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# Pteridine Chemistry. VII. Methylation Studies. II. Some 8-Methyl Derivatives

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The methylation of 2-amino-4-hydroxypteridine-6-carboxylic acid (I) with excess dimethyl sulfate in an alkaline solution has been shown to give a mixture of the 1-methyl derivative, III, the 3-methyl derivative, II, and the 3,8-dimethyl derivative, IV, of the starting material I. Similarly, the methylation of 2,4-dihydroxypteridine-6-carboxylic acid (X) gave a mixture of the 1,3-dimethyl derivative, XI, and the 3,8-dimethyl derivative, XII, of X while the methylation of 2-amino-4-hydroxypteridine-7-carboxylic acid gave only the two monomethyl derivatives.

The reaction between 2-amino-4-hydroxypteridines and acrylonitrile has been shown to produce 8,9-dihydro-11*H*-pyrimido[2,1-*b*]pteridine-7(6*H*),11-diones.[1] This reaction involved the alkylation of the nitrogen in the 3-position of the pteridine nucleus and no isomeric compounds were detected. In contrast, we have shown that the methylation of 2-amino-4-hydroxy-6,7-dimethylpteridine with dimethyl sulfate in an aqueous alkaline solution gives a mixture of 1- and 3-monomethyl derivatives in nearly equal amounts.[2] As 2-amino-4-hydroxypteridine-6-carboxylic acid (I) had given the best yield of a single isomer in the acrylonitrile reaction,[1] comparison of these two different types of alkylations was continued by studying the methylation of I. This report describes the somewhat different results of this study.

Compound I was methylated with excess dimethyl sulfate in an aqueous alkaline solution in a manner similar to that used with 2-amino-4-hydroxy-6,7-dimethylpteridine.[2] Acidification of the reaction mixture to *p*H 1 gave a crude product (31% yield) which consisted primarily of the 1- and 3-monomethyl derivatives of I. The two products were separated by fractional crystallization from dilute hydrochloric acid and their structures finally proved by reaction with a dilute sodium hydroxide solution, whereupon the 3-methyl derivative (II) rearranged to 2-methylamino-4-hydroxypteridine-6-carboxylic acid (V) while the 1-methyl derivative (III) was hydrolyzed to 1-methyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (VI). These are reactions which had previously been shown to occur with the 1- and 3-monomethyl derivatives of 2-amino-4-hydroxy-6,7-dimethylpteridine.[3]

The reaction solution left after removal of II and III contained a third compound which was obtained as a crystalline product either by adjustment of the *p*H to 3.5 or by the addition of concentrated hydrochloric acid to give a 2.5*N* hydrochloric acid solution. In the latter case the product (25% yield) was a hydrochloride. Elemental analysis showed this to be a dimethyl derivative of I. It was shown to be 3,8-dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (IV) by means of several observations and reactions. The methylation of the 3-methyl derivative (II) with dimethyl sulfate either in an aqueous alkaline solution at *p*H 8 to 11.5 or in a dimethylformamide–acetic acid solution gave IV in yields of 40% and 34%, respectively, whereas the attempted methylation of the 1-methyl derivative (III) in water at *p*H 8 to 11.5 gave nothing but starting material. Assuming no rearrangement had occurred, this showed the presence of a 3-methyl substituent in IV. That no rearrangement had occurred was indicated when it was shown that IV in dilute sodium hydroxide at room temperature or in hot sodium bicarbonate solution did undergo the now well known rearrangement[1,3] to an isomeric compound which was shown to be 2-methylimino-8-methyl-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (VII).[4] The ultraviolet absorption spectra of IV and VII are quite characteristic and entirely unlike the spectra of such compounds as I, II, and III. In 0.1*N* hydrochloric acid and at *p*H 7, IV and VII both exhibit strong absorption in the region of 395–405 mμ while in 0.1*N* sodium hydroxide the long wave-length maxima are at 348 mμ (IV) and 363 mμ (VII). These spectra very closely resemble the spectra reported by Fidler and Wood[5] for 2-imino-6,7,8-trimethyl-4-oxo-2,3,4,8-tetrahydropteridine prepared from 2,5-diamino-6-methylamino-4-hydroxypyrimidine and butane-2,3-dione. In addition, these compounds (IV and VII) are more basic than II or III, as evidenced by their ready conversion to hydrochlorides and their solubility in dilute acid. In this property they also resemble the compound prepared by Fidler and Wood.

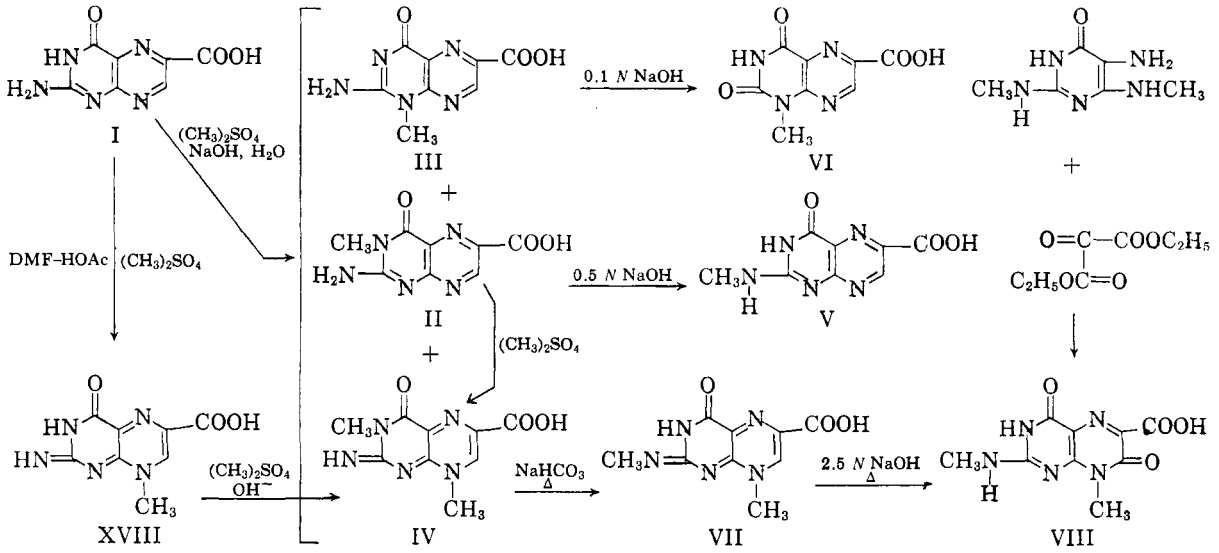
(1) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, 81, 5650 (1959).

