NEW ALKALOIDS, LEUCOTAMINE AND O-METHYLLEUCOTAMINE, FROM *LEUCOJUM ASETIVUM* L.

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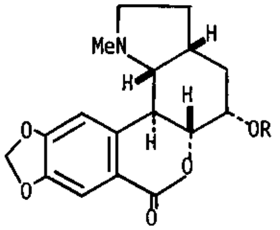
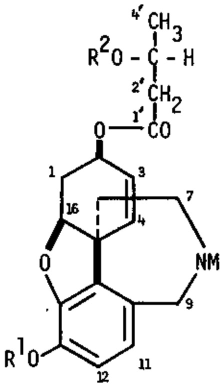
Abstract —— The structures of leucotamine and O-methylleucotamine isolated from the leaves of *Leucojum asetivum* L., have been determined as 3 and 4, respectively, on the basis of spectral and chemical evidence.

In previous reports,[1,2] we have reported the isolation of two novel alkaloids, clivacetine (1) and clivatine (2), possessing the acetoacetyl and 3-hydroxylbutyryl group,[3] respectively, from *Clivia minata* Regel (Amaryllidaceae): these alkaloids are important from biosynthetic point of view. Our continuing search for the alkaloid constituents of this family has now led to the isolation of two new alkaloids, named leucotamine (3) and O-methylleucotamine (4). These are the first members of the galanthamine-type alkaloids having 3R-hydroxybutyryl group and are interesting from biogenetic point of view. These alkaloids seem to be precursors of sanguinine (5)[4] and galanthamine (6)[4,5]. We wish to report the stereostructures of these new alkaloids.

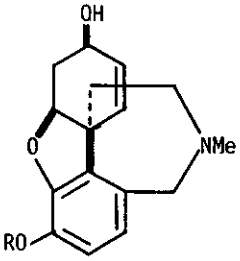
Leucotamine (3) was isolated from an ethanol extract of the fresh leaves of *Leucojum asetivum* L. (Amaryllidaceae) as needles, $C_{20}H_{25}NO_5$, mp 168-171°, $[\alpha]_D^{20}$ $-52.6°(c=0.7,CHCl_3)$. The base (3) gave a blue-violet color with ferric



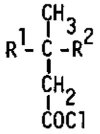
1 : R = $COCH_2COMe$
2 : R = $COCH_2CH(OH)Me$



3 : $R^1=R^2=H$
4 : $R^1=Me$, $R^2=H$
7(9b): $R^1=Me$, $R^2=Ac$



5 : R=H
6 : R=Me



$R^1-C(CH_3)(R^2)-CH_2-COCl$

8a : R^1=H,
R^2=OAc
8b : R^1=OAc,
R^2=H

chloride reagent and was assigned to be 2-(3'-hydroxybutyryl)sanguinine by the ^1H NMR study. The presence of sanguinine-moiety in this base was assigned due to the following peaks ($CDCl_3$) : δ 6.71 (1H, d, J=8 Hz, 12-H), 6.46 (1H, d, J=8 Hz, 11-H), 6.30 (1H, d, J=10 Hz, 4-H), 5.91 (1H, dd, J=10 and 6 Hz, H-3), 5.42 (1H, t-like, J=6 Hz, 2-H), 4.59 (1H, b s, 16-H), 4.09 and 3.66 (each 1H, d, J=14 Hz, 9-H_2), 2.40 (3H, s, NCH_3). The following data [δ 4.08 (1H, m, 3'-H), 2.48 (2H, d, J=7 Hz, 2'-H_2), and 1.18 (3H, d, J=7 Hz, 4'-H_3); ν_{max} (KBr) 3550 and 1730 cm^{-1}] are due to 3-hydroxybutyryl group in 3.

This assignment was supported by chemical correlation of 3 with O-methylleucotamine (4). Thus, methylation of 3 with diazomethane gave O-methylated product as an oil, which was found to be identical in all respects with a new base, O-methylleucotamine (4), isolated from both the leaves and bulbs of this plant. The base (4), $C_{21}H_{27}NO_5$, $[\alpha]_D^{24}$ -36.0°(c=0.8,$CHCl_3$), was crystallized as its methiodide [mp 199-200°(dec.), $C_{21}H_{27}NO_5\cdot CH_3I\cdot H_2O$] by the treatment of 4 with methyl iodide. The ^1H NMR spectrum ($CDCl_3$) of 4 showed the following peaks on which it was assumed that 4 is an ester of galanthamine (6) and 3-hydroxybutyric acid : the peaks [δ 6.66 and 6.54 (each 1H, d, J=8 Hz, 12- and 11-H), 6.31 (1H, d, J=10 Hz, 4-H), 5.86 (1H, dd, J=10 and 6 Hz, 3-H), 5.42 (1H, t-like, J=6 Hz, H-2), 4.56 (1H, m, 16-H), 4.11 and 3.64 (each 1H, d, J=15 Hz, 9-H_2), 3.83 (3H, s, OCH_3), and 2.38 (3H, s, NCH_3)] belong to galanthamine-part in this base. The presence of 3-hydroxybutyryl group was supported by the spectral data: δ 4.20 (1H, m, 3'-H), 2.44 (2H, d, J=6 Hz, 2'-H_2), and 1.16 (3H, d, J=6 Hz, 4'-H_3); ν_{max} (KBr), 3400 and 1720 cm^{-1}.

