## DISCUSSION AND CONCLUSIONS

Following detection of unknown alkaloids in the cactus *C. runyonii*, one of the alkaloids was isolated in crystalline form by employing ion-exchange and adsorption column chromatography. Attempts at characterization of the unknown alkaloid resulted in spectral and chemical data which are in accord with *l*-α-3,4-dimethoxyphenyl-β-dimethylaminoethanol. This compound has recently been isolated by other workers from a related cactus, *C. macromeris*, and has been given the common name *l*-macromerine. Comparison of spectral and chemical data revealed that the unknown alkaloid from *C. runyonii* is identical to *l*-macromerine from *C. macromeris*. Thus, the occurrence of macromerine is not restricted to the latter species.

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*Keyphrases*

Alkaloids, cactus—*Coryphantha runyonii*
Macromerine—isolation
Column chromatography—separation
TLC—analysis
IR spectrophotometry—structure
UV spectrophotometry—structure
NMR spectrometry
Mass spectrometry

# Deoxyalloxazines (Benzopteridines) II. Methylation of 2,4-Diamino-6,7-dimethylbenzo(*g*)pteridine

By S. L. MUKHERJEE, Z. F. CHMIELEWICZ, and T. J. BARDOS*

**Methylation of 2,4-diamino-6,7-dimethylbenzo(*g*)pteridine (I) with excess methyl iodide in boiling cellosolve gave a red methyl-methiodide derivative (II) which, on treatment with hot aqueous sodium carbonate solution was converted to the $N_1$-methyl derivative (III), as shown by hydrolysis of the product to the corresponding dioxo-compound (IV) and its further degradation to the quinoxaline derivative (V). Reaction of I with methyl iodide in nitromethane solution afforded a quaternary methiodide derivative (VI) which, through a series of reactions with cold, concentrated acid and base reagents, was converted to III. On several occasions, the latter was obtained in what appeared to be a different, unstable tautomeric form. Hydrolysis of the corresponding intermediate methiodide (VI) or, of the hydrochloride salt (VII), with acid or alkali, gave IV; thus the methylation of I in nitromethane, as in cellosolve, appears to have occurred exclusively in the $N_1$-position of the pyrimidine ring.**

THE SYNTHESIS of a series of deoxyalloxazines (benzopteridines) was reported several years ago (1). One of these compounds, 2,4-diamino-6,7-dimethylbenzo(*g*)pteridine (2,4-diamino-2,4-deoxylumichrome, I) was found to be a highly active antimetabolite of both folinic acid and riboflavin in various microbiologic test systems (1, 2), and it also inhibited the growth of several transplanted tumors in mice (3, 4). Unfortunately, the very poor solubility and tissue absorption properties of this interesting compound sharply limited its potential therapeutic usefulness. For this reason, the synthesis of more soluble derivatives was attempted.

Substitution in the $N_{10}$-position of the central ring appeared to be of particular interest because the resulting flavin-type compounds would display greater structural similarity to riboflavin and may prove to possess higher "anti-riboflavin" activities than I. It was also of interest to investigate the possibility of obtaining quaternary derivatives of I which would bear some structural resemblance to the chemotherapeutically effective acridines and phenanthridines.

Methylations of 4-aminopteridine, 2,4-diaminopteridine, and related compounds, with methyl iodide, were reported by Brown and Jacobsen (5, 6) to give the $N_1$- and/or $N_8$-methyl substituted derivatives in the form of their hydroiodides or quaternary methiodides (the $N_8$-position of the pteridine nucleus corresponds to the $N_{10}$-position in the benzopteridine system). The $N_1$-substituted derivative of 2,4-diamino-6,7-diphenylpteridine was obtained by Boon and Bratt (7) by methylation of the parent compound with methyl iodide. In a series of papers, Angier (8) reported his studies on the methylations of 2-amino-4-hydroxypteridines with dimethyl sulfate; substitution in the $N_1$, $N_3$, and/or $N_8$ position was shown to occur under the various conditions employed. Preliminary experiments indicated that I could not be methylated with dimethyl sulfate under the conditions employed by Angier, while the use of methyl iodide appeared to be more promising.