(2) R. B. Angier and W. V. Curran, *J. Org. Chem.*, 26, 2129 (1961).

(3) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, 80, 6095 (1958).

(4) In subsequent methylations using larger quantities of 2-amino-4-hydroxypteridine-6-carboxylic acid (I), the rearranged 2-methylimino-8-methyl derivative VII was also isolated. In such cases the yield of the 3,8-dimethyl derivative IV was lower than in smaller scale experiments.

(5) W. E. Fidler and H. C. S. Wood, *J. Chem. Soc.*, 4157 (1957).



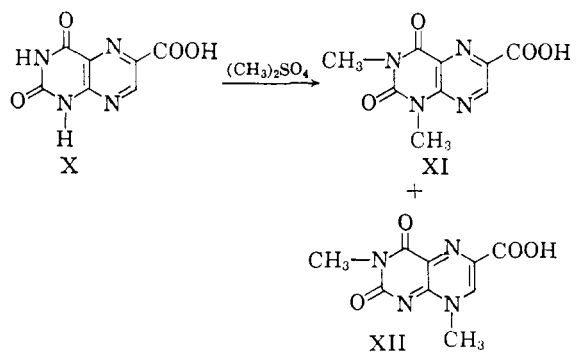

The final proof of structure of these compounds was obtained in a rather unexpected manner. When a solution of either VII or IV in 2.5*N* sodium hydroxide was heated forty five minutes on a steambath and cooled, a crystalline sodium salt separated (25% yield). The purified acid obtained from this salt had elemental analyses and ultraviolet absorption spectra[6] which suggested that it was 2-methylamino-4-hydroxy-8-methyl-7-oxo-7,8-dihydropteridine-6-carboxylic acid (VIII). This structure was confirmed by an independent synthesis of VIII from 2,6-bis(methylamino)-5-amino-4-hydroxypyrimidine and diethyl ketomalonate.

The production of VIII from VII in an alkaline solution has some precedent. Albert has described the disproportionation of 6-hydroxypteridine in dilute sodium hydroxide, the products being 6,7 - dihydroxypteridine and 6-hydroxy-7,8-dihydropteridine.[7] Chromatographic examination of our reaction mixture has shown the presence of several products in addition to VIII, but they have not been obtained in a pure state. That it was not a simple air oxidation of VII was indicated by the failure to change the yield of the 7-oxo derivative VIII when either oxygen or nitrogen was bubbled through the reaction mixture.

With these results before us, a reinvestigation of the methylation of 2-amino-4-hydroxy-6,7-dimethylpteridine[2] has now led to the isolation of 2-imino-3,6,7,8-tetramethyl-2,8-dihydro-4(3*H*)-pteridinone in an 8–10% yield and 2-imino-1,3,6,7-tetramethyl-1,2-dihydro-4(3*H*)-pteridinone in a 1% yield. Details of this work are being published in a subsequent paper.

The fact that the 6-carboxylic acid derivative I gave a higher proportion of 8-substitution than 2-amino-4-hydroxy-6,7-dimethylpteridine might be attributed to one or more of several factors. Although not easily explained, the presence of an electron withdrawing carboxyl group versus the electron donating methyl group in the 6-position may be the controlling element in the reaction. On the other hand, the important factor may be the difference in the steric effect resulting from the presence or absence of a methyl group in the 7-position.

As the first step in investigating the effect of various substituents on this type of reaction, we undertook the methylation of 2,4-dihydroxypteridine-6-carboxylic acid (X). 2,4-Dihydroxypteridine has been methylated with dimethyl sulfate[8] and with diazomethane.[9] In each case the only product reported was 1,3-dimethyl-2,4(1*H*,3*H*)-pteridinedione. However, when X was methylated with dimethyl sulfate in aqueous alkali in the usual manner, two dimethyl derivatives were obtained. The major product (73% yield) was 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (XI) contaminated with a little of its pyrazine degradation product XIII, while the minor product (16% yield) was 3,8-dimethyl-2,4-dioxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (XII). The 1,3-dimethyl derivative XI is a white compound




(6) E. C. Taylor and H. M. Loux, *J. Am. Chem. Soc.*, **81**, 2474 (1959).

(7) A. Albert, *J. Chem. Soc.*, 2690 (1955).

(8) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).

(9) W. Pfleiderer, *Chem. Ber.*, **90**, 2582 (1957).

with ultraviolet absorption spectra similar to the spectra of other 1,3-dimethyl-2,4-pteridinediones[8,10] and essentially identical with the spectra of 1,3-bis(2 - cyanoethyl) - 2,4 - dioxo - 1,2,3,4 - tetrahydropteridine-6-carboxylic acid.[10] As with other 1,3-dimethyl-2,4-pteridinediones,[8] compound XI underwent a very facile ring cleavage in dilute alkali to give 5-methylamino-6-(*N*-methyl)carboxamidopyrazine-2-carboxylic acid (XIII). The isomeric 3,8-dimethyl derivative XII is a yellow compound with ultraviolet absorption spectra very similar to the spectra of the corresponding 2-imino-3,8-dimethyl derivative IV. Compound XII is more stable than its isomer XI in an alkaline solution, although it does slowly decompose to products whose structures have not been determined. An attempt to relate the two series by converting the 2-imino derivative IV to the 2-oxo derivative XII was unsuccessful; the 2-imino derivative IV was completely stable to refluxing 8*N* hydrochloric acid for fourteen hours and was not hydrolyzed by hot nitrous acid.

A methylation reaction was then carried out on 2-amino-4-hydroxypteridine-7-carboxylic acid (XIV). Once again the 3-methyl XV and 1-methyl XVI derivatives were obtained. However, in this case no 8-methyl derivative was detected. Furthermore, when the 3-methyl derivative XV was treated with dimethyl sulfate in a hot dimethylformamide–acetic acid solution, although the starting material slowly disappeared, decomposition occurred and no product could be isolated. Thus, while a carboxylic acid group in the 6- position does seem to facilitate methylation at position 8, the same group in the 7- position appears to hinder this reaction.

