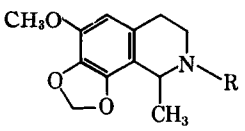
Peyote Alkaloids VI. Peyophorine, a Tetrahydroisoquinoline Cactus Alkaloid Containing an *N*-Ethyl Group

Sir:

During a recent investigation (1–3) of the peyote cactus (*Lophophora williamsii*) alkaloids, anhalonine (I*a*) and lophophorine (I*b*) were isolated in addition to eight other compounds. However, gas chromatography[1] of the "purified" I*b* hydrochloride {m.p. 233–235.5°; $[\alpha]_{589}^{25} = -13.6°$ (c = 0.59, H_2O); lit. (4) $[\alpha]_{589}^{25} = -9.47°$ (c = 1, H_2O)} and the base {$[\alpha]_{589}^{25} = -45°$; $[\alpha]_{436}^{25} = -83.7°$ (c = 0.82, $CHCl_3$); lit. (5) $[\alpha]_{589}^{25} = -47°$ (c = 1, $CHCl_3$)} disclosed the presence (*ca.* 10%) of a new alkaloid. The structure of this alkaloid, designated peyophorine, was clearly established as *N*-ethylanhalonine (I*c*), the *N*-ethyl homolog of I*b*, by its characteristic mass spectrum [base peak *m/e* at 234 (P—CH_3)] completely analogous with I*b* [base peak *m/e* at 220 (P—CH_3), *cf.* pilocereine (6)]. The same compound I*c* was also found in authentic samples obtained from the collection of Spaeth and coworkers as well as a sample acquired from a commercial source.[2] To eliminate the possibility of an artifact (*e.g.*, ethanol plus acid, *etc.*), de-



I*a* (R = H)
I*b* (R = CH_3)
I*c* (R = C_2H_5)
I*d* (R = $COCH_3$)

fatted plant material was extracted with ethanol-free chloroform and the chloroform-soluble hydrochlorides were found to contain *ca.* 20% I*c* (compared to I*b*) as determined by the combined GLC-mass spectrum.

I*c* was separated from I*b* by TLC on Silica Gel G using benzene–*n*-propanol–triethylamine (65:20:1) and the isolated purified oily base afforded a crystalline picrate m.p. 155–156°.[3]

N-Ethylanhalonine was prepared by ethylation of I*a* with diethyl sulfate (removing unreacted I*a* by acetylation) and was found to be identical (IR, GLC, mass spectra) with natural I*c*.[4] The prepared I*c* picrate showed the same m.p., mixed m.p., and IR spectrum as the picrate of natural I*c* suggesting that they were of the same optical configuration.

Anal.—Calcd. for $C_{20}H_{22}N_4O_{10}$: C, 50.21; H, 4.64; N, 11.71. Found: C, 50.23; H, 4.63; N, 11.76.

The ethiodide of I*c* (m.p. 203–204°) derived from I*a* showed a negative Cotton effect with the first maximum at 289 mμ $[\alpha]_{289}^{25} = -232°$ (c = 0.52, H_2O); *cf.* the methiodide of natural lophophorine (I*b*, containing *ca.* 10% I*c*) first maximum at 289 mμ $[\alpha]_{289}^{25} = -257°$ (c = 0.016, H_2O).

Alkaloids containing *N*-ethyl group are extremely rare in nature (7), occurring mainly in terpenoid alkaloids (8), *e.g.*, delpheline, aconitine, and lycoctonine, where their presence is clearly related to acetate biosynthesis.

Battersby *et al.* (9) have recently shown that the *1*-methyl group of tetrahydroisoquinoline cactus alkaloids is not derived from methionine. Although acetate is a logical alternative [*cf.* the presence of *N*-acetylmescaline in the plant (10)] randomization of the label during 1-^{14}C acetate feedings was observed. However, the *N*-ethyl group of I*c* is more obviously derived from acetate than C_1 and its attached methyl group and tracer experiments are in progress to determine this point.

An examination of the mother liquor from which isolation of additional I*a* was reported by us (11), has indeed revealed the occurrence of the *N*-acetyl derivative (I*d*). The latter compound was identified by comparison with synthetic I*d* (m.p. 151.5–153°; $[\alpha]_{589}^{25} = 206°$) using the combined GLC-mass spectra technique.

Anal.—Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.93; H, 6.64; N, 5.32.