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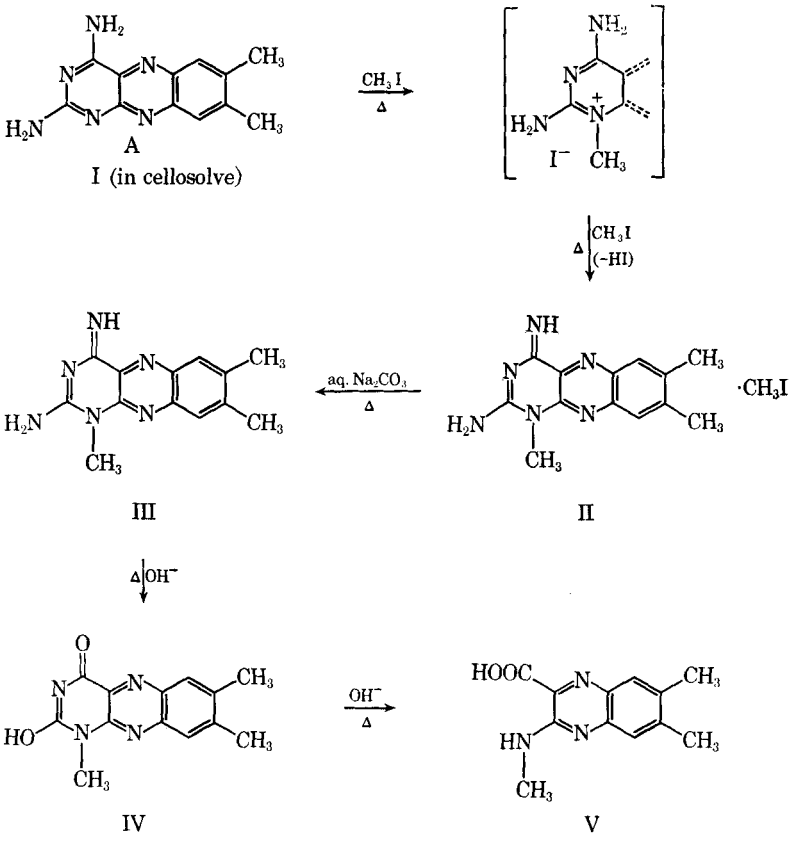
In all of the reactions studied, the very low solubility of I in organic solvents caused considerable difficulties. Boiling ethanol dissolves the compound at less than 0.05 mg./ml. concentration; the resulting yellow, green-fluorescent solution shows absorption maxima at 265, 343, and 420 mμ, almost identical to those reported for the anion of 2-amino-4-hydroxybenzo(*g*)pteridine (9) and the di-anion of lumichrome (1). On the basis of Jones' rule (10), structure A is, therefore, assigned to the tautomeric form of I in ethanol (Scheme I). Somewhat higher solubility, with similar spectrum, was obtained in boiling cellosolve. Treatment of I in cellosolve with excess methyl iodide at reflux temperature resulted in complete dissolution of the starting material; on cooling, an orange-red compound precipitated which, after recrystallization, gave an elemental analysis corresponding to a methyl-methiodide (or, dimethyl-hydroiodide) derivative of I. Subsequent reactions and spectral comparisons suggest that the most probable structure for this compound is the one indicated in formula II.

