[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

# Pteridine Chemistry. VI. The Synthesis and Alkaline Degradation of 3-(2-Cyanoethyl)-7-methyl-4(3H)-pteridinone and Some Related Reactions

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The reaction of acrylonitrile with 4-hydroxy-7-methylpteridine (I) in pyridine-water (5-1) has been shown to proceed to 3-(2-cyanoethyl)-7-methyl-4(3H)-pteridinone (II) and 3-formamido-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (III). Both II and III gave rise to the same products when treated with hot 1*N* sodium hydroxide. 3,7-Dimethyl-4(3H)-pteridinone (VII) and 3-formamido-5-methylpyrazine-2-(*N*-methyl)carboxamide (VIII) also have been synthesized and have been shown to exist in equilibrium in a hot pyridine-water (5-1) solution. A possible mechanism for this ring opening is discussed.

In continuing our study of the reaction of acrylonitrile with hydroxypteridines[1,2] we decided to investigate a simple 4-hydroxypteridine. Therefore 4-hydroxy-7-methylpteridine (I) was synthesized from 3-amino-5-methyl-2-pyrazinamide *via* the ethyl orthoformate-acetic anhydride method.[3,4]

When this pteridine (I) was treated with acrylonitrile by refluxing for four hours in a 50% aqueous-pyridine solution, 3-amino-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (IV) was isolated in approximately 50% yield. The structure of this product was established by comparison with an authentic specimen which was synthesized by treating methyl 3-amino-5-methyl-2-pyrazinoate with 3-aminopropionitrile. It was therefore evident that the conditions under which the reaction was carried out resulted in cleavage of the cyanoethylated pteridine and, furthermore, this must have been the 3-cyanoethyl derivative (II). In an attempt to preserve the intact pteridine ring, many other variations in reaction conditions and solvents were tried, the most satisfactory of which was refluxing in pyridine-water (5:1) for three hours. This gave a crude product which consisted of two compounds as shown by paper chromatography in 3% ammonium chloride. These were conveniently separated by extracting with cold water. The water soluble compound, after purification, gave elemental analyses and spectral characteristics indicative of 3-(2-cyanoethyl)-7-methyl-4-(3H)-pteridinone (II). This structure was confirmed when it was found that boiling for thirty seconds in 1*N* sodium hydroxide resulted in the formation of the cyanoethyl amide (IV) along with a small amount of 3-amino-5-methyl-2-pyrazinoic acid (V). Compound V was not formed by hydrolysis of the cyanoethylamide (IV), as heating the latter compound in 1*N* sodium hydroxide for one minute gave no reaction. However, longer heating (one hour on the steam bath) resulted in hydrolysis of the nitrile function to give 3-amino-5-methylpyrazine-2-[*N*-(2-carboxyethyl)] carboxamide (VI). Albert *et al.*[5a] and Wood[5b] have described a similar series of reactions during the alkaline degradation of 3-methyl-4-pteridinone. These authors found that 3-aminopyrazine-2(*N*-methyl)carboxamide and 3-amino-2-pyrazinoic acid were obtained by treating the above-mentioned pteridinone with refluxing 1*N* sodium hydroxide for thirty seconds. As the methylamide was unaffected by the same reagent under more vigorous conditions, it was concluded by Wood[5b] that ring fission of the 3-methyl-4-pteridinone took place in two ways, namely, cleavage of the $N_1$—$C_2$ bond or the $C_2$—$N_3$ bond resulting finally in the formation of the pyrazinemethylamide and cleavage of the $N_3$—$C_4$ bond which would lead to 3 amino-2-pyrazinoic acid.