As this portion of the work was finished, Brown and Jacobsen[11] reported on the reaction between 2-amino-4-hydroxypteridine and methanolic methyl iodide at 100° for twelve hours in which the sole product was 2-amino-4,8-dihydro-8-methyl-4-oxopteridine. Although we had methylated several 3-methyl-4-pteridinones under neutral or acidic conditions, no such reaction had been run on 2-amino-4-hydroxypteridines which lacked an *N*-methyl group. Therefore, 2-amino-4-hydroxypteridine-6-carboxylic acid (I) was treated with excess dimethyl sulfate in a boiling dimethylformamide-acetic acid solution for ten minutes. The sole isolated product was indeed an 8-monomethyl derivative, 2-imino-8-methyl-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (XVIII) (58% yield), as shown by the very close similarity of its ultraviolet absorption spectra to the spectra of VII. However, paper chromatography showed the presence of small amounts of the 1-methyl derivative III and the 3,8-dimethyl derivative IV. The 8-monomethyl derivative XVIII was readily converted to the 3,8-dimethyl derivative IV by treatment with dimethyl sulfate in water at *p*H 8–11.

A tentative conclusion which can be made from the results of this portion of our work and Brown's report[11] is that a neutral pteridine molecule similar to I undergoes preferential *N*-methylation in the pyrazine ring at the 8-position, but that in a basic solution the negative charge which is generated is located primarily in the pyrimidine ring so that methylation occurs preferentially at the 1- and 3-nitrogens.

In order to study in more detail the effect of the hydrogen ion concentration and the solvent on this reaction, the 3-methyl derivative II and the 8-methyl derivative XVIII were treated separately with excess dimethyl sulfate under four sets of conditions: (1) aqueous alkali at *p*H 8 to 11 at room temperature, (2) aqueous sodium bicarbonate (*ca.* *p*H 7.5) at room temperature, (3) aqueous sodium acetate (*ca.* *p*H 4.5) at room temperature, and (4) a dimethylformamide–acetic acid solution at 100°. The 3-methyl derivative II was readily converted to the 3,8-dimethyl derivative IV under all four sets of conditions. The 8-methyl derivative XVIII was converted to IV at about the same rate under conditions (1) and (2), while under condition (3) there was no reaction and under condition (4) there was only a very slow and incomplete reaction. This further emphasizes that the easy methylation of the pyrimidine ring nitrogens of a 2-amino-4-hydroxypteridine requires the presence of a pteridine anion.

Finally, the treatment of the 3-methyl derivative XVIII with dimethyl sulfate at 100° in dimethylformamide containing a small amount of sulfuric acid resulted in a slow and incomplete reaction indicating that acid inhibits methylation and that it is actually the neutral molecule which is readily methylated in the 8- position.

## EXPERIMENTAL[12]

All of the compounds reported here as well as most of the reaction mixtures were examined by paper chromatography using the descending technique with Whatman No. 1 paper.

All evaporations were carried out under reduced pressure unless otherwise noted.

*Methylation of 2-amino-4-hydroxypteridine-6-carboxylic acid* (I). A. 2-Amino-4-hydroxypteridine-6-carboxylic acid (9.0 g., 43.5 mmoles) was dissolved in a solution of 300 ml. of water and 90 ml. of 1.0*N* sodium hydroxide. The solution was stirred continuously at room temperature and 4.4 ml. (45 mmoles) of dimethyl sulfate was added. After a period of 45 min., 22.5 ml. of 1.0*N* sodium hydroxide and 2.2 ml. of dimethyl sulfate were added. Thereafter at intervals of about 30 min., 22.5-ml. portions of 1.0*N* sodium hydroxide and 2.2-ml. portions of dimethyl sulfate were added five additional times so that a total of 17.6 ml. of dimethyl sulfate had been used (the *p*H varied between about 8.0 and 11.5 during this period). After the final addition the mixture was

(10) W. V. Curran and R. B. Angier, *J. Org. Chem.*, **27**, in press (1962).

(11) D. J. Brown and N. W. Jacobsen, *Tetrahedron Letters*, No. **25**, p. 17 (1960).

(12) The melting points have been corrected for the exposed stem of the thermometer.

stirred for 2 hr. and then acidified to approximately *p*H 1 with 9 ml. of concentrated hydrochloric acid. This was heated to boiling, then cooled to 5° for 1 hr., and the crystalline product was collected; yield 3.0 g. (31%). This was primarily a mixture of the 1- and 3-monomethyl derivatives of the starting material. Its purification will be described later.

After having been treated with Norit,[13] the filtrate (550 ml.) was diluted with 125 ml. of concentrated hydrochloric acid and cooled overnight; yield of yellow crystalline product 3.4 g. (25%). This was dissolved in 380 ml. of hot 0.3*N* hydrochloric acid, which was treated with Norit, filtered, diluted with 70 ml. of concentrated hydrochloric acid, and cooled to give a yellow crystalline product; yield 2.6 g. (19%).

For analytical purposes a sample (500 mg.) was recrystallized in the same manner; yield 430 mg. of 3,8-dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (IV) as its dihydrate, monohydrochloride; $R_f$ 0.84 (3% $NH_4$ Cl) (bluish-green but became blue when fumed with ammonia), 0.73 (0.5% $Na_2CO_3$) (blue); ultraviolet absorption spectra in 0.1*N* sodium hydroxide, $\lambda_{max}$ 251 mμ (ε15, 100), 283 mμ (ε 7,700), 348 mμ (ε 12,600): 0.1N HCl, $\lambda_{max}$ 272 mμ (ε 17,700), 296 mμ (ε 14,100), 393 mμ (ε 12,300).

*Anal.* Calcd. for $C_9H_9N_5O_3 \cdot 2H_2O \cdot HCl$ (308): C, 35.1; H, 4.6; N, 22.7; Cl, 11.5. Found: C, 35.0; H, 4.7; N, 22.6; Cl, 11.5.

A sample was dried at 100° and converted to the anhydrous material.

*Anal.* Calcd. for $C_9H_9N_5O_3 \cdot HCl$ (272): N, 25.8. Found: N, 25.5.

A sample (140 mg.) was converted to the free base by a recrystallization from 30 ml. of water; yield 90 mg.

*Anal.* Calcd. for $C_9H_9N_5O_3$ (235): C, 46.0; H, 3.9; N, 29.8. Found: C, 45.7; H, 4.4; N, 29.4.

The mixture (3 g.) of the 1- and 3-monomethyl derivatives obtained as the first product in this reaction was dissolved in a hot solution of 5 ml. of pyridine in 750 ml. of water. This solution was treated with Norit, filtered, reheated to boiling, and then acidified with 32 ml. of concentrated hydrochloric acid. After about 3 min. this was treated with Norit and filtered. After the filtrate had been cooled overnight, the product was collected, washed with water, acetone, and ether, and dried; yield, 1.5 g. The solid was purified once more in the same manner using 140 ml. of water, 3.3 ml. of pyridine, and finally 25 ml. of concentrated hydrochloric acid; yield of crystalline product, 0.8 g. This material (Fraction A) was primarily the 3-methyl derivative (II) of the starting material.