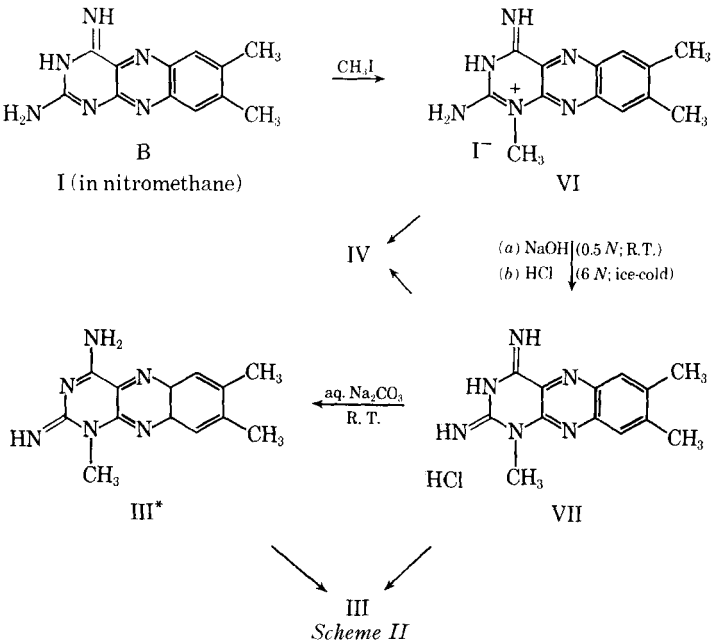
Further treatment of II with an aqueous solution of sodium carbonate at 100° gave the $N_1$-methyl derivative (III). The position of the methyl group was established by alkaline degradation which yielded 3-methylamino-6,7-dimethylquinoxaline-2-carboxylic acid (V). Milder alkali treatment of III resulted in hydrolysis to the corresponding dioxo-derivative (IV).

Solutions of I in more polar solvents (nitromethane or dimethylsulfoxide) showed no fluorescence, and the second and third absorption bands in the ultraviolet spectra appeared at 360 and 395–400 mμ, respectively (the first absorption band cannot be established because of the absorption of these solvents in the 200–300 mμ region). Structure B (Scheme II) was tentatively assigned to the tautomeric form of I present in these solvents. Reaction of I with excess methyl iodide in boiling nitromethane yielded a water-soluble, red crystalline compound which gave elemental analysis and spectral properties corresponding to a quaternary methyl-iodide (VI) of the starting material. Treatment of this compound with hot sodium carbonate solution, under conditions employed for the conversion of II to III, led to decomposition (evolution of ammonia). However, when the aqueous solution of VI was added at *room temperature* to a solution of 0.5 *N* sodium hydroxide, immediately a red solid precipitated; this could not be purified but could be converted to a crystallizable mono-hydrochloride (VII). The latter was dissolved in water and neutralized with aqueous sodium carbonate to give III.

It should be mentioned that, on several occasions, this series of reactions led to a final product which gave analysis corresponding to a monomethyl derivative of I but appeared to differ from III in appearance, solubility, fluorescence, and ultraviolet spectrum in absolute ethanol. Due to the strong fluorescence and longer-wavelength absorption ($\lambda_{max.}$ 422 mμ) of this compound in absolute ethanol, it was believed, at first, that the methylation in nitromethane occurred at the $N_{10}$-position; how-




*Scheme I*




*Scheme II*

ever, hydrolysis of the corresponding hydrochloride (VII) with either acid or alkali gave a dioxo-compound which was identical with IV (as shown by spectra and thin-layer chromatography). The same dioxo-benzopteridine was obtained by alkaline hydrolysis of VI. It was also found that addition of water to their alcoholic solutions changed the ultraviolet spectra of both III and the "new" monomethyl compound, and the two spectra became identical, both showing in the range above 300 mμ a single absorption maximum (at 360 mμ) and an inflection (at 395 mμ). The spectra of the two compounds in 0.1 *N* HCl were also identical (see under *Experimental*). Moreover, after a sample of the "new" compound was stored in a desiccator for more than a year, all the above-mentioned characteristic differences disappeared, and the sample became indistinguishable from III. It was concluded that the "new" compound represented an unstable tautomeric form of III. Consequently, the methylation of I in nitromethane (as in cellosolve) appears to occur exclusively in the $N_1$-position of the pyrimidine ring.