The water-insoluble product from the cyanoethylation reaction gave elemental analyses consonant with a formyl derivative of compound IV. When this compound was refluxed in 1*N* sodium hydroxide for thirty seconds the same two compounds, IV and V, were obtained as were found after similar treatment of the pteridinone II. Furthermore, in 0.1*N* sodium hydroxide a third compound was present as shown by paper chromatography. At this point we felt that the the nitrile function might be responsible for some of the seemingly anomalous behavior and therefore we decided to investigate a simple 3-alkyl-4-pteridinone. As a result of the latter study the water-insoluble compound was subsequently shown to be 3-formamido-

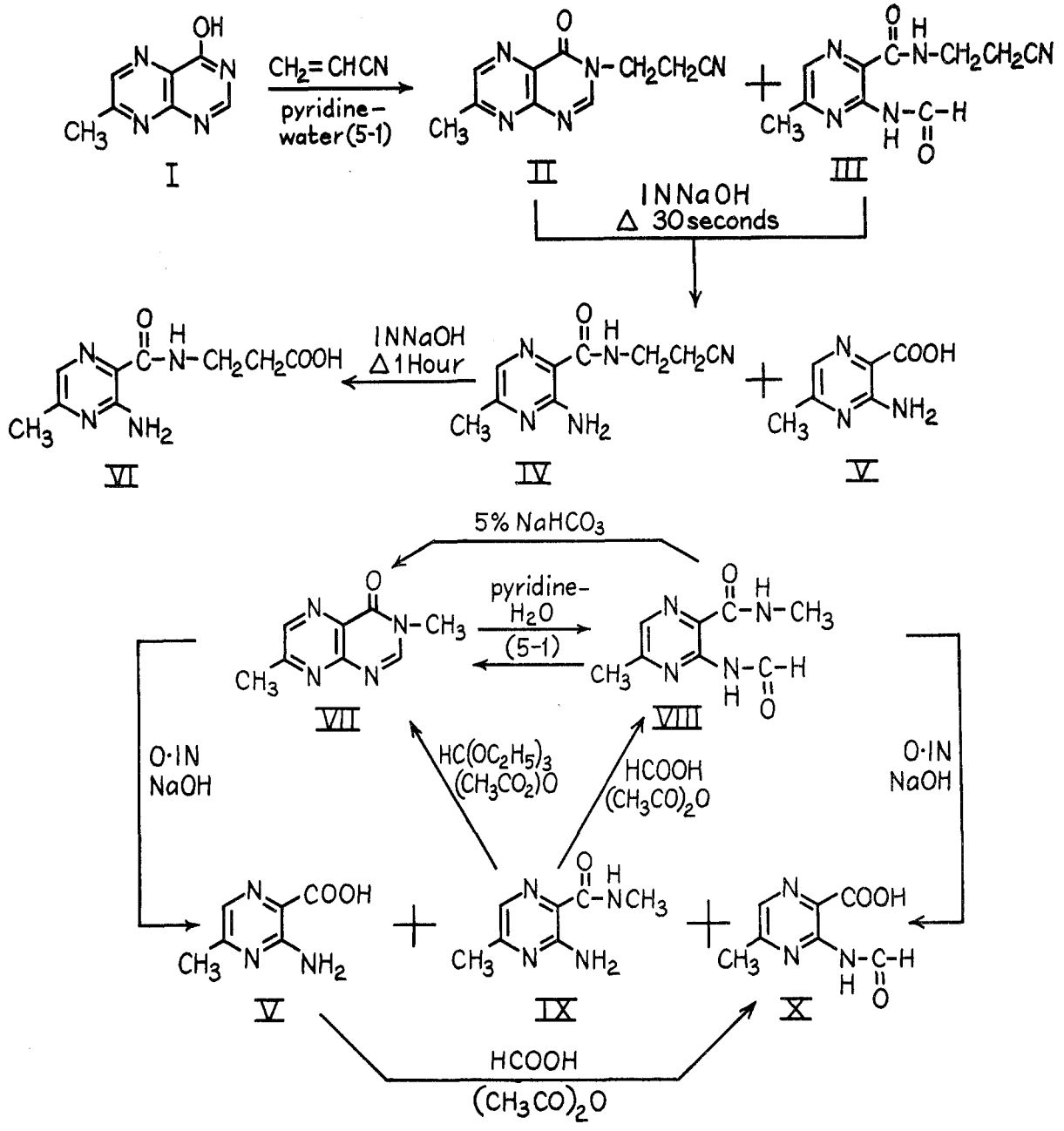
(1) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, 81, 5650 (1959).

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

(3) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(4) This compound has previously been synthesized by A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952), *via* the condensation of 4,5-diamino-6-hydroxypyrimidine with methylglyoxal in the presence of sodium sulfite.

