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ON THE STRUCTURE OF VARIOSE

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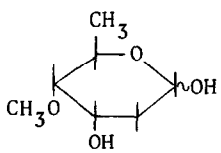
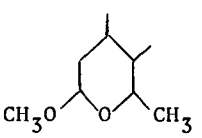
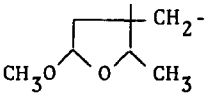
Variose is a constituent of an antibiotic, variamycin, and its structure was presented by Lokshin et al. as 2,6-dideoxy-4-O-methyl-D-*ribo*-hexose (1).[1] Their structure determination depends mostly on analysis of p.m.r. spectrum of methyl varioside (II) which was isolated from a natural product. First, they assumed formula IIa or IIb from identification of one $\overset{O}{O}>CH\text{-}CH_2$ (τ 7.85, 2-proton m and 4.84, 1-proton q), three O-CH (τ *ca.*6, 3-proton m), one $\underline{CH_3}\text{-}CH<\overset{O}{C}$ (τ 8.7, 3-proton d), two O-CH_3 (τ 6.56 and 6.5, 3-proton s), and one OH (τ 7.99, 1-proton s) groups by measurement of p.m.r. spectrum and molecular formula of $C_8H_{16}O_4$ obtained by mass spectrum. The basic structure was then assigned to IIa from decoupling p.m.r. spectrum of methyl benzoyl varioside (III). Position of OCH_3 group was decided to C-4 from its negative periodate reaction excluding C-4,C-5 diol structure. Finally, they concluded the structure of II to be methyl 2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside (VII). However, it seemed to be doubtful in the following points; i) the proton signal at C-5 is shifted to unusually low magnetic field (τ 4.8), ii) the signal pattern of protons at C-2 is analogous to those of other 2-deoxy sugars having furanoside structure rather than pyranoside, iii) a possible structure IIc is



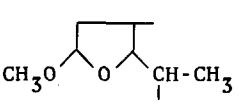
I



IIa



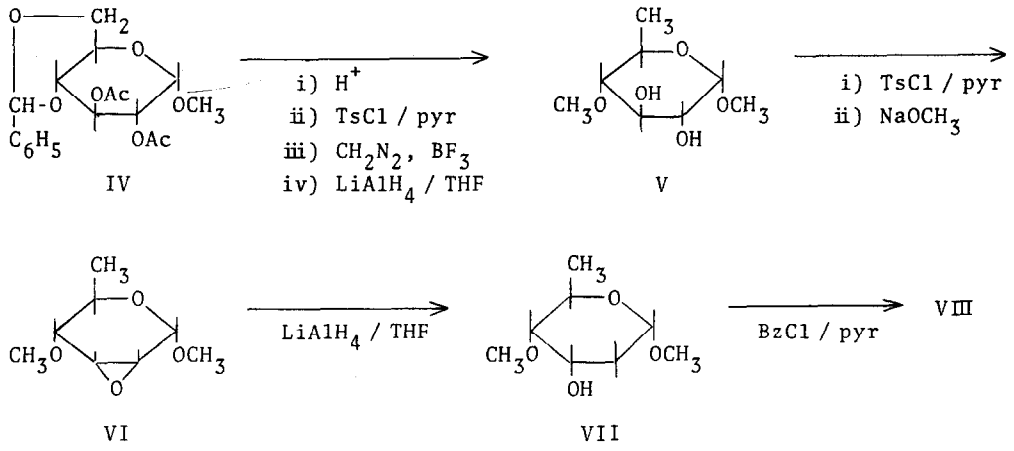
IIb



IIc

not considered, and iv) periodate reaction of diol at C-4 and C-5, if any, is so slow when it formed a pyranose or furanose ring structure that it is undeniable with ease.

The authors have synthesized methyl 2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside (VII) and its benzoate (VIII), and found some informations on the structure of variose.



IV V VI VII

Ac : acetyl, Ts : tosyl THF : tetrahydrofuran,
Bz : benzoyl, pyr : pyridine

Methyl 2,3-di-O-acetyl-4,6-O-benzylidene-α-D-glucopyranoside (IV)[2] was hydrolyzed with dil. hydrochloric acid to remove benzylidene group, and the primary hydroxyl group liberated was tosylated with tosyl chloride in pyridine to yield syrup which gave one spot on t.l.c. The secondary hydroxyl group at C-4 was methylated with diazomethane in the presence of BF_3-etherate as a catalyst.[3] Purified methyl 2,3-di-O-acetyl-4-O-methyl-6-O-tosyl-α-D-glucopyranoside was obtained as colorless crystals of mp 102-103°. Tosyl and acetyl groups were then removed by reduction with $LiAlH_4$ to give 6-deoxy compound (V). Structure of V was supported by mass spectrum of its acetyl derivative (M^+=276, M^+-OCH_3=245). Two hydroxyl groups of V were tosylated with tosyl chloride in stronger reaction conditions, and then detosylated with $NaOCH_3$ to afford an anhydro compound (VI). C-1 proton of VI showed