The filtrates from the last two filtrations were combined, brought to *p*H 2 with 10.0*N* sodium hydroxide, and cooled. The product was collected and redissolved in 80 ml. of a hot 2% sodium carbonate solution which was then treated with Norit and filtered. Sodium carbonate (1.8 g.) was added to the hot filtrate which was then cooled quickly to give a crystalline sodium salt of the 1-methyl derivative (III); yield 0.6 g.; paper chromatography showed this to be pure.

For analyses, a portion (200 mg.) of this material was converted to the acid by solution in 75 ml. of water followed by acidification to *p*H about 1 with concentrated hydrochloric acid. 2-Amino-1-methyl-4-oxo-1,4-dihydropteridine-6-carboxylic acid (III) separated as pale yellow crystals; yield 120 mg.; m.p. 295–299° (dec.); $R_f$ 0.80 (0.5% $Na_2CO_3$) (abs.), 0.69 (3% $NH_4Cl$) (abs.); ultraviolet absorption spectra in 0.1*N* HCl, $\lambda_{max}$ 233 mμ (ε 11,500) 264 mμ (ε 12,000), 319 mμ (ε 10,100); *p*H 7.0 and .1*M* $Na_2B_4O_7$(pH 9.2), $\lambda_{max}$ 250 mμ (ε 21,200), 330 mμ (ε 10,200).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221); C, 43.4; H, 3.2; N, 31.7. Found: C, 43,3; H, 3.5; N, 31.5.

The 3-methyl derivative (Fraction A; 0.8 g.) was recrystallized as its sodium salt from 65 ml. of a 0.5% sodium carbonate solution; yield 0.65 g.; paper chromatography showed this to be pure.

For analyses a solution of 150 mg. of the sodium salt in 50 ml. of hot water was treated with Norit, filtered, reheated to boiling, and acidified to *p*H 1 with 0.3 ml. of concentrated hydrochloric acid. 2-Amino-3-methyl-4-oxo-3,4-dihydropteridine-6-carboxylic acid (II) crystallized quickly; yield 100 mg.; m.p. 300–301° (dec.); $R_f$ 0.70 (0.5% $Na_2CO_3$) (deep blue); 0.63 (3% $NH_4Cl$) (deep blue); ultraviolet absorption spectra in 1.0 *N* HCl, $\lambda_{max}$ 240 mμ (ε 13,700), 260 mμ (sh) (ε 9,900), 322 mμ (ε 9,500); pH 7.0 and .1*M* $Na_2B_4O_7$ (*p*H 9.2), $\lambda_{max}$ 243 mμ (ε 15,000), 288 mμ (ε 16,100), 355 mμ (ε 8,200).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221): C, 43.4; H, 3.2; N, 31.7. Found: C, 43.3; H, 3.2; N, 31.7.

B. 2-Amino-4-hydroxypteridine-6-carboxylic acid (27.0 g., 0.13 mole) was methylated with dimethyl sulfate in an aqueous alkaline solution in exactly the same manner as described under A above; yield of the first crop of product 9.7 g. This again was primarily a mixture of the 1- and 3-monomethyl derivatives of the starting material.

In this run, the initial yield of 3,8-dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid · dihydrate hydrochloride (IV) was 8.0 g. (20%).

The filtrate from IV was brought to *p*H 3.5 by the addition of about 1 lb. of sodium acetate and cooled overnight. A crystalline product separated; yield 1.6 g. A solution of this product in 35 ml. of hot 1*N* hydrochloric acid was treated with Norit, filtered, and mixed with 25 ml. of concentrated hydrochloric acid. When cooled the solution deposited a yellow crystalline product; yield 1.4 g. (4%). Paper chromatography and ultraviolet and infrared absorption spectra showed this to be 2-methylimino-8-methyl-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (VII). Another preparation of **VII** is described below.

*3,8-Dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid* (**IV**). A. Compound IV was first prepared during the methylation of I as described above.

B. A solution of 4 ml. of water, 0.75 ml. of 1.0*N* sodium hydroxide, and 100 mg. (0.45 mmole) of 2-amino-3-methyl-4-oxo-3,4-dihydropteridine-6-carboxylic acid (II) was treated immediately with 0.05 ml. (0.5 mmole) of dimethyl sulfate. The solution was stirred for 45 min. at room temperature and then treated with 0.5 ml. of 1.0*N* sodium hydroxide and 0.05 ml. of dimethyl sulfate. After 45 min. this was repeated once more and stirring was continued for 1 hr. The mixture was then brought to pH 1.0 with hydrochloric acid, heated to 75°, cooled well for about 1 hr., and filtered to remove a little solid. The filtrate (6.0 ml.) was mixed with 2.0 ml. of concentrated hydrochloric acid and cooled. The yellow crystalline product was collected; yield 55 mg. (40%) of the dihydrate monohydrochloride of IV. The infrared spectra and chromatographic behavior of this product and the corresponding product obtained by the methylation of I were identical.

C. A mixture of 10.0 ml. of dimethylformamide, 90 mg. (0.41 mmole) of II, 0.5 ml. of acetic acid, and 0 25 ml. (2.7 mmole) of dimethyl sulfate was heated on the steam bath for 45 min. with an additional 0.25 ml. of dimethyl sulfate being added after 20 min. heating. The solution was evaporated to about 2 ml., diluted to 6 ml. with water, heated to boiling, treated with Norit, and filtered. The solution was cooled, brought to *p*H 3.5–4.0 with sodium acetate, and cooled further. A yellow crystalline product separated; yield 32 mg. (34%) of IV as the free base.

D. A solution of 3.5 ml. of water, 1.25 ml. of 1.0*N* sodium hydroxide, and 120 mg. (0.5 mmole) of 2-imino-8-methyl-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (XVIII) was methylated with dimethyl sulfate exactly as described under B above; yield 80 mg. (58%) of the dihydrate monohydrochloride of IV identical with the product obtained under B.

*Ethyl 3,8-dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylate hydrochloride* (IX). A solution of 0.90 g. (2.9 mmoles) of IV in 200 ml. of ethanol saturated with

(13) Norit is the trademark of the American Norit Co. for activated charcoal.

hydrogen chloride was heated to reflux for 3.5 hr. and then evaporated to dryness several times with ethanol. During this process a crystalline product separated. Finally 50 ml. of ethanol was added, the mixture was cooled and the product collected; yield 0.70 g. (80%); m.p. 238–241°.