(5) (a) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956). (b) H. C. S. Wood, *The Chemistry and Biology of Pteridines*, a Ciba Foundation Symposium, J. and A. Churchill, Ltd., England, 1954, p. 35.




5 - methylpyrazine - 2 - [*N* - (2 - cyanoethyl)]-carboxamide (III).[6]

3,7-Dimethyl-4-(3H)-pteridinone (VII) was synthesized by ring closure of 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) using ethyl orthoformate-acetic anhydride. When this pteridinone (VII) was refluxed for twelve hours in pyridine-water (5:1), a small amount of a new compound was isolated which was identical to the product obtained by treating the pyrazineamide (IX) with formic acid–acetic anhydride. This demonstrated that the compound was 3-formamido-5 - methylpyrazine - 2 - (*N* - methyl)carboxamide (VIII).[7] Furthermore, by treating compound VIII with hot pyridine-water (5:1) for eight hours a 40% yield of 3,7-dimethyl-4(3H)-pteridinone (VII) was

(6) Albert *et al.*[5a] have shown that the methylation of 4-hydroxypteridine at *p*H 8 with dimethyl sulfate and dilute sodium hydroxide gave both the 1- and 3-methyl isomers. No 1-cyanoethyl isomer has been isolated from any of the reactions carried out on I. However, it is not possible to conclude that it was not formed. In many attempts, such a variety of products were formed, as shown by paper chromatography, that one may well have been the 1-substituted isomer. The isolation of the 3-cyanoethyl product (II) and the formyl compound (III), which is a degradation product of II, in recrystallized yields of 36% and 10.5%, respectively, indicates that, at least in the pyridine-water (5:1) reaction, the acrylonitrile adds predominantly to the 3-nitrogen of the pteridine ring system.

(7) The ultraviolet absorption spectrum in methanol of this product was almost identical to that given by the water-insoluble product obtained in the cyanoethylation reaction allowing the assignment of structure III to this compound.

obtained, showing that, under these conditions, an equilibrium exists between the pteridinone VII and the formylpyrazine VIII. A more convenient method of cyclizing compound VIII involved warming for four to five minutes on a steam bath in a 5% sodium bicarbonate solution, in which case a slightly higher yield of the pteridinone was obtained. However, when either the formyl derivative (VIII) or the pteridinone (VII) was subjected to more rigorous alkaline treatment (hot 1*N* sodium hydroxide), it was shown by paper chromatography that they were both converted to the same products, namely 3-amino-5-methylpyrazine-2-carboxylic acid (V) and 3-amino-5-methylpyrazine-2-(*N*-methyl)-carboxamide (IX). This indicates that the mechanism for the alkaline degradation of 3-alkyl-4-pteridinones may be a nucleophilic attack of hydroxide ion at $C_2$ followed by rupture of the $C_2$—$N_3$ bond with the formation of the 3-formyl derivative (VIII). The fact that compound VIII is capable of hydrolyzing to give both the acid (V) and the amide (IX) obviates the necessity for two different methods of ring cleavage as previously proposed.[8]

When the formamidoamide (VIII) or the pteridinone (VII) was heated in 0.1*N* sodium hydroxide on a steam bath for one minute a third compound appeared. This was the same "third compound" noted in the similar treatment of the 3-cyanoethylpteridinone (II) and was shown to be 3-formamido-5-methylpyrazine-2-carboxylic acid (X) by comparison of the $R_f$ values in several different solvent systems with an authentic specimen synthesized by formylation of compound V with formic acid-acetic anhydride. The lability of the formyl group accounts for the absence of X when hot 1*N* sodium hydroxide was employed.

It is interesting to note the striking contrast in the stability of the secondary amide linkages of compounds VIII and IX. The amide (IX) is unaffected by boiling for one minute in 1*N* sodium hydroxide while the 3-formyl derivative (VIII), by heating for one minute on a steam bath on 0.1*N* sodium hydroxide gives, in addition to IX, two products (V and X) in which the *N*-methylamide portion of the molecule has been hydrolyzed.