τ 6.28 ($J_{1,2}$=1.6Hz) and C-4 proton τ 6.82 ($J_{3,4}$=0.5Hz), respectively. Ferrier and Prasad[4] reported that J value between *trans*-located protons, such as C-1,C-2 and C-3,C-4 of 2,3-anhydro derivatives in α-D-*manno*-configuration, showed zero, and those between *cis*-located protons, such as C-1,C-2 and C-3,C-4 of 2,3-anhydro compounds in α-D-*allo*-configuration, showed smaller coupling constant than 4.5Hz. From these data, the structure of VI should be methyl 2,3-anhydro-6-deoxy-4-O-methyl-α-D-allopyranoside. VI was reduced with $LiAlH_4$, and the product was benzoylated to VIII; p.m.r. data of VIII: τ 5.25 (1-proton d, H-1, $J_{1,2a}$=4.3Hz, $J_{1,2e}$=∿0Hz), 8.00 (1-proton sextet, H-2*a*, $J_{2a,3}$=3.2Hz), 7.75 (1-proton q, H-2*e*, $J_{2e,3}$=2.6Hz), 4.32 (1-proton q, H-3, $J_{3,4}$=3.0Hz), 6.95 (1-proton q, H-4, $J_{4,5}$=9.7Hz), 5.73 (1-proton m, H-5, $J_{5,6}$=6.2Hz), and 8.68 (3-proton d, H-6). The J values of the anomeric proton showed C1 conformation. Hence, C-3 and C-4 protons should be in *cis*-configuration considering its J value (3.0Hz) and C1 conformation. Consequently, the structure of VIII was obvious to be methyl 3-O-benzoyl-2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside.

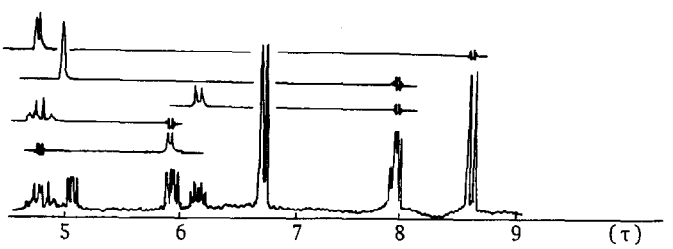


Fig. 1 Partial p.m.r. spectrum of methyl benzoyl-varioside (III) presented by Lokshin et al.[1]

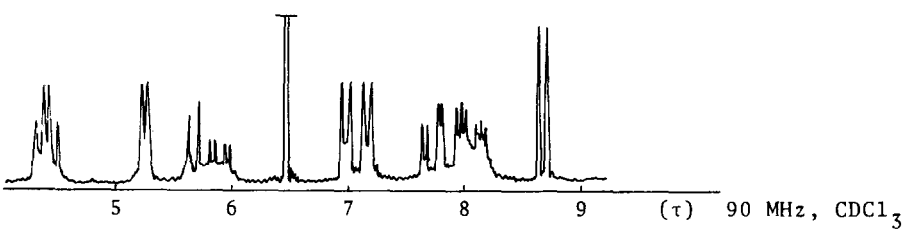
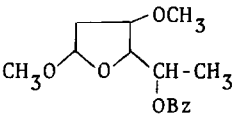


Fig. 2 Partial p.m.r. spectrum of methyl 3-O-benzoyl-2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside (VIII).

P.m.r. spectrum of VIII, thus obtained, definitely differed from those presented by Lokshin et al. (Fig. 1 and 2). Considering that the proton signal at C-5 coupling with CH_3 of C-6 was found in unusually low magnetic field (τ 4.8) as is seen in Fig. 1, assignment of the position of benzoyl group to the hydroxyl group of C-5 is reasonable rather than to that of C-3. Then as an inevitable result, a furanose ring is formed and signals of protons at C-2 show furanose like pattern. So, the compound presented as methyl 3-O-benzoyl-varioside in Fig. 1 may be methyl 5-O-benzoyl-furanoside. From these data, it was concluded that the structure of methyl 3-O-benzoyl-varioside presented by Lokshin et al. is not methyl 3-O-benzoyl-2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside (VIII). The actual structure is very likely to be methyl 5-O-benzoyl-2,6-dideoxy-3-O-methylhexofuranoside (IX). The further structure investigation is in progress. The detail will be reported elsewhere



IX

REFERENCES

1) G. B. Lokshin, Yu. V. Zhdanovich, A. D. Kuzovkov, and V. I. Sheichenko, Khim. Prir. Soedin., 9, 418 (1973).

2) D. S. Mathers and G. J. Robertson, J. Chem. Soc., 696 (1933).

3) J. O. Deferrari, E. G. Gros, and I. M. E. Thiel, Methods in Carbohyd. Chem., 6, 365 (1972).

4) R. J. Ferrier and N. Prasad, J. Chem. Soc. (C), 575 (1969).