These studies indicated that, due to the fused benzene ring, the aromaticity of the pyrazine ring and its resistance to *N*-methylation is greatly enhanced in the benzopteridine system.

## EXPERIMENTAL[1]

**2 - Amino - 4 imino - 1,6,7 - trimethyl - 1,4 - dihydrobenzo(g)pteridine - methiodide**—2,4 - Diamino-6,7-dimethylbenzo(*g*)pteridine (I) (2.0 Gm., 0.0083 mole), was added to a solution of methyl iodide (5.0 ml., 0.1 mole) in 40 ml. of cellosolve, and the reaction mixture was heated at refluxing temperature for 45 min. under vigorous stirring. The resulting clear, deep-red colored solution was concentrated to about one-third of its original volume, then cooled and stored in the refrigerator overnight during which time an orange-red solid precipitated. This was collected by filtration and triturated at room temperature with 125 ml. of methanol; the methanolic extract was filtered from the undissolved solids and concentrated to dryness. The residue of the methanolic filtrate was washed with 60 ml. of acetone. Yield: 1.0 Gm. (30%) of essentially pure product, a portion of which was crystallized from methanolic solution by very slow and careful evaporation of the solvent. Long, orange needles which, however, on repeated crystallization changed into small, red flakes, m.p. > 360°. Similar result was obtained by precipitation of the compound from methanolic solution with slow addition of ether. This process was repeated several times until the UV absorption maxima reached constant values. $\lambda_{max.}^{0.1\ N\ HCl}$ 365 mμ (ε 14,130); 260 mμ (ε 46,770). $\lambda_{max.}^{EtOH}$ 396 mμ (ε 11,090); 360 mμ (ε 12,670); 256 mμ (ε 44,540).

*Anal.*—Calcd. for $C_{14}H_{17}IN_6$: C, 42.42; H, 4.29; I, 32.07; N, 21.21. Found: C, 42.21; H, 4.15; I, 32.10; N, 21.10.

**2 - Amino - 4 - imino - 1,6,7 - trimethyl - 1,4 - dihydrobenzo(g)pteridine (III)**—To a boiling, 10% aqueous sodium carbonate solution (25 ml.) was added 170 mg. (0.0043 mole) of the above compound (II), and the mixture was stirred for 15 min. without further heating. A green precipitate was obtained which was allowed to settle at room temperature, filtered, and washed with water followed by acetone. Yield: 100 mg. (92%) of crude III. This was purified by dissolving in boiling methanol and treatment of the hot solution with charcoal (Darco); on cooling, the compound crystallized in the form of yellow micro-needles, no melting point (apparently decomposes above 250°). $\lambda_{max.}^{0.1\ N\ HCl}$ 365 mμ (ε 10,400); 260 mμ (ε 32,760). $\lambda_{max.}^{EtOH}$ 390 mμ (ε

[1] Microanalyses by Galbraith Laboratories, Knoxville, Tenn., and by Dr. S. N. Nagy, Microchemical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass. The melting points were taken on the Kofler block and are uncorrected. The ultraviolet spectra were determined on a Beckman DU spectrophotometer attached to a Gilford model 2000 absorbance indicator. The infrared spectrum was determined on a Perkin-Elmer model 137 Infracord spectrophotometer. The NMR spectrum was determined on a Varian A-60, with tetramethylsilane as external standard.

7,340); 345 mμ (ε 8,100); 258 mμ (ε 32,100).

*Anal.*—Calcd. for $C_{13}H_{14}N_6$: C, 61.42; H, 5.51; N, 33.07. Found: C, 61.79; H, 5.35; N, 32.87.