Several mechanisms involving intramolecular hydrogen bonding or neighboring group participation have been considered to explain this ready hydrolysis of VIII. However, the simplest explanation is that in compound IX the amide linkage is resonance stabilized by the electron donating amino group while in VIII the electron withdrawing carbonyl of the formyl group partially counteracts this stabilization to permit ready hydrolysis of VIII to X. Partial confirmation of this explanation was obtained when it was found that pyrazinecarboxamide was quickly hydrolyzed to pyazinoic acid by a 1.0*N* sodium hydroxide solution under conditions where IX was completely stable.

Both formyl compounds behave normally in dilute aqueous acid. Compound VIII, after two hours in 0.1*N* hydrochloric acid at room temperature, suffered loss of the formyl group as shown by the change in the ultraviolet absorption spectra. Similarly the formyl acid (X) was converted to 3-amino-5-methylpyrazine-2-carboxylic acid (V). In fact, the formyl group of X was hydrolyzed even in boiling water. Apparently this was caused by acid catalysis from the ionization of the carboxyl group since no hydrolysis occurred in hot dilute sodium acetate solution. The pteridinone (VII) was unaffected by 0.1*N* hydrochloric acid at room temperature.

## EXPERIMENTAL

Paper chromatographic experiments were carried out using the descending technique. The spots were detected with an ultraviolet lamp provided with a filter to give mainly light of 254 mμ. A zinc silicate plate coated with DuPont phosphor No. 609235[9] was used to facilitate the detection of absorbing spots. Considerable variation in $R_f$ values was noticed using acetone-water (4:1) depending on the size of the chromatographic jar. The best results were obtained using a jar 15 cm. in diameter and 45 cm. in length. A beaker of the solvent was placed in the bottom of the jar while the paper strips were being run.

*Methyl 3-amino-5-methyl-2-pyrazinoate.* 3-Amino-5-methyl-2-pyrazinoic acid[10] (12.2 g., 0.078 mole) was suspended in 600 ml. of absolute methanol, cooled in an ice bath, and saturated with anhydrous hydrogen chloride. After the solution had been refluxed for 1 hr. it was stored in the cold for 48 hr., then retreated with hydrogen chloride and refluxed again for 1.5 hr. The solution was then evaporated to half volume, treated with Norit and filtered. The filtrate was taken down to an oil *in vacuo*, dissolved in 75 ml. of absolute methanol, and again evaporated *in vacuo*. The residue was dissolved in 200 ml. of water and the free ester obtained by adding sodium acetate to *p*H 4; yield 9.8 g. (78%),[11] m.p. 161–165°. Recrystallization of a portion of this product from water for analytical purposes raised the melting point to 167–169°. $R_f$ 0.68 in 0.5% sodium carbonate 0.66 in 3% ammonium chloride, 0.75 in ethanol–water–concentrated ammonium hydroxide (80:16:4) (purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium

(8) As it has been proved that an equilibrium exists between 3,7-dimethyl-4(3H)-pteridinone (VII) and 3-formamido-5-methylpyrazine-2-(*N*-methyl)carboxamide (VIII) in hot aqueous-pyridine and also as compound VIII is not stable in hot 1*N* sodium hydroxide, it is not possible to rule out two modes of cleavage of VII.[5b] However, we feel that the isolation and degradation of the formyl derivative (VIII) described herein lends greater support for only one method of ring rupture.

(9) Commercially available from E. I. du Pont de Nemours, Inc., Polychemicals Dept., 350 5th Ave., New York 1, N. Y.

(10) This pyrazine derivative has been synthesized by C. K. Cain, M. F. Mallette, and E. C. Taylor, *J. Am. Chem. Soc.*, **70**, 3026 (1948) from 2,4-diamino-7-methylpteridine and also by J. Weijlard, M. Tishler, and A. Erickson, *J. Am. Chem. Soc.*, **67**, 802 (1945) using 7-methyllumazine. We have obtained this compound from 2-amino-4-hydroxy-7-methylpteridine employing conditions similar to the above-mentioned references.

(11) The yields of ester obtained in this manner were much superior to those employing sulfuric acid as a catalyst.

hydroxide $\lambda_{max}$ 244 mμ (ε 9,030), 340 mμ (ε 7,240); 0.1*N* hydrochloric acid, $\lambda_{max}$ 247 mμ (ε 9,830), 357 mμ (ε 8,870).

*Anal.* Calcd. for $C_7H_9N_3O_2$ (161.2): C, 50.3; H, 5.4; N, 25.2. Found: C, 50.4; H, 5.7; N, 24.9.