A portion (160 mg.) of this material was recrystallized from 25 ml. of ethanol containing a small amount of hydrogen chloride, yield 90 mg.; m.p. 242–243° (dec.) when placed in a bath at 210° with the temperature rising at 4° per minute at 240°.

*Anal.* Calcd. for $C_{11}H_{13}N_5O_3 \cdot HCl$ (300): C, 44.2; H, 4.8; N, 23.4; Cl, 11.9. Found: C, 43.9; H, 4.9; N, 23.8; Cl, 12.1.

*8-Methyl-2-methylimino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid* (VII). A. A solution of 310 mg. (1.0 mmole) of 3,8-dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid dihydrate hydrochloride (IV), 300 mg. of sodium bicarbonate, and 12 ml. of water was heated on the steambath for 30 min., then treated with Norit, filtered and acidified to *p*H 3.0 with concentrated hydrochloric acid. After having been cooled the mixture was filtered. The collected solid was suspended in 4 ml. of water containing 0.3 ml. of concentrated hydrochloric acid, warmed to 35°, treated with Norit, and filtered to remove a small amount of solid. The filtrate was mixed with 4 ml. of concentrated hydrochloric acid and cooled to give a yellow crystalline product; yield 140 mg. (50%); $R_f$ 0.70 (3% $NH_4Cl$) (greenish-yellow); ultraviolet absorption spectra in 0.1 *N* NaOH $\lambda_{max}$ 254 mμ (ε 12,700), 282 mμ (ε 8,900), 364 mμ (ε 13,000); pH 7.0, $\lambda_{max}$ 285 mμ (ε 21,600), 408 mμ (ε 10,000); 0.1*N* HCl, $\lambda_{max}$ 296 mμ (ε 18,300), 392 mμ (ε 11,500).

*Anal.* Calcd. for $C_9H_9N_5O_3 \cdot HCl$ (272): C, 39.8; H, 3.7; N, 25.8; Cl, 13.1. Found: C, 39.5; H, 3.9; N, 25.4; Cl, 13.0.

B. A low yield of VII was also obtained from the methylation of I as described above.

C. IV could also be converted to VII using 1.0*N* sodium hydroxide at room temperature for one day.

*2-Imino-8-methyl-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid* (XVIII). 2-Amino-4-hydroxypteridine-6-carboxylic acid (5.0 g., 24 mmole), 100 ml. of dimethylformamide, 10 ml. of acetic acid, and 17.5 ml. of dimethyl sulfate were mixed and heated to boiling with intermittent stirring for 12 min. The solution was evaporated to a small volume. Water (50 ml.) was added and the solution was heated 15 min. on the steam bath and then evaporated again to a small volume. The residue was dissolved in 100 ml. of water and the resulting hot solution was treated with Norit, filtered, and brought to *p*H 3 with sodium acetate. The solution was cooled overnight and the crystalline product was collected; yield 3.1 g. (58%). This product was recrystallized (Norit) from 150 ml. of 1.0*N* hydrochloric acid to give the hydrochloride of XVIII; tan crystals; yield 2.0 g. (32%); $R_f$ 0.77 (3% $NH_4Cl$); ultraviolet absorption spectra in 0.1*N* NaOH $\lambda_{max}$ 253 mμ (ε 14,500), 277 mμ (ε 6,200), 360 mμ (ε 13,200); pH 7.0, $\lambda_{max}$ 280 mμ (ε 21,800), 400 mμ (ε 10,300); 0.1*N* HCl, $\lambda_{max}$ 272 mμ (ε 11,900), 298 mμ (ε 15,700); 390 mμ (ε 11,400).

*Anal.* Calcd. for $C_8H_7N_5O_3 \cdot HCl$ (258): C, 37.2; H, 3.1; N, 27.1; Cl, 13.8. Found: C, 37.4; H, 3.3; N, 27.5; Cl, 13.5.

*2-Methyl-amino 4-hydroxypteridine-6-carboxylic acid* (V). A solution of 135 mg. (0.61 mmoles) of 2-amino-3-methyl-4-oxo-3,4-dihydropteridine-6-carboxylic acid (II) in 20 ml. of 0.5*N* sodium hydroxide was heated on the steam bath for 30 min., treated with Norit, and filtered. The filtrate was heated to boiling, acidified to *p*H 1 with concentrated hydrochloric acid (about 1.0 ml.) and cooled. The crystalline solid was collected; yield 95 mg. (70%).

This was dissolved in 20 ml. of hot water containing 0.15 ml. of pyridine. The boiling solution was acidified with 0.4 ml. of concentrated hydrochloric acid, treated with Norit, filtered and cooled. The crystalline product was collected; yield 75 mg. (55%). The $R_f$'s of this product in 0.5% sodium carbonate and 3% ammonium chloride were the same as starting material. However, in isopropyl alcohol-1*N* ammonium hydroxide (7:3) the two compounds were readily differentiated. Ultraviolet absorption spectra in 0.1*N* NaOH, $\lambda_{max}$ 273 mμ (ε 21,800), 370 mμ (ε 10,000); *p*H 7.0, $\lambda_{max}$ 290 mμ (ε 18,600), 354 mμ (ε 8,300); 1.0*N* HCl, $\lambda_{max}$ 264 mμ (ε 12,600), 321 mμ (ε 9,400).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221): C, 43.4; H, 3.2; N, 31.7. Found: C, 43.5; H, 3.6; N, 31.6.

*1-Methyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid* (VI). A solution of 145 mg. (0.66 mmole) of 2-amino-1-methyl-4-oxo-1,4-dihydropteridine-6-carboxylic acid (III) in 7.0 ml. of 0.1*N* sodium hydroxide was heated on the steam bath for 20 min. The solution was then treated with Norit, filtered, and acidified while hot with 2.0 ml. of 1.0*N* hydrochloric acid. The resulting mixture was cooled and the crystalline product was collected; yield 100 mg. (69%). This was suspended in 25 ml. of 0.6*N* hydrochloric acid, heated to boiling and cooled. The crystalline product was collected and redissolved in 20 ml. of hot water by adding 0.1 ml. of pyridine. Acidification of this solution with 1 ml. of concentrated hydrochloric acid followed by cooling gave a crystalline product; yield 50 mg.; m.p. 277–280° (dec.) $R_f$ 0.77 (3% $NH_4Cl$) (absorption spot became a purple fluorescent spot when fumed with ammonia); ultraviolet absorption spectra in 0.1*N* NaOH, $\lambda_{max}$ 255 mμ (ε 18,900), 341 mμ (ε 8,800); pH 7.0, $\lambda_{max}$ 235 mμ (ε 11,900), 264 mμ (ε 13,600), 333 mμ (ε 8,700); 0.1*N* HCl, $\lambda_{max}$ 238 mμ (ε 9,800), 271 mμ (ε 13,200), 332 mμ (ε 8,700).

