate and evaporated to leave 12.0 g. (93%) of the syrupy ketal; λ (film) 4.50 (C≡N), 4.75 (N_3), 9.50 (ketal), *no* C=O at 5.80 μ.

The ketal (11.8 g.), 9.5 g. of sodium borohydride and 240 ml. of 2-propanol was stirred at reflux for 20 hours. The solvent was removed and the residue partitioned between 50 ml. of dichloromethane and 100 ml. of water. The aqueous portion was extracted twice more with 50 ml. portions of dichloromethane. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to leave 9.4 g. (88%) of XXI as a syrup; λ (film) 3.0 μ (NH_2) 4.50 (C≡N), 9.50 (ketal), *no* N_3 at 4.75 μ.

1-Amino-4-phenyl-2-butanone (XXIV).

A mixture of 1.45 g. (5.3 mmoles) of di-*t*-butyl acetamidomalonate (7), 0.24 g. (5.6 mmoles) of sodium hydride (56% oil suspension), 0.03 ml. of *t*-amyl alcohol and 13 ml. of benzene was stirred at reflux for 4.75 hours. The mixture was cooled to room temperature and a solution of 0.89 g. (5.3 mmoles) of hydrocinnamoyl chloride in 8 ml. of benzene was added over 5 minutes. The mixture was stirred at reflux for 1.75 hours and cooled. A little Dry Ice was added followed by 15 ml. of water and 10 ml. of ether. The organic extract was washed with 10 ml. of saturated sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent left 2.05 g. of a syrup, which was digested with 12 ml. of hexane to leave 1.26 g. of the insoluble keto malonate intermediate.

The intermediate (1.05 g.) was refluxed with 15 ml. of 3 *N* hydrochloric acid for 6 hours and the solution was evaporated to dryness *in vacuo*. Ethanol (10 ml.) was added and evaporated followed by trituration with 20 ml. of ether to afford 0.33 g. of white, crystalline hydrochloride salt, m.p. 115-123°. The picrate, m.p. 131-134°, was prepared in water (30% yield overall) and recrystallized from ethanol for analysis.

Anal. Calcd. for $C_{16}H_{16}N_4O_8$: C, 49.0; H, 4.11; N, 14.3. Found: C, 49.4; H, 4.18; N, 14.5.

The semicarbazone (XXV) picrate, m.p. 177-179° (69%) and hydrochloride, m.p. 188-190° (87%) were prepared in a manner analogous to XII.

Anal. Picrate:--Calcd. for $C_{17}H_{19}N_7O_8$: C, 45.4; H, 4.27; N, 21.9. Found: C, 45.6; H, 4.38; N, 22.1. Hydrochloride:--Calcd. for $C_{11}H_{16}N_4O{\cdot}HCl$: C, 51.4; H, 6.67; N, 21.8. Found: C, 51.4; H, 6.84; N, 21.7.

1-Amino-5-phenyl-2-pentanone (XXVII).

The amino ketone picrate, m.p. 125-126° was prepared in a 24% yield from 4-phenylbutyryl chloride and di-*t*-butyl acetamidomalonate.

Anal. Calcd. for $C_{17}H_{18}N_4O_8$: C, 50.2; H, 4.47; N, 13.8. Found: C, 50.3; H, 4.55; N, 13.9.

Semicarbazone (XXVIII).

Anal. Picrate (55%), m.p. 168-169°;-- Calcd. for $C_{18}H_{21}N_7O_8$: C, 46.7; H, 4.57; N, 21.2. Found: C, 46.7; H, 4.73; N, 21.2. Hydrochloride (74%) m.p. 188-189°:--Calcd. for $C_{12}H_{18}N_4O{\cdot}HCl$: C, 53.2; H, 7.07; N, 20.7. Found: C, 53.2; H, 7.11; N, 20.3.

2-Amino-4-hydroxy-5-phenylazo-6-pyrimidinylamino Ketone Hydrochlorides.