By employing the same method the presence of I*d* has also been demonstrated in a neutral fraction of the peyote cactus. The occurrence of I*d* in the plant suggests that it may be a precursor of I*c*. Biosynthesis of I*c* and other peyote alkaloids is currently being studied.

(1) Kapadia, G. J., Shah, N. J., and Zalucky, T. B., *J. Pharm. Sci.*, **57**, 254(1968).

[1] GLC-mass spectra were determined on the LKB-Producter mass spectrometer using a 183-cm. (6-ft.) column containing 3% OV-7 on 100 mesh Gas Chrom Q at 200° at a helium flow rate of 15 ml./min. Mass spectra were obtained at 70 ev., 100 μamp. trap current at 3.5 kv., accelerating voltage.

[2] Authentic sample of lophophorine hydrochloride from the collection of the late Prof. E. Spaeth was obtained from Smith, Kline and French Laboratories, and a sample of the base hydrochloride was furnished by S. B. Penick & Co.

[3] The identification of I*c* in the "purified" sample of I*b* suggests that the recently reported (1) quaternary alkaloid lophotine, the iodide of which was found to be identical with the methiodide of the isolated I*b*, is a mixture of the metho-derivatives of I*b* and I*c*.

[4] The same compound was obtained by lithium aluminum hydride reduction of *N*-acetylanhalonine (see text). During the ethylation of I*a* with diethyl sulfate a minor reaction product isolated was identified by NMR and mass spectrometry as *N*-carboethoxyanhalonine. The formation of the latter compound is presumed to be due to the reaction of a halonine with phosgene (from chloroform, used as a solvent) and ethanol (from diethyl sulfate).

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Keyphrases

Peyote alkaloids
Peyophorine—identity confirmation
TLC—separation
GLC—identity
IR spectrophotometry—identity
Mass spectroscopy—identity

Books

REVIEW

Dictionary of Pharmaceutical Sciences and Techniques. Vol. 1. By A. SLIOSBERG. American Elsevier Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017, 1968. approx. 1000 pp. 16.5 × 23 cm. Price $30

This dictionary is the first attempt to give the equivalents in English, French, Italian, Spanish, and German, of technical terms which are used in pharmaceutical technology. Approximately 7500 major entries with cross-referencing of English synonyms are included. The book is made up of a basic table of the English terms, with the synonyms arranged alphabetically, and then followed by the translations in the other languages. The terms in the languages other than English are included in an index with a reference back to the numbered item in the basic table where the several translations are found.

This is the first of two volumes; the second volume will be "Materia Medica" and publication is expected in about two years. Dr. Sliosberg has also authored a similar work in five languages on medicine entitled "The Medical Dictionary."

Staff review

Actinomycin: Nature, Formation, and Activities. Edited by S. A. WAKSMAN. Interscience Publishers, Inc., 605 Third Avenue, New York, NY 10016, 1968. ix + 231 pp. 16 × 23.5 cm. Price $8.95.

The isolation in 1940 of actinomycin by Waksman and Woodruff was the result of a comprehensive screening program on the production of antimicrobial substances by soil-inhabiting microorganisms especially the *Actinomycetes*. Although many hundreds of antibiotics have been described in the 28 years since the initial actinomycin report, more research is now probably underway concerning the biological properties, clinical uses, chemistry, and biogenesis of this antibiotic than any other single antibiotic presently being examined. The contributors to this monograph have summarized current research progress on actinomycin chemistry (A. W. Johnson), actinomycin biogenesis (E. Katz), effects of actinomycin on virus replication (A. J. Shatkin), actinomycin action on experimental tumors (Ch. Hackmann), and clinical use of actinomycin (S. Farber, A. T. Mitus, and D. A. Karnofsky). Other chapters include an evaluation of actinomycin in developmental biology (P. R. Gross), the history of actinomycin (S. A. Waksman), and modification of the immune response by actinomycin (W. J. K. Tannenberg and R. S. Schwartz). Some aspects of large-scale production are also included in a chapter by H. B. Woodruff and S. A. Waksman.

Each chapter contains previously unpublished facts, hypotheses, and conclusions which should stimulate discussion by those readers previously unacquainted with the present knowledge of this interesting antibiotic. Although the monograph does not contain all the available information on this antibiotic, those who carefully read the clearly written chapters and consult the bibliography will quickly grasp the essential features and properties of this important antibiotic.

The monograph contains few typographical errors and is reasonably free of other errors. The adequate subject index and bibliography (more than 700 references) are of use to both the newcomer and the antibiotic expert. This monograph should be included in any library on antibiotics.

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