**2 - Hydroxy - 4 - oxo - 1,6,7 - trimethyl - 1,4 - dihydrobenzo(g)pteridine (IV)**—To a boiling solution of 2 - amino - 4 - imino - 1,6,7 - trimethyl - 1,4-dihydrobenzo(*g*)pteridine (III) (100 mg., 0.0004 mole) in 2-methoxyethanol (30 ml.), 1 *N* sodium hydroxide (20 ml.) was added, and the resulting solution was heated for 60 min. on the steam bath (9). The hot, greenish yellow solution was acidified with glacial acetic acid (about 10 ml.) and cooled in the refrigerator overnight. The precipitate obtained was collected by filtration and washed with water until the washings were neutral to litmus paper. The residue (30 mg., 30%) was further purified by dissolving in methanol and treatment with charcoal. Concentration of the solution afforded yellow microcrystals; yield, 20 mg. (20%), m.p. 292–294°. $\lambda_{max.}^{EtOH}$ 392 mμ (ε 8,800); 336 mμ (ε 9,000); 250 mμ (ε 36,500). $\lambda_{max.}^{0.1\ N\ NaOH}$ 400–392 mμ (ε 9,972); 358–332 mμ (ε 8,976); 252 mμ (ε 39,060). Due to sparing solubility of the compound in 0.1 *N* HCl, the cationic spectra of the compound could not be taken.

*Anal.*—Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.68; N, 21.87. Found: C, 60.96; H, 4.99; N, 21.75.

**3 - Methylamino - 6,7 - dimethylquinoxaline - 2-carboxylic Acid (V)**—To a suspension of III (300 mg., 0.0012 mole) in 2-methoxyethanol (30 ml.) was added 50 ml. of 10% aqueous sodium hydroxide. The mixture was refluxed for 52 hr. with stirring. A white amorphous solid appeared which was filtered after cooling. The filtrate was concentrated to one-third of its original volume and then acidified with excess concentrated hydrochloric acid, whereupon a white precipitate was formed. Without separation, the mixture was further concentrated, under reduced pressure to dryness. The residue was then extracted in a Soxhlet apparatus with a chloroform–benzene mixture (3:1 v/v) until no more colored material was eluted by the solvent (about 15 hr.). The yellow solution was evaporated to dryness and the residue was extracted with boiling ether. The hot ether extract was filtered and evaporated to dryness. The residue was dissolved in minimum quantity of methanol, and crystallized at 0°, to yield an orange-colored solid (50 mg., 18%), m.p. 172–175°. Ultraviolet $\lambda_{max.}^{0.1\ N\ HCl}$ 400 (ε 6,650); 340 mμ (ε 8,529); 252 mμ (20,900). $\lambda_{max.}^{EtOH}$ 405mμ (ε 4,650); 315 mμ (ε 4,620); 258 mμ (ε 27,900). Infrared $\nu_{max.}^{KBr}$ (cm.$^{-1}$): 3400(s) (OH, NH); 2920 (m) ($CH_3$); 2700 (vw); 1720(s) (C=O); 1660, 1620(w) (NH); 1570(s), 1535(sh), 1510(m) (aromatic C=C, C=N); 1460 (m) (C—$CH_3$); 1400(m) (COOH); 1370(m) (C—$CH_3$); 1345(s) (C—N); 1290(w) (COOH); 1240(m), 1100(m), 1000(m) (ring-vibrations); 835 (benzene-C—H). NMR (in $CF_3COOH$): 2.15, 3.10, 7.3, and 7.7 p.p.m. Integrated ratio: 6:3:1:1 (2 benzene-$CH_3$, 1 N—$CH_3$, 1 + 1 benzene ring-protons).