*3-Amino-5-methyl-2-pyrazinecarboxamide.* Methyl 3-amino-5-methyl-2-pyrazinoate (9.8 g., 0.061 mole) was stirred for 4 hr. in 250 ml. of concd. ammonium hydroxide. After chilling, the product was collected and dried; yield 7.1 g. (85%), m.p. 239–242° with some previous softening.[12] $R_f$ 0.57 and 0.61 (purple fluorescence) in 0.5% sodium carbonate and 3% ammonium chloride. Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, $\lambda_{max}$ 249 mμ (ε 11,000), 349 mμ (ε 7,950); 0.1*N* hydrochloric acid $\lambda_{max}$ 244 mμ (ε 11,800), 356 mμ (ε 9,340).

*4-Hydroxy-7-methylpteridine* (I). 3-Amino-5-methyl-2-pyrazine-carboxamide (7.1 g., 0.052 mole) was refluxed for 2 hr. 15 min. in a solution of 200 ml. of acetic anhydride and and 200 ml. of ethyl orthoformate. After chilling the mixture overnight the product was collected and dried; yield 4.5 g. The addition of 300 ml. of ether to the mother liquor gave another crop of 1.4 g. (70.5%) total). Both of these products gave the same paper chromatographic pattern in several solvent systems (see below). A small portion of the first crop was recrystallized from water for analysis. $R_f$ 0.72 (dull blue fluorescence) in 0.5% sodium carbonate, 0.71 (absorption) in 3% ammonium, chloride 0.51 (absorption) in butanol-5*N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide $\lambda_{max}$ 244 mμ (ε 17,800), 330mμ (ε 7,140); 0.1*N* hydrochloric acid, $\lambda_{max}$ 207 mμ (ε 16,200), 232 mμ (ε 10,150), 310 mμ (ε 8,350).

*Anal.* Calcd. for $C_7H_6N_4O$ (161.15): C, 51.9; H, 3.7; N, 34.6. Found: C, 51.6; H, 3.7; N, 34.5.

*3-Amino-5-methylpyrazine-2-[N-(2-cyanoethyl)]carboxamide* (IV). Methyl 3-amino-5-methyl-2-pyrazinoate (1.0 g., 6.2 mmoles) and 5 ml. of 3-aminopropionitrile were added to 20 ml. of 95% ethanol and refluxed for 12 hr. Paper chromatography in methyl ethyl ketone–water (9:1) revealed that a substantial amount of starting ester was still present. The solution was concentrated to 10 ml. and 10 ml. of 1-propanol added. After the solution had been refluxed for an additional 8 hr., paper chromatography indicated that the reaction was practically complete. The solvents were removed *in vacuo* to give an oil. This oil was taken up in absolute alcohol and again evaporated *in vacuo* to an oil which was crystallized from 20 ml. of 50% ethanol; yield 0.37 g., m.p. 123–130°. Recrystallization from water gave 0.23 g. (18%), m.p. 135–137°. $R_f$ 0.67 in 3% ammonium chloride, and 0.67 in 0.5% sodium carbonate (bright purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, $\lambda_{max}$ 251 mμ (ε 12,500), 350 mμ (ε 8,900); in 0.1*N* hydrochloric acid $\lambda_{max}$ 246 mμ (ε 12,500), 358 mμ (ε10,000).

*Anal.* Calcd. for $C_9H_{11}N_5O$ (205.2): C, 52.7; H, 5.4; N, 34.1. Found: C, 52.2; H, 5.5; N, 33.8.

*3-Amino-5-methylpyrazine-2-[N-(2-carboxyethyl)]carboxamide* (VI). 3-Amino-5-methylpyrazine-2[*N*-2-cyanoethyl)] carboxamide (IV) (250 mg., 1.2 mmoles) was heated in 10 ml. of 1*N* sodium hydroxide for 1 hr. on a steam bath. Acidification of the hot solution to *p*H 3 with concentrated hydrochloric acid gave crystals which were collected after cooling; yield 170 mg. This product was recrystallized from about 15 ml. of water; yield 120 mg. (44%), m.p. 207–209.°. $R_f$ 0.80 (purple fluorescence) in 0.5% sodium carbonate and 0.87 (purple fluorescence) in butanol-5*N* acetic acid (7:3). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, $\lambda_{max}$ 250 mμ (ε 12,770), 349 mμ (ε 8,970); 0.1*N* hydrochloric acid, $\lambda_{max}$ 244 mμ (ε 12,770), 357 mμ (ε 10,300).