The final evidence for the stereochemistry of 3 and 4 was obtained by conversion of 4 into galanthamine (6) and by partial synthesis of O-methylleucotamine acetate (7) from 6. Thus, the ester (4) was hydrolyzed with 5% NaOH-EtOH to give 6 [66% yield, mp 125-127°, $[\alpha]_D^{23}$ -112.1°(c=0.7, EtOH)]. Acetylation of the base (4) with acetyl chloride in the presence of boron trifluoride etherate gave the acetate (7) as an oil [46% yield, $C_{23}H_{29}NO_6$, $[\alpha]_D^{24}$ -65.7°(c=0.9, $CHCl_3$), $[\alpha]_D^{23}$ -33.9°(c=0.6, EtOH); ($CDCl_3$), δ_H 1.261 (3H, d, J=6.4 Hz, 4'-H_3) and 1.942 (3H, s, 3'-$OOCCH_3$); ν_{max} (KBr) 1740 cm^{-1}]. On the other hand, according to Paquette and Freeman,[6] commercially available (±)-3-hydroxybutyric acid was acetylated and partially resolved with quinine to give optically impure (S)-(+)- and (R)-(-)-3-acetoxybutyric acids ($[\alpha]_D^{23}$ +3.4°(c=2.3, EtOH) and -4.0°(c=0.9, EtOH), respectively), which were treated with oxalyl chloride in benzene to give the corresponding acid chlorides, (8a) and (8b), respectively. Treatment of galanthamine (6) with the acid chloride (8a) or (8b) in the presence of boron trifluoride etherate gave optically impure product ($[\alpha]_D^{22}$ -68.2°(c=0.7, EtOH) or $[\alpha]_D^{23}$ -64.6°(c=0.9, EtOH)) of 3'S- and 3'R-O-methylleucotamine acetates (9a) and (9b). The former product ($[\alpha]_D$ -68.2°) consists of (9a) and (9b)[8:2], and the latter ($[\alpha]_D$ -64.6°) (9a) and (9b) [4:6] judging from the relative intensities of C-methyl and acetyl protons in their ^{1}H NMR spectra: 4'-H_3 of 9a at δ 1.277 (3H, d, J=6.1 Hz) and that of 9b at δ 1.259 (3H, d, J=6.4 Hz), and 3'-$OOCCH_3$ of 9a at δ 1.971(3H, s) and that of 9b at δ 1.941(3H,s). Comparison of these signals of the acetate (7) with those of 9a or 9b showed that the stereostructure of 7 could be assigned to 9b. Therefore, the structures of O-methylleucotamine and leucotamine were established as 4 and 3 having 3'R-hydroxybutyryl group, respectively.

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REFERENCES AND NOTES

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3. The configuration of 3'-hydroxyl group in **2** is uncertain.
4. S. Kobayashi, S. Takeda, H. Ishikawa, H. Matsumoto, M. Kihara, T. Shingu, A. Numata, and S. Uyeo, *Chem. Pharm. Bull.*, 1976, **24**, 1537.
5. O-Methylleucotamine (**4**) in this plant seems to be a precursor of galanthamine (**6**), since it was found that even under the conditions of TLC using SiO_2-Et_2NH-CCl_4 a part of **4** was hydrolyzid to **6** and in fact previous workers [N. F. Proskurnina, *Zhur. Obshchei Khim.*, 1957, **27**, 3365(*C.A.*, 1958, **52**, 9169e),and L. Bubeva-Ivanova and V. Ivanov, *Tr. Nauchnoizsled. Inst. Farm.*, 1962, **3**, 89(*C.A.*, 1964, **61**, 8128g)] and we[7] isolated **6** from *L. asetivum.*
6. L. A. Paquette and J.P. Freeman, *J. Org. Chem.*, 1970, **35**, 2249.
7. The isolation of **6** from this plant will be reported elsewhere.

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