To a solution of 250 mg. (10.9 mg.-atoms) of sodium in 70 ml. of absolute ethanol was added 3.7 g. (11.2 mmoles) of the semicarbazone hydrochloride (XIII). The mixture was stirred 15 minutes, then treated with 2.80 g. (11.2 mmoles) of 2-amino-4-hydroxy-5-phenylazo-6-chloropyrimidine in 28 ml. of dimethylformamide, followed by 2.20 ml. (16.8 mmoles) of *s*-collidine. The mixture was stirred at ambient temperature for 3 days and was diluted with an equal volume of water. After one hour the solid was collected, stirred with 25 ml. of ethanol and again collected by filtration. A solution of the yellow solid in 50 ml. of acetic acid was treated with 30 ml. of 2 *N* hydrochloric acid and the mixture allowed to stand for 1.5 hours. The yellow crystalline precipitate was collected, washed with 30 ml. of 0.5 *N* hydrochloric acid and dried to leave 3.4 g. of the pyrimidinylamino ketone hydrochloride (XIV). This general method was used to prepare the other ketones listed in Table II. However, the *p*-cyanophenylpropyl compound (XXII) was obtained from the ketal intermediate (XXI). In this case the sodium ethoxide treatment was omitted. The crude products were recrystallized from acetic acid-hydrochloric acid mixtures.

2-Amino-4-hydroxy-6-(*p*-carbethoxyphenethyl)pteridine (XV).

A hot (90-100°) solution of 2.0 g. of the phenylazo ketone (XIV) in 40 ml. of acetic acid was treated with 1.0 g. of zinc dust in small portions over a 30 minute period. The red solution became pale yellow and a precipitate appeared. The mixture was decanted from excess zinc and was diluted to 250 ml. with water. Concentrated hydrochloric acid (3 ml.) was added, with subsequent warming to give a yellow-green solution, which was filtered. The filtrate was cooled and treated with 3 ml. of 30% hydrogen peroxide. After 40 minutes the *p*H was adjusted to 4-5 with ammonia and the precipitate collected, washed with water and acetone and dried to leave 1.04 g. (77%) of off-white crystals. Digestion with warm dimethylformamide, followed by filtration and thorough washing with water afforded an analytical sample; UV λ (*p*H 13) 253 (ε 24,300), 365 (6,070).

Anal. Calcd. for $C_{17}H_{17}N_5O_3$: C, 60.2; H, 5.05; N, 20.6. Found: C, 59.9; H, 4.88; N, 20.6.

Closure to the dihydropteridine ring by catalytic reduction of XIV gave very poor yields apparently because of overreduction to a tetrahydro compound.

2-Amino-4-hydroxy-6-(*p*-carboxyphenethyl)pteridine (I).

A mixture of 1.05 g. of the ester (XV) and 10 ml. of 8% sodium hydroxide was heated for 1 hour on the steam bath under a nitrogen atmosphere. The resulting solution was chilled overnight and the crystalline sodium salt was collected. The solid was washed with a little 10% sodium hydroxide and redissolved in 70 ml. of water. The hazy solution was filtered and the clear filtrate was adjusted to *p*H 5 with concentrated hydrochloric acid to give a pale yellow precipitate. The material was collected, washed with water and dried to leave 0.78 g. (81%); UV λ (*p*H 13) 253 (ε 28,100), 367 (7,000).

Anal. Calcd. for $C_{15}H_{13}N_5O_3$: C, 57.9; H, 4.21; N, 22.5. Found: C, 57.9; H, 4.38; N, 22.1.

2-Amino-4-hydroxy-6-(*p*-cyanophenylpropyl)pteridine (XXIII).