*Anal.* Calcd. for $C_8H_8N_4O_4$ (220): C, 43.3; H, 2.7; N, 25.2. Found: C, 43.0; H, 2.9; N, 25.4.

*2-Methylamino-4-hydroxy-8-methyl-7-oxo-7,8-dihydropteridine-6-carboxylic acid* (VIII). A. 3,8-Dimethyl-2-imino-4-oxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid dihydrochloride (IV) (1.0 g., 3.25 mmoles) was dissolved in a preboiled hot solution of 50 ml. of 2.5*N* sodium hydroxide. This was heated on the steam bath for 45 minutes and then cooled overnight. The white crystalline product was collected; yield, 220 mg. (25%). Chromatography indicated that this material was pure. The product was dissolved in 2.2 ml. of warm water and then diluted with 2.5 ml. of 10*N* sodium hydroxide. The solution was cooled to give a white crystalline product; yield 120 mg. This sodium salt was converted to the free acid using 50 ml. of water and 1 ml. of concentrated hydrochloric acid; yield 60 mg.; $R_f$ 0.70 (0.5% $Na_2CO_3$) (deep blue); ultraviolet absorption spectra in 0.1*N* NaOH, $\lambda_{max}$ 265 mμ (ε 12,000), 375 mμ (ε 19,300); pH 7.0, $\lambda_{max}$ 220 mμ (ε 32,200), 296 mμ (ε 9,800), 359 mμ (ε 17,000).

*Anal.* Calcd. for $C_9H_9N_5O_4$ (251): C, 43.0; H, 3.6; N, 27.9. Found: C, 43.3; H, 4.1; N, 28.2.

Using the same procedure, VII was converted to VIII in approximately the same yield.

B. 2,4-Bis(methylamino)-5-amino-6-hydroxypyrimidine (1.2 g., 7.1 mmoles) was dissolved in 100 ml. of hot water containing a pinch of sodium hydrosulfite. To the resulting light yellow solution was added 5 ml. of diethyl ketomalonate to give a deep orange solution. This was heated on the steam bath for about 5 min. after which the reaction mixture was allowed to stand at room temperature for several days before the product was collected and dried The yield of ethyl 2-methylamino-4-hydroxy-8-methyl-7-oxo-7,8-dihydropteridine-6-carboxylate was 1.3 g. (66%); $R_f$ 0.49 (0.5% $Na_2CO_3$) (purple) with a small amount of $R_f$ 0.72 (purple) which undoubtedly was the corresponding free acid.

One gram (3.6 mmoles) of this ester was heated for 30 min. on a steam bath in a solution of 20 ml. of 1*N* sodium hydroxide and 40 ml. of water. The resulting solution was poured into 500 ml. of water, brought to boiling, and acidified to *p*H 5 with 2.0 ml. of glacial acetic acid to give immediate crystallization of the product. Paper chromatography of the isolated product (0.85 g.) in 0.5% sodium carbonate revealed that hydrolysis was incomplete, therefore it was retreated with 0.5*N* sodium hydroxide (150 ml.) on a steam bath for 30 minutes, diluted with 350 ml. of boiling water and finally acidified to *p*H 2.0 with 7 ml. of concentrated hydrochloric

acid; yield 0.75 g. (77% from ester) of chromatographically pure material. This was shown to be identical with the product (VIII) prepared as described under A above by infrared and ultraviolet absorption spectra and paper chromatography in 0.5% sodium carbonate.

*2,4-Dihydroxypteridine-6-carboxylic acid* (X).[14,15] A solution of 10.0 g. of 2-amino-4-hydroxypteridine-6-carboxylic acid (I) in 500 ml. of hot 0.2*N* sodium hydroxide was mixed with 1000 ml. of concentrated hydrochloric acid and heated to reflux for 30 hr. The product was collected by filtering the hot solution; yield 7.0 g. The filtrate was returned to the flask and heated to reflux for 18 hr. The mixture was evaporated to a volume of 1100 ml. and filtered at 50°; yield 2.4 g.; total yield 94%. Both fractions were chromatographically pure and identical with a sample prepared by another method[14]; $R_f$ 0.75 (0.5% $Na_2CO_3$) (blue); 0.67 (3% $NH_4Cl$) (absorption spot which turns blue when fumed with ammonia).

*Methylation of 2,4-dihydroxypteridine-6-carboxylic acid* (X). A solution of 9.2 g. (44.6 mmoles) of X in 270 ml. of water and 89 ml. of 1.0*N* sodium hydroxide was stirred well at room temperature and treated with 4.2 ml. (45 mmole) of dimethyl sulfate. With continuous stirring, portions of dimethyl sulfate (DMS) and 1.0*N* sodium hydroxide (base) were added at the times and in the amounts indicated: 20 minutes, 22.5 ml. of base, 4.2 ml. of DMS; 60 min., 45 ml. of base, 4.2 ml. of DMS; 110 min., 45 ml. of base, 4.2 ml. of DMS; 4.5 hr., 22 ml. of base, 4.2 ml. of DMS; 5 hr., 22 ml. of base. After stirring for an additional hour concentrated hydrochloric acid was added to *p*H 1. The mixture was cooled and the product was collected; yield 7.7 g. (73%) (Fraction A). As shown below, this was primarily the 1,3-dimethyl derivative (XI) of the starting material (X) but contained a small amount of the pyrazine degradation product XIII.

The filtrate was evaporated to 50 ml., treated with Norit, filtered, and brought to *p*H 4 with sodium acetate. A small amount (65 mg.) of product which separated was quickly removed by filtration and discarded. The filtrate was then cooled overnight and the crystalline product was collected; yield 1.8 g. (16%). This was the sodium salt of XII.

This latter product was recrystallized from 15 ml. of hot water by the addition of 20 ml. of ethanol. The purified sodium salt was converted to the free acid by solution in 25 ml. of hot water followed by acidification with 2.5 ml. of concentrated hydrochloric acid; yellow platelets; yield 0.9 g. (9%). This was chromatographically pure 3,8-dimethyl-2,4-dioxo-2,3,4,8-tetrahydropteridine-6-carboxylic acid (XII).

