# CHEMICAL MODIFICATION OF STREPTOVARICIN C. II THE INTRAMOLECULAR ALDOL CONDENSATION OF 19-O-ACETONYL-DAMAVARICIN C AND ITS ANALOGS

Sir:

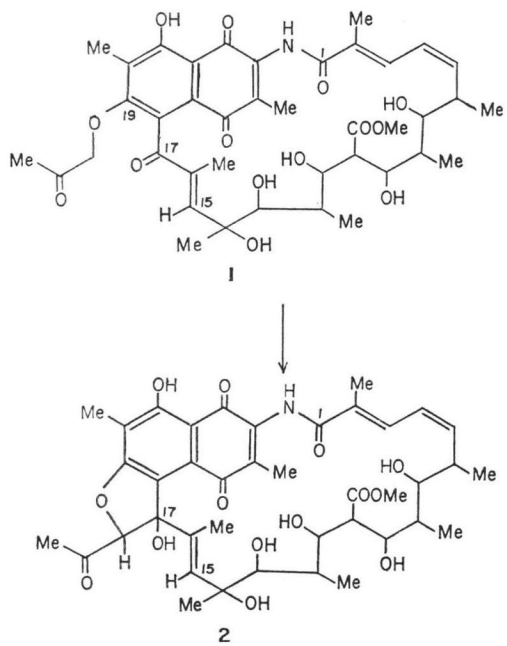
In the previous paper[1] we reported a series of 19-O-substituted derivatives of damavaricin C, a degradative derivative of streptovaricin C, along with their biological properties. We wish to describe here the intramolecular aldol condensation of 19-O-acetonyldamavaricin C[1] and its analogs which gives products with a new carbon skeleton structure still possessing biological activity against gram-positive bacteria including *Mycobacterium tuberculosis in vitