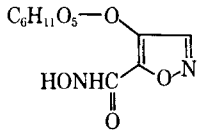
Structure of Hiptagin as 1,2,4,6-Tetra-*O*-(3-nitropropanoyl)-β-D-glucopyranoside, Its Identity with Endecaphyllin X, and the Synthesis of Its Methyl Ether

Sir:

Although *Hiptage madablota* Geartn. (family *Malpighiaceae*) does not grow widely in Java, the plant was apparently well known to the natives, who ascribed aphrodisiacal properties to an extract of the roots and provided detailed instructions for dispensation to bulls (1). Ritsema (1) reported the isolation in rather high yield of a white, crystalline, nitrogenous compound from this extract but was unable to duplicate the purported physiological effects when the substance was administered subcutaneously.[1] Ritsema's compound was named hiptagin by Gorter (2), who repeated and improved the original isolation procedure, assigned the (incorrect) formula $C_{10}H_{14}N_2O_9 \cdot {}^1/_2H_2O$, and carried out a number of hydrolysis experiments with this substance, m.p. 110°. Hiptagin could be hydrolyzed under a variety of acidic and basic conditions and Gorter was able to identify a formidable array of products, among them glucose. Aside from glucose, however, the product most directly relevant to the structure of hiptagin was hiptagenic acid, a compound subsequently shown by Carrie (3) to be identical with the aglycone derived from karakin and finally identified by Carter and McChesney (4) as the long known (5) 3-nitropropanoic acid. The plethora of hydrolytic transformations observed by Gorter were somewhat ingeniously rationalized by his proposal (2) of structure I for hiptagin although, in retrospect, they are readily traced to the presence of the 3-nitropropanoyl moiety. In view of the challenge to structure I inherent in Carter's formula-



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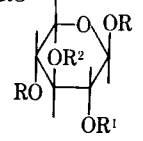
tion (6) of karakin, a closely related glucoside, as 1,4,6-tri-*O*-(3-nitropropanoyl)-β-D-glucopyranoside (II), the structure of hiptagin was clearly in need of revision.

We were led naturally to a consideration of this problem in connection with work with the endecaphyllins (7), a group of glucose polyesters of 3-nitropropanoic acid isolated from a toxic extract of *Indigofera endecaphylla* Jacq. (family (*Leguminosae*, subfamily *Papilionatae*). Following the directions of Gorter (2), we have easily isolated from an acetone extract[2] of defatted root-bark of *H. madablota* a white, crystalline glucoside, m.p. 102–104°, which we believe to be hiptagin and for which the structure 1,2,4,6-tetra-*O*-(3-nitropropanoyl)-β-D-glucopyranoside (III) is required by the evidence presented below.

At the outset, this substance proved to be identical with endecaphyllin X (7) by mixed melting point, optical rotation, and infrared spectral comparisons and thus could be formulated as a glucose tetraester of 3-nitropropanoic acid ($C_{18}H_{24}N_4O_{18}$).[3] In addition, acid-catalyzed diazomethylation (7,8) provided a monomethyl ether, m.p. 139–141° (IV), which was shown to be indistinguishable from the derivative similarly prepared from endecaphyllin X. The NMR spectra of III and IV (hexadeuteroacetone solution) revealed the anomeric proton as a doublet centered at τ4.10 with $J_{1,2}$ = 8.3 c.p.s. These values indicate that the C-1 hydroxyl group is acylated and is in the β-configuration. Detailed analysis of these spectra allowed assignment of a triplet centered at τ5.90 (separation, 8.5 c.p.s.) to the C-3 proton in III which corresponds to a triplet at τ6.1 (separation, 9 c.p.s.) in the spectrum of IV. This upfield shift of the C-3 proton on methylation requires that the free hydroxyl group in III be located at the 3-position.



II, karakin; R = $O_2NCH_2CH_2CO$-
$R^1 = R^2 = H$

III, hiptagin; R = $R^1 = O_2NCH_2CH_2CO$-
$R^2 = H$

IV, hiptagin methyl ether;
R = $R^1 = O_2NCH_2CH_2CO$-
$R^2 = CH_3$

[1] As pointed out by Gorter (2), this result must be considered inconclusive since the pure compound is insoluble in water and, insofar as we are aware, no additional biological data have been reported.

[2] This extract was kindly supplied by Dr. G. Ganguli, Department of Chemistry, University College of Science, Calcutta, India. A solid which precipitated during this acetone extraction has been identified as mangiferin. Finnegan, R. A., Stephani, R. A., Ganguli, G., Ganguly, S. N., and Bhattacharya, A. K., to be published.

[3] Interestingly, we have also repeated the isolation of karakin from the kernels of *Corynocarpus laevigata* Forst. (family *Anacardiaceae*) and find it to be identical with endecaphyllin B (7). Although the data upon which Carter based the assignment of structure II to karakin (6) are equivocal, we have adduced spectroscopic evidence in support of II.

This conclusion was verified by a synthesis of IV which made use of the known (9) 3-*O*-methyl-α-D-glucose, m.p. 164–166°. Acylation with 3-nitropropanoyl chloride in *N*-methylpyrrolidone solution provided an oily tetra-ester whose NMR spectrum showed it to be an anomeric mixture (C-1 proton of α-anomer at τ3.63, $J_{1,2}$ = 4 c.p.s.; C-1 proton of β-anomer at τ4.10 $J_{1,2}$ = 8.3 c.p.s.). However, crystallization from methylene chloride solution afforded an authentic sample of the β-anomer, m.p. 136–140°, whose infrared and NMR spectra were indistinguishable from those of naturally derived IV and whose mixed melting point was undepressed.

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Keyphrases

Hiptagin–*Hiptage madablota*
Endecaphyllin X–hiptagin, identical structures
Optical rotation
IR spectrophotometry–structure
NMR spectrometry

Books

REVIEWS

Advances in Chromatography. Vol. 4. Edited by J. CALVIN GIDDINGS and ROY A. KELLER. Marcel Dekker, Inc., 95 Madison Ave., New York, NY 10016, 1967. 15.5 × 23 cm. xiv + 380 pp. Price $16.50.

Most of the topics included in vols. 1–3 of this series, by and large, provided the balance of breadth and depth of coverage which is needed to present the reader with an overall view of the progress in the entire field of chromatography. It was noted in the reviews of these volumes [*J. Pharm. Sci.*, **55**, 863(1966); **56**, 1047(1967)], however, that not all of the chapters achieved this goal set by the editors.

The latter case is true to a greater extent in vol. 4 than in its predecessors. The one chapter relating directly to pharmaceutical chemistry (Steroid Separation and Analysis: The Techniques Appropriate to the Goal, by R. Neher) is disappointingly superficial; the other chapters, for the most part, emphasize depth of coverage at the expense of breadth. The chapter which achieves the desired balance is "Mass-Spectrometric Analysis of Gas-Chromatographic Eluents," by W. H. McFadden.

In addition, vol. 4 contains the following chapters: "R_f values in Thin-Layer Chromatography on Alumina and Silica," by Lloyd R. Snyder; "Some Fundamentals of Ion-Exchange-Cellulose Design and Usage in Biochemistry," by C. S. Knight; "Adsorbents in Gas Chromatography," by A. V. Kiselev; "Packed Capillary Columns in Gas Chromatography," by István Halász and Erwin Heine; "The Polarity of Stationary Liquid Phases in Gas Chromatography," by Lutz Rohrschneider.

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Ganglion-Blocking and Ganglion-Stimulating Agents. By. D. A. KHARKEVICH. First English Edition, translated from the Russian by R. Crawford. Pergamon Press, Inc., 44-01 21st St., Long Island City, NY 11101, 1967. xi + 367 pp. 14 × 22 cm. Price $14.00.

Most medicinal chemistry researchers have probably had occasion to encounter both the interesting reports in such journals as *Farmakol. Toksikol.* and *Zhur. Obsh. Khim.* and the reluctance of the scientists to communicate *via* letters or reprints. Dr. Kharkevich's contribution is welcome, not only for the wealth of information and the quality of his book, but perhaps as evidence that more rapport between workers in this field may be imminent. While the reviewer is hardly competent in Russian, Dr. Crawford's translation is very obviously good English and appears to be faithful to the facts.

A study of agents affecting the ganglia is pullulate with experimental problems. The difficulties of obtaining and interpreting accurate data are well known. This book begins with a brief summary of