For analyses, a portion (120 mg. ) was recrystallized from 8 ml. of 1*N* hydrochloric acid; yield 90 mg.; m.p. 253–255° (dec.); $R_f$ 0.84 (3% $NH_4Cl$) (yellow, then blue when fumed with ammonia), 0.15 [butanol-5*N* HOAc (7:3)]; $pK_a$, 4.1 (50% DMF-water), 3.2 (water)[16]; ultraviolet absorption spectra in 0.1*N* NaOH, $\lambda_{max}$ 256 mμ (ε 11,300), 282 mμ (ε 7,600), 350 mμ (ε 14,200); *p*H 7.0 and *p*H 9.2, $\lambda_{max}$ 269 mμ (ε 19,100), 290 mμ (shoulder) (ε 11,400), 391 mμ (ε 8,900); 0.1 N HCl, $\lambda_{max}$ 275 mμ (ε 19,400), 294 mμ (shoulder) (ε 11,700), 391 mμ (ε 11,500); 4.0*N* $H_2SO_4$, $\lambda_{max}$ 260 mμ (ε 14,500), 350 mμ (ε 9,800).

*Anal.* Calcd. for $C_9H_8N_4O_4$ (236): C, 45.8; H, 3.4; N, 23.7. Found: C, 45.6; H, 3.7; N, 23.8.

Fraction A (7.7 g.) was suspended in 90 ml. of water containing 1.0 ml. of 10*N* sodium hydroxide. The mixture was stirred vigorously while being adjusted to *p*H 10 by the dropwise addition of 1.0*N* sodium hydroxide. The solid dissolved and the sodium salt crystallized. The mixture was cooled and the product was collected (the filtrate was saved). The wet filter cake was redissolved in 125 ml. of hot water which was then treated with Norit, filtered, reheated to boiling and acidified with 4 ml. of concentrated hydrochloric acid. The product crystallized immediately; white crystals; yield 5.0 g. (48%). This was chromatographically pure 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (XI).

For analytical purposes, a portion (200 mg.) of this material was recrystallized from 30 ml. of 1.0*N* hydrochloric acid; yield 150 mg.; m.p. 249–250°; $R_f$ 0.85 (3% $NH_4Cl$) (abs)., 0.45 [butanol-5*N* HOAc (7:3)] (abs.); $pK_a$ 4.2 (50% DMF-$H_2O$), 3.2 ($H_2O$); ultraviolet absorption spectra at *p*H 7.0 and 9.2, $\lambda_{max}$ 242 mμ (ε 17,700), 262 mμ (shoulder) (ε 10,900), 333 mμ (ε 8,700); 0.1*N* HCl, $\lambda_{max}$ 247 mμ (ε 16,600), 270 mμ (shoulder) (ε 10,900), 333 mμ (ε 9,400).

*Anal.* Calcd. for $C_9H_8N_4O_4$ (236): C, 45.8; H, 3.4; N, 23.7. Found: C, 46.1; H, 3.5; N, 23.1.

The filtrate from the sodium salt of XI above was made more strongly alkaline by the addition of 5 ml. of 10*N* sodium hydroxide. The solution was heated to boiling for one minute and acidified with 9 ml. of concentrated hydrochloric acid. The white product crystallized immediately; yield 1.3 g. (14%). This was the pyrazine degradation product XIII in a chromatographically pure state.

*5-Methylamino-6-(N-methyl)carboxamidopyrazine-2-carboxylic acid* (XIII). A solution of 500 mg. (2.1 mmoles) of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropteridine-6-carboxylic acid (XI) in 20 ml. of 0.5*N* sodium hydroxide was heated to boiling for one minute. When the hot solution was acidified with 1 ml. of concentrated hydrochloric acid, a crystalline precipitate formed and a gas was evolved. The mixture was cooled and the product was collected; yield 385 mg. (86%); m.p. 304–306°. This was recrystallized from 250 ml. of 0.1*N* hydrochloric acid; white hair-like crystals; yield 285 mg. (64%); m.p. 306–307°; $R_f$ 0.66 (3% $NH_4Cl$) (pale blue); $pK_a$ 4.7 (50% DMF-$H_2O$); ultraviolet absorption spectra in 0.1*N* NaOH and at *p*H 7.0, $\lambda_{max}$ 281 mμ (ε 21,000), 367 mμ (ε 6,500); 0.1*N* HCl, $\lambda_{max}$ 288 mμ (ε 18,300), 362 mμ (ε 6,300).

*Anal.* Calcd. for $C_8H_{10}N_4O_3$ (210): C, 45.7; H, 4.8; N, 26.6. Found: C, 45.9; H, 5.1; N, 26.5.

*Methylation of 2-amino-4-hydroxypteridine-7-carboxylic acid* (XIV). 2-Amino-4-hydroxypteridine-7-carboxylic acid (9.0 g.; 43.5 mmoles) was methylated with dimethyl sulfate in an aqueous alkaline solution in exactly the same manner as described above for the methylation of the corresponding pteridine-6-carboxylic acid derivative (I). At the end of the reaction the solution was brought to *p*H 1.5, warmed to 60°, then cooled overnight. The dark precipitate was collected and dried; yield 5.5 g. Paper chromatography indicated that this was primarily a mixture of the 1- and 3-monomethyl derivatives of XIV. There was no indication of the presence of an 8-methyl derivative either in the solid or in the filtrate and no more material could be obtained from the filtrate by adjustment of the *p*H.

This crude product (5.5 g.) was separated into the isomeric monomethyl derivatives by crystallization from dilute hydrochloric acid just as described for the monomethyl derivatives (II and III) of I above. After the second crystallization, 2-amino-3-methyl-4-oxo-3,4-dihydropteridine-7-carboxylic acid (XV) was obtained in a 1.0 g. yield; $R_f$ 0.26 [isopropyl alcohol–1*N* $NH_4OH$ (7:3)] (blue), 0.68 (3% $NH_4Cl$) (blue); ultraviolet absorption spectra at pH 7.0, $\lambda_{max}$ 247 mμ (ε 13,000), 273 mμ (ε 9,500), 366 mμ (ε 5,900); 0.1*N* HCl, $\lambda_{max}$ 239 mμ (ε 14,000), 331 mμ (ε 8,100).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221): C, 43.4; H, 3.2; N, 31.7. Found: C, 43.4; H, 3.3; N, 32.0.

