

in polyoxypropylene polyoxyethylene surfactants. The HLB numbers can be calculated from the derived equation which closely agree with the observed values for this series of surfactants. Conversely, part of the molecular structure of the surfactant can be determined, e.g., the molecular weight of the hydrophobic group or the percent hydrophilic groups in the total molecule, when the HLB number and one of the other variables of a particular surfactant of this series are given

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Keyphrases

Polyoxyethylene polyoxypropylene surfactants
Griffin HLB numbers—multiregressional analysis
Hydrophobic group, M.W.—HLB relation
Hydrophilic group, percent—HLB relation

Cactus Alkaloids IV. Macromerine from *Coryphantha runyonii*

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Macromerine, a β -phenethylamine alkaloid previously isolated from *Coryphantha macromeris*, has been isolated from *Coryphantha runyonii*

HODGKINS *et al.* (1) have recently isolated a new β -phenethylamine, macromerine, from the cactus, *Coryphantha macromeris* (Engelm.) Lemaire. Physiological tests demonstrated that macromerine has potential hallucinogenic and sympatholytic activities. From physical data, spectra, and elemental analysis they proposed that macromerine is *l*- α -3,4-dimethoxyphenyl- β -dimethylaminoethanol, and they have confirmed this structure by synthesis of the racemic mixture.

Working independently in this laboratory using thin-layer chromatography (TLC) several unknown alkaloids were detected in a related species of cactus, *Coryphantha runyonii* Britton and Rose (2). Since the alkaloids detected produced TLC patterns different from those of previously known cactus alkaloids, isolation attempts were initiated.

EXPERIMENTAL

Using large Soxhlet extractors, alkaloids were extracted with ethanol from 1.8 Kg. of dried and pulverized plant material.¹ Nonphenolic alkaloids were isolated from the ethanolic residue using the procedures and ion-exchange column technique of purification method No. 2 (3). The total nonphenolic alkaloid fraction was chromatographed over 560 Gm. of activated alumina in a 40 \times 150 cm. column using chloroform as the developer. Eluant fractions of 15-20 ml. each were collected and analyzed by TLC. Those fractions richest in concentrations of the major alkaloid were combined. The crystalline residue obtained (1.314 Gm.; yield 0.07%) was recrystallized several times from ethyl ether (m.p. 65-65.5°; picrate m.p. 159°; optical rotation: $[\alpha]_D^{25} = -54.2$, $c = 0.0120$ Gm./ml. in methanol).

Received August 17, 1967 from the College of Pharmacy, University of Michigan, Ann Arbor, MI 48104

Accepted for publication September 26, 1967

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¹ Obtained from Davis Cactus Garden, Kerrville, Tex., and D. E. Wiley, Corpus Christi, Tex. Identification confirmed by Dr. E. U. Clover, Botany Department, University of Michigan.

The isolated alkaloid appeared as a single spot upon TLC analysis in several solvent systems, indicating its homogeneity.

Permanganate oxidation (4) of the alkaloid produced a crystalline derivative which was identified as 3,4-dimethoxybenzoic acid by melting point, mixed melting point, and IR spectral comparison. Elemental analysis² of the alkaloid indicated an empirical formula of $C_{12}H_{13}NO_3$.

Calcd. for C, 63.98; H, 8.50; N, 6.22; mol. wt. 225.29. Found: C, 65.02; H, 8.39; N, 6.29.

The UV spectrum (0.016 mg./ml. methanol) showed a λ_{max} at 202 $m\mu$ and smaller peaks at 230 $m\mu$ and 278 $m\mu$, indicating typical benzene ring absorption. The IR spectrum in KBr revealed a broad band at 3120 cm^{-1} (hydroxyl). NMR spectra in $CDCl_3$ showed peaks at 6.99 δ and 6.89 δ , indicative of three aromatic hydrogens, and a doublet of doublets centered at 4.67 δ , indicative of a benzylic hydrogen adjacent to two nonequivalent methylene protons (5). An alcohol hydrogen (3.96 δ) showed shifts with varying concentrations and disappeared with D_2O exchange. A doublet centered at 3.90 δ indicated two methoxyl groups, a doublet centered at 2.48 δ indicated a methylene group, and a singlet at 2.35 δ indicated two methyl groups attached to nitrogen.

Analysis by high resolution mass spectrometry³ showed a weak molecular ion peak at $m/e = 225.1362$, in agreement with the proposed empirical formula. Prominent peaks appeared at $m/e = 208$, 207, 192, 180, 167, 166, 165, 164, and 151, postulated structures of which are compatible with the expected fragmentation pattern of macromerine.

The UV, IR, and NMR spectra of the alkaloid and the spectra of natural *l*-macromerine from *C. macromeris* as well as synthetic *d,l*-macromerine are essentially identical. In addition the melting point of *l*-macromerine (m.p. 65-65.5°) was not depressed by admixture (mixed m.p. 65-65.5°) with the alkaloid isolated from *C. runyonii*.⁴

² Spang Microanalytical Lab., Ann Arbor, Mich.

³ The authors are indebted to Dr. A. Brossi and Dr. F. Vane, Hoffmann-LaRoche, Inc., for the mass spectral data.

⁴ The authors are indebted to Dr. J. E. Hodgkins, Department of Chemistry, Texas Christian University, for samples and spectra of natural and synthetic macromerine.

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. macomeris*, and has been given the common name *l*-macomerine. Comparison of spectral and chemical data revealed that the unknown alkaloid from *C. runyonii* is identical to *l*-macomerine from *C. macomeris*. Thus, the occurrence of macomerine is not restricted to the latter species.

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 Keyphrases

Alkaloids, cactus—*Coryphantha runyonii*
 Macomerine—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

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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-deoxy-lumichrome, I) was found to be a highly active antimetabolite of both folic 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 benzo-pteridine 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.

Received July 18, 1967, from the Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214

Accepted for publication October, 9, 1967.

This investigation was supported by research grant CA-06695 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

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