*Anal.* Calcd. for $C_9H_{12}N_4O_3$ (224.3): C, 48.2; H, 5.4; N, 25.0. Found: C, 48.3; H, 5.6; N, 25.1.

*Cyanoethylation of 4-hydroxy-7-methylpteridine.* 4-Hydroxy-7-methylpteridine (1.0 g., 6.2 mmoles) was added to a solution of 50 ml. of pyridine and 10 ml. of water containing 2 ml. of acrylonitrile and refluxed for 3 hr. The solvents were removed *in vacuo* and the resulting oil was taken up in 12 ml. of absolute alcohol, treated with Norit and filtered. The solution was cooled and the crystals were collected and dried; yield 0.85 g. This crude product was extracted with 20 ml. of water and filtered, leaving an insoluble residue (0.236 g.). The filtrate was evaporated to dryness *in vacuo* and taken up in about 10 ml. of absolute alcohol, treated with Norit, and filtered to remove a small amount of amorphous solid. The filtrate deposited crystals of 3-(2-cyanoethyl)-7-methyl-4 (3H)-pteridinone (II) on standing; yield 0.42 g. (31.6%), m.p. 172–173.5°. $R_f$ 0.86 (absorption) in 3% ammonium chloride. Ultraviolet absorption spectra in 0.1*N* hydrochloric acid $\lambda_{max}$ 236 mμ (ε 11,900), 308 mμ (ε 7,750); in methanol the spectra is essentially the same as in 0.1*N* hydrochloric acid.

*Anal.* Calcd. for $C_{10}H_9N_5O$ (215.2): C, 55.8; H, 4.2; N, 32.5. Found: C, 55.7; H, 4.5; N, 32.2.

The water-insoluble portion (0.236 g.) was recrystallized from aqueous-ethanol to give 0.152 g. of III (10.5%), m.p. 186.5–189°. $R_f$ 0.90 (dull purple fluorescence) in butanol-5*N* acetic acid (7:3). This compound gave a dull purple, tailed spot which traveled directly behind II in 3% ammonium chloride. Ultraviolet absorption spectra in methanol, $\lambda_{max}$ 265 mμ (ε 22,000), 315 mμ (ε 8,600).

*Anal.* Calcd. for $C_{10}H_{11}N_5O_2$ (233.2): C, 51.5; H, 4.8; N, 30.0. Found: C, 51.3; H, 30.2.

*Alkaline degradation of 3-(2-cyanoethyl)-7-methyl-4(3H)-pteridinone* (II). Two hundred and fifty milligrams (1.16 mmoles) of II was boiled for 30 seconds in 2.5 ml. of 1*N* sodium hydroxide, then cooled in an ice bath immediately. After standing several hours in the cold, the crystals were collected and dried; yield 141 mg. (59.3%), of 3-amino-5-methylpyrazine-2-[*N*-(2-cyanoethyl)]carboxamide (IV), m.p. 134.5–137.5°. The filtrate, after acidification to *p*H 3 with concentrated hydrochloric acid, deposited 23 mg. (13%) of 3-amino-5-methyl-2-pyrazinoic acid (V), m.p. 210–212° dec.[13] Both of these products traveled side by side with authentic specimens when chromatographed in several different solvent systems.

*Alkaline degradation of 3-formamido-5-methypyrazine-2-[N-(2-cyanoethyl)]carboxamide* (III). The formyl compound (100 mg., 0.43 mmole) was treated in the same manner as described above for I to give 56 mg. (63.5%) of the cyanoethylamide (IV), m.p. 136–139° and 7 mg. (10.6%) of the pyrazinoic acid (V), m.p. 206–210° dec.[13] Confirmation of the structures was again provided through paper chromatography.