The acidic filtrates from the purification of the 3-methyl derivative (XV) were combined and adjusted to pH 2.5. The product (primarily the 1-methyl isomer) which precipitated was collected; yield 1.2 g. This was dissolved in a solution of 40 ml. of water and 2.5 ml. of concentrated ammonium hydroxide. After a short time, a crystalline ammonium salt appeared; yield 600 mg. This was recrystallized from 15 ml. of water. The white crystalline product was

(14) R. B. Angier, J. H. Boothe, J. H. Mowat, C. W. Waller, and J. Semb, *J. Am. Chem. Soc.*, **74**, 408 (1952).

(15) R. L. Dion and Ti Li Loo, *J. Org. Chem.*, **26**, 1857 (1961).

(16) The $pK_a$'s were determined potentiometrically.

collected, redissolved in 70 ml. of boiling water, and precipitated by the addition of concentrated hydrochloric acid to *p*H 1.5; yield 420 mg.; white microcrystalline solid. This was 2-amino-1-methyl-4-oxo-1,4-dihydropteridine-7-carboxylic acid (XVI). $R_f$ 0.17 [isopropyl alcohol–1*N* $NH_4OH$ (7:3)] (abs.); ultraviolet absorption spectra at pH 7.0, $\lambda_{max}$ 245 mμ (ε 14,600), 337 mμ (ε 10,200); 0.1*N* HCl, $\lambda_{max}$ 238 mμ (ε 12,800), 329 mμ (ε 9,500).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221): C, 43.4; H, 3.2; N, 31.6. Found: C, 43.2; H, 3.3; N, 31.2.

*2-Methylamino-4-hydroxpteridine-7-carboxylic acid* (XVII). A solution of 150 mg. (0.62 mmole) of 2-amino-3-methyl-4-oxo-3,4-dihydropteridine-7-carboxylic acid (XV) in 15 ml. of 0.5*N* sodium hydroxide was heated 25 min. on the steam bath, treated with Norit, filtered, and acidified to *p*H 1.5 with 0.7 ml. of concentrated hydrochloric acid. This was cooled and the crystalline product was collected; yield 120 mg. (80%). This was purified by solution in 50 ml. of hot water containing 1.6 ml. of pyridine followed by acidification with 2 ml. of concentrated hydrochloric acid; yield of product 80 mg. (53%); $R_f$ 0.58 (3% $NH_4Cl$) (blue); ultraviolet absorption spectra in 0.1*N* NaOH, $\lambda_{max}$ 265 mμ (ε 19,000), 380 mμ (ε 6,900); pH 7.0, $\lambda_{max}$ 248 mμ (ε 12,200), 274 mμ (ε 12,500), 358 mμ (ε 6,400); 0.1 *N* HCl, $\lambda_{max}$ 241 mμ (ε 13,500), 332 mμ (ε 6,900).

*Anal.* Calcd. for $C_8H_7N_5O_3$ (221): C, 43.4; H, 3.2; N, 31.7. Found: C, 43.2; H, 3.4; N, 31.7.

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[CONTRIBUTION FROM THE NAVAL STORES LABORATORY, OLUSTEE, FLORIDA][1]

# The Chemistry of Pinolic Acid. I. Rearrangement by Acid-Catalyzed Acylation[2]

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*cis-dl*-Pinolic acid has previously been reported to yield *dl*-2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid by normal acylating procedures. It has been found that in acetylation of the acid in the presence of *p*-toluenesulfonic acid, 40 grams per mole of pinolic acid, rearrangement occurs producing *dl*-2,2,4-trimethyl-3-acetoxycyclopentaneacetic acid and a delta lactone of 2,2,4-trimethyl-3-hydroxycyclopentaneacetic acid. Pyrolysis of the acetate gave *dl*-2,2,4-trimethyl-3-cyclopenteneacetic acid. Elucidation of the structure of these materials was achieved by chemical evidence and comparison of nuclear magnetic resonance spectra of the 2,2,4-trimethyl and 2,2,3-trimethyl unsaturated acids.

Pinolic acid, 2,2-dimethyl-3-(1-hydroxyethyl)-cyclobutaneacetic acid (I), is an easily obtainable acid derived from turpentine. Tiemann and Kerschbaum[4] were first to prepare *cis-dl*-pinolic acid and observed that upon distillation, an unsaturated acid was formed which these authors named pinocampholenic acid. They later believed this to be α-campholenic acid, 2,2,3-trimethyl-3-cyclopenteneacetic acid (II) formed by molecular rearrangement.

A number of other workers[5–8] have reported the product from either the acid catalyzed or thermal rearrangement of pinolic acid to be the same as that obtained by Tiemann and Kerschbaum.

With the availability of vapor phase chromatography and spectrographic equipment, which were not used by earlier workers, except for infrared spectroscopy used by Kergomard, a study was undertaken in this laboratory to investigate the chemistry of pinolic acid. This paper is primarily concerned with the rearrangement of pinolic acid under the conditions for acid catalyzed acetylation. A second paper will describe results obtained on reinvestigation of earlier reports on the rearrangement of pinolic acid. A third paper will deal with the mechanism of the rearrangement.

During the course of studies on acylation of pinolic acid to produce 2,2-dimethyl-3-(1-acetoxyethyl)cyclobutaneacetic acid (III) using *p*-toluenesulfonic acid as a catalyst[9] it was observed that, under certain conditions of acetylation, an abnormal acetate was formed. This material, has been identified as 2,2,4-trimethyl-3-acetoxycyclopentaneacetic acid (V). Characterization of the acetate was accomplished by saponification, pyrolysis, degradative oxidation, and infrared and NMR spectral analyses.

The two most likely structures for an acetate produced by rearrangement from pinolic acid, explainable by a simple mechanistic scheme, are 2,2,3-trimethyl-4-acetoxycyclopentaneacetic acid (IV), formed by migration of the gem dimethyl group, and 2,2,4-trimethyl-3-acetoxycyclopentane-

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(4) F. Tiemann and M. Kerschbaum, *Ber.*, **33**, 2661 (1900).

(5) L. Ruzicka and H. Trebler, *Helv. Chim. Acta*, **3**, 756 (1920).

(6) Le-Van-Thoi, *Ann. chim.*, **10**, 35 (1955).

(7) A. Kergomard, *Bull. soc. chim. France*, 1161 (1957).

(8) M. Harrispe and D. Mea, *Bull. soc. chim. France*, 1562 (1960).

(9) B. A. Parkin, Jr., and G. W. Hedrick, *J. Org. Chem.*, **25**, 1417 (1960).