A mixture of 6.4 g. of phenylazo ketone (XXII), 700 mg. of 5% palladium/carbon and 130 ml. of 50% methanol was stirred under one atmosphere of hydrogen for 22 hours. The theoretical amount of gas was consumed. The mixture was acidified with 6 *N* hydrochloric acid, the catalyst removed by filtration and the filtrate was treated with 2.1 ml. of 3% peroxide. The solution was kept at 25° for one hour and adjusted to *p*H 7-8 with ammonia to precipitate the pteridine. The solid was collected, washed with water and dried to leave 3.55 g. The crude material was treated with 25 ml. of hot dimethylformamide and filtered. After washing with water and drying 2.83 g. (70%) of product was obtained; UV λ (*p*H 13) 241 (ε 23,800), 252 (21,700), 370 (5,925); IR λ (Nujol) 4.50 μ (C≡N).

Anal. Calcd. for $C_{16}H_{14}N_6O$: C, 62.7; H, 4.61; N, 27.4. Found: C, 62.7; H, 4.67; N, 27.0.

2-Amino-4-hydroxy-6-(*p*-carboxyphenylpropyl)pteridine (II).

A solution of 2.0 g. of the cyano compound (XXIII) in 40 ml. of 10% sodium hydroxide was refluxed 19 hours and filtered. The filtrate was chilled for 4 hours and the crystallized sodium salt was collected. The material was dissolved in 40 ml. of water and the product precipitated at *p*H 4-5 by the addition of 6 *N* hydrochloric acid. The material was collected, washed with water and dried to leave 1.22 g. (58%). Treatment with hot dimethylformamide afforded an analytical sample; UV λ (*p*H 13) 252 (ε 27,300), 365 (7,070).

Anal. Calcd. for $C_{16}H_{15}N_5O_3{\cdot}1/4\ H_2O$: C, 58.3; H, 4.71; N, 21.2. Found: C, 58.1; H, 4.42; N, 21.2.

2-Amino-4-hydroxy-6-phenethylpteridine (III).

This compound was obtained from the phenylazo ketone (XXVI) by the method used to prepare XXIII. Treatment of the crude product with hot dimethylformamide afforded a 35% yield of pale yellow crystals; UV λ (*p*H 13) 253 (ε 22,600), 367 (6,600).

Anal. Calcd. for $C_{14}H_{13}N_5O$: C, 62.9; H, 4.90; N, 26.2. Found: C, 62.9; H, 4.90; N, 25.9.

Baker and Ho (5) prepared this compound by a route that did not exclude formation of the 7-isomer. They observed λ (*p*H 13) 254 (ε 23,200) and 365 (7,200).

2-Amino-4-hydroxy-6-phenylpropylpteridine (IV).

This pteridine was prepared from XXIX in a 73% yield by the above procedure; UV λ (*p*H 13) 253 (ε 19,100), 368 (5,900).

Anal. Calcd. for $C_{15}H_{15}N_5O$: C, 64.0; H, 5.37; N, 24.9. Found: C, 64.0; H, 5.32; N, 25.0.

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REFERENCES

(1) Stanford Research Institute.

(2) Tufts University School of Medicine, Boston, Mass. 02111.

(3) J. I. DeGraw, V. H. Brown, M. Cory, P. Tsakotellis, R. L. Kisliuk and Y. Gaumont, *J. Med. Chem.*, (in press).

(4) J. I. DeGraw, J. P. Marsh, E. M. Acton, O. P. Crews, C. W. Mosher, A. Fujiwara and L. Goodman, *J. Org. Chem.*, **30**, 3404 (1965).

(5) B. R. Baker and B. T. Ho, *J. Pharm. Sci.*, **54**, 1261 (1965).

(6) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(7) A. W. Schrecker and M. M. Trail, *J. Am. Chem. Soc.*, **80**, 6077 (1958).

(8) W. Löw, *Ann. Chem.*, **231**, 361 (1885).

(9) L. R. Moffett and H. W. Vaughn, *J Org. Chem.*, **25**, 1238 (1960).