*3-Amino-5-methylpyrazine-2-(N-methyl)-carboxamide* (IX). 3-Amino-5-methyl-2-pyrazinoic acid (15.0 g., 0.098 mole) was converted to the methyl ester as described above. The crude ester was added to 250 ml. of 25% aqueous methylamine solution and stirred for 20 min. at room temperature, then chilled for several days; yield 6.9 g. (42%), m.p. 126–128°. $R_f$ 0.85 in butanol-5*N* acetic acid (7:3), 0.64 in 3% ammonium chloride, 0.88 in acetone-water (4:1), 0.63 in 0.5% sodium carbonate (purple fluorescence in all cases). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, $\lambda_{max}$ 250 mμ (ε 11,500), 348 mμ (ε 8,080); in 0.1*N* hydrochloric acid, $\lambda_{max}$ 244 mμ (ε 11,900), 358 mμ (ε 9,550); in methanol, $_{max}\lambda$ 250 mμ (ε 12,400), 351 mμ (ε 8,700).

*Anal.* Calcd. for $C_7H_{10}N_4O$ (166.2): C, 50.6; H, 6.1; N, 33.7. Found: C, 50.6; H, 6.2; N, 33.7.

*3,7-Dimethyl-4(3H)-pteridinone* (VII). Two grams (12 mmoles) of 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) was added to a solution of 20 ml. of ethyl orthoformate and 20 ml. of acetic anhydride and refluxed for 2 hr. The reaction mixture was cooled and the product collected; yield 1.9 g. (90%). The crude product was recrystallized from 80 ml. of hot water using Norit to give 1.3 g. (62%), dec. slowly above 300°. $R_f$ 0.83 in 3%, ammonium

(12) E. C. Taylor, J. W. Barton, and T. S. Osdene, *J. Am. Chem. Soc.*, **80**, 421 (1958), give m.p. 235–236°.

(13) M.p. 211–212° dec. reported in ref. 12.

chloride 0.80 in acetone-water (4:1), 0.58 in butanol-5*N* acetic acid (7:3) (absorption in all cases). Ultraviolet absorption spectra in methanol, $\lambda_{max}$ 238 mμ (ε 12,100), 312 (ε 7,200); in 0.1*N* hydrochloric acid the spectra is essentially the same as methanol.

*Anal.* Calcd. for $C_8H_8N_4O$ (176.2): C, 54.5; H, 4.6; N, 31.8. Found: C, 54.5; H, 4.8; N, 31.6.

*Method 2.* 3-Formamido-5-methylpyrazine-2-(*N*-methyl)-carboxamide (VIII) (100 mg., 0.52 mmole) was heated on a steam bath for 8 hr. in a solution of 5 ml. of pyridine and 1 ml. of water. After the solution stood at room temperature overnight the crystals were collected; yield 40 mg. (44%). The infrared spectra of this product and that obtained by method 1 were identical.

*Method 3.* Compound VIII (100 mg., 0.52 mmole) was warmed on a steam bath in 10 ml. of 5% sodium bicarbonate solution until solution was complete (4–5 min). The crystals were filtered off after standing 2 days at room temperature, yield 54 mg. (59%). The infrared spectrum of this material was identical to spectra of the products obtained by methods 1 and 2.

*3-Formamido-5-methylpyrazine-2-(N-methyl)carboxamide* (VIII). *Method 1.* 3-Amino-5-methylpyrazine-2-(*N*-methyl)-carboxamide (1.0 g., 6.0 mmoles) was dissolved in a solution containing 5 ml. of formic acid and 10 ml. of acetic anhydride and warmed on a steam bath for several minutes to initiate the reaction. After standing at room temperature for a few minutes, crystals separated; yield 0.75 g. (71%), m.p. 225–231° (resolidifies to give crystals which do not melt below 300° indicating ring closure to VII). $R_f$ 0.84 in butanol-5*N* acetic acid (7:3), 0.87 in acetone-water (4:1) (dull purple fluorescence), tailed spot between VII and IX in 3% ammonium chloride. Ultraviolet absorption spectra in methanol, $\lambda_{max}$ 256 mμ (ε 19,000), 316 mμ (ε 7,480).

*Anal.* Calcd. for $C_8H_{10}N_4O_2$ (194.2): C, 49.5; H, 5.2; N, 28.9. Found: C, 49.2; H, 5.4; N, 29.2.