*Anal.*—Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.63; N, 18.18. Found: C, 62.16; H, 5.89; N, 17.91

**2 - Amino - 4 - imino - 1,6,7 - trimethyl - 3,4 - dihydrobenzo(g)pteridinium Iodide (VI)**—To nitromethane (75 ml.) was added, under continuous stirring, 2,4-diamino-6,7-dimethyl(*g*)benzopteridine (*a*) (500 mg., 0.00207 mole), and this was followed by dropwise addition of methyl iodide (3.0 ml., 0.059 mole). The mixture was refluxed for 3–4 hr. (during which time its color turned black) and, while still hot, filtered through a diatomaceous earth[2] bed. From the red filtrate the solvent was removed on the flash evaporator, and the residue was taken up in boiling methanol. The hot methanolic solution was treated with charcoal (Darco) and filtered through a diatomaceous earth bed. On concentrating the solution to about 30 ml., red micro-needles separated out; yield, 250 mg. (32%), m.p. 360°. This was further purified by repeated crystallization from the same solvent. $\lambda_{max.}^{0.1\ N\ HCl}$ 460 mμ (ε 2,188); 372 mμ (ε 12,880); 260 mμ (ε 41,690); 220 mμ (ε 35,480). $\lambda_{max.}^{EtOH}$ 460 (ε 4200); 394 mμ (shoulder; ε 11,140); 358 mμ (ε 13,050); 258 mμ (ε 38,200); 219 mμ (ε 45,000).

*Anal.*—Calcd. for $C_{13}H_{15}IN_6$: C, 40.83; H, 3.92; N, 21.99. Found: C, 40.82; H, 4.09; N, 21.88.

**2,4 - Diimino - 6,7 - dimethyl - 1,2,3,4 - tetrahydrobenzo(g)pteridine Hydrochloride (VII)**—The quaternary iodide (VI) (450 mg., 0.0012 mole) was dissolved in hot water, and the red solution was added at room temperature to a 0.5 *N* aqueous sodium hydroxide solution (50 ml.) at room temperature. Immediately a red solid precipitated. The reaction mixture was cooled in the refrigerator overnight, then centrifuged, and the clear supernatant was decanted. The residue was washed with one portion of cold water and centrifuged, then added to ice cold 6 *N* HCl (50 ml.); on further cooling in an ice bath, a solid separated out. After filtration, the residue was dissolved in methanol, the solution was charcoaled, and the resulting yellow filtrate was concentrated in the flash evaporator to about 25 ml., whereupon a yellow solid began to separate at room temperature. This was collected by filtration (100 mg., 29%) and further purified by repeating the same process, until an analytically pure sample was obtained.

*Anal.*—Calcd. for $C_{13}H_{14}N_6 \cdot HCl$: C, 53.70; H, 5.16; N, 28.91. Found: C, 53.42; H, 5.40; N, 28.93.

**Conversion of VII to Free Base**—Sixty milligrams (0.0002 mole) of VII was dissolved in water (15 ml.), without heating. To the cold aqueous solution, 10% aqueous sodium carbonate solution was added until the solution became neutral to litmus. A red precipitate separated immediately after addition. This was centrifuged, washed thoroughly with water, and then with a minimum quantity of acetone. The crude residue was then dissolved in boiling methanol and treated with charcoal. The yellow filtrate (which showed green fluorescence) was concentrated, until a yellowish-green solid separated. This was further purified by repeated crystallizations from methanol. $\lambda_{max.}^{0.1\ N\ HCl}$ 364 mμ (ε 10,910); 259 mμ (ε 33,400). $\lambda_{max.}^{EtOH}$ 422 mμ (ε 9,612); 355–340 mμ (ε 7,600); 258 mμ (ε 34,370). In some preparations, the 422 mμ absorption of the ethanolic solution was partially or wholly shifted to 390–400 mμ, and the spectrum of the product was similar to the "normal" spectrum of III (see above) in absolute ethanol as well as in 0.1 *N* HCl.

*Anal.*—Calcd. for $C_{13}H_{14}N_6$: N, 33.07. Found: N, 32.76.