*Method 2.* 3,7-Dimethyl-4(3H)-pteridinone (0.50 g., 2.8 mmoles) was refluxed for 12 hr. in 30 ml. of a pyridine-water (5 : 1) solution. On cooling 0.33 g. of starting material was filtered off and the filtrate was taken to dryness *in vacuo*. This was extracted with 30 ml. of water and filtered from the insoluble residue; yield 106 mg., m.p. 226.5–230°. Recrystallization from 10 ml. of 50% ethanol yielded 50 mg., m.p. 232–235°. This material was identical to that prepared by Method 1 as shown by infrared spectra, mixed melting point, and paper chromatography.

When this formyl compound (VIII) or 3,7-dimethyl-4-(3H)-pteridinone (VII) was refluxed for 1 min. in 1*N* sodium hydroxide, they were converted to 3-amino-5-methyl-2-pyrazinoic acid (V) and 3-amino-5-methylpyrazine-2-(*N*-methyl)carboxamide (IX) as shown by chromatography in 3% ammonium chloride 0.5% sodium carbonate and acetone-water (4:1). By heating for 1 min. on a steam bath in 0.1*N* sodium hydroxide a third yellow-green fluorescent product was formed which, traveled side-by-side with compound X in the three above-mentioned solvent systems. This compound (X) was slowly hydrolyzed to the acid (V) on standing in 0.1*N* sodium hydroxide at room temperature.

*3-Formamido-5-methylpyrazine-2-carboxylic acid* (X). One gram of 3-amino-5-methylpyrazine-2-carboxylic acid was added to a solution of 5 ml. of formic acid in 10 ml. of acetic anhydride and warmed on the steam bath for a few minutes to initiate the reaction. After standing at room temperature for 5 min. the solution was refluxed for 30 min., then treated with Norit and filtered. Twenty milliliters of anhydrous ether was added to the filtrate. This solution was protected with a tube of Drierite and allowed to stand for several hours at room temperature, then chilled overnight. The product was collected and dried; yield 0.45 g. (38%), m.p. 184–185° dec. $R_f$ 0.82 in 3% ammonium chloride 0.84 in 0.5% sodium carbonate, 0.64 in acetone-water (4:1) (yellow-green fluorescence). Ultraviolet absorption spectra in methanol, $\lambda_{max}$ 252 mμ (ε 15,500), 311 mμ (ε 6,920).

*Anal.* Calcd. for $C_7H_7N_3O_3$ (181.2): C, 46.4; H, 3.9; N, 23.2. Found: C, 46.6; H, 4.2; N, 23.4.

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[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

# Benzacridines. V.[1] Dibenz[a,c]acridine and 1,4-Dimethylbenz[c]acridine

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Application of the α-dehydrobromination-rearrangement reaction previously reported for 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine has led to a new synthesis of dibenz[a,c]acridine. Several other possible conditions for carrying out this transformation have been investigated. A new benz[c]acridine, namely, 1,4-dimethylbenz[c]acridine, is reported.

The initial paper in this series[2] reported a new pathway to benz[c]acridine derivatives substituted in the five and six positions. These positions, which involve the carbon atoms of the "K-region" for this ring system, provide interesting derivatives for further studies of chemical carcinogenosis.[3] It was also of importance to find further examples of the "α-dehydrobromination-rearrangement" of 6-bromo-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VIII) that led to the isolation of 5,6-dimethylbenz[c]acridine (XI) in high yield.

Condensation of 4,4-tetramethylene-1-tetralone (I) with *o*-nitrobenzaldehyde was carried out in the presence of acetic acid and sulfuric acid providing 2-(*o*-nitrobenzal)-4,4-tetramethylene-1-tetralone (II) in 84% yield. Reduction of the ketone II with iron and acetic acid followed by direct cycliza-

(1) For paper IV, see N. H. Cromwell and J. C. David, *J. Am. Chem. Soc.*, 82, 2046 (1960).

(2) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, 23, 789 (1958).

(3) See (a) C. A. Coulson, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56 and (b) A. Lacassagne, N. P. Buu-Hoi, R. Daudel, and F. Zajdela, *Advances in Cancer Research*, Academic Press, Inc., New York, N. Y., 1956, Vol. IV, pp. 316–369.