**Structure Determination of Compounds Derived from the Reaction in Nitromethane**—*Acid Hydrol-*

[2] Celite. Johns-Manville Corp., New York, N. Y.

*ysis of VII*—The hydrochloride salt (VII) (100 mg., 0.00034 mole) was mixed with 2-methoxyethanol (50 ml.), and concentrated hydrochloric acid (10 ml.) was added. The mixture was refluxed for 36 hr., during which time additional quantities (5 ml.) of concentrated hydrochloric acid were added, after 8 hr. and again after 14 hr. Initially the color of the solution was light brown; on heating for 7–8 hr., some solid separated and the color of the solution turned yellow. On continued heating, the solid dissolved and the solution turned deep brown in color. After evaporation to dryness, the residue was boiled with water for 20 min. and filtered. The residue (35 mg., 40%) was thoroughly washed with acetone and crystallized from ethanol, m.p. 295–296°. $\lambda_{max.}^{EtOH}$ 390 mμ (ε 8,772); 334 mμ (ε 8,772); 250 mμ (ε 36,600).

*Anal.*—Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.68; N, 21.87. Found: C, 61.39; H, 5.04; N, 21.97.

*Alkaline Hydrolysis of VII*—This was conducted in the same manner as described in the preparation of IV from III. $\lambda_{max.}^{EtOH}$ identical with acid hydrolysis product.

*Alkaline Hydrolysis of VI*—The quaternary methyl iodide (VI) was hydrolyzed, in the same manner, and the product obtained showed the same spectrum as the acid and base hydrolysis products from VII above.

**Thin-Layer Chromatography**—The above compounds obtained from VII by acid and alkaline hydrolysis, respectively, were compared with IV (obtained by alkaline hydrolysis of III) by simultaneously conducted thin-layer chromatography, using alumina as the adsorbent and dimethylformamide–water (9:1) mixture as the solvent. Each compound gave a single fluorescent spot under ultraviolet light, corresponding to an $R_f$ value of 0.55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*Keyphrases*

Deoxyalloxazines (benzopteridines)
2,4-Diamino-6,7-dimethylbenzo(*g*)-pteridine—methylation
UV spectrophotometry—structure
IR spectrophotometry—structure
NMR spectrometry
TLC—UV light fluorescence

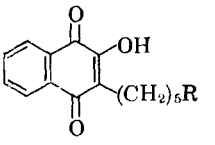

# Lawsone Derivatives IV. 3-ω-Substituted Alkyllawsones and Related Compounds

By H. MACHATZKE, W. R. VAUGHAN*, C. L. WARREN, and G. R. WHITE

**This paper reports the preparation of two 3-alkyllawsones in which there is a nitrogen mustard function in the ω-position. In addition, a potentially general route to the preparation of 3-ω-aminoalkyllawsones is described. The method involves introduction of an ω-amino group *via* an ω-azido group.**

THE OBJECTIVES of this continuing research have been discussed in a previous paper (1), and the purpose of the present paper is to report preparation of lawsones (2-hydroxy-1,4-naphthoquinone) with 3-alkyl substituents terminating in an alkylating function. In addition, the development of a potentially general route to preparation of 3-ω-aminoalkyllawsones has been studied, and various ancillary problems have been delineated.

Two related series of lawsone derivatives have been investigated: one in which the 3-position carries a normal pentyl chain terminating in a functional group (general structural formula I, in which lower case letters refer to known starting materials involved in synthesis); and one in which the 3-position carries a normal decyl chain terminating in a functional group (general structural formula II, with notation as for I).



I

R

| | |
|---|---|
| *Ia* —$CO_2C_2H_5$ | *IA* —$CO_2CH_3$ methyl ether |
| *Ib* —COCl | *IB* —$CH_2OH$ |
| *Ic* macrocyclic lactide derived from *Ib* | *IC* —$CON(CH_2CH_2OH)_2$ |
| | *ID* —$CON(CH_2CH_2Cl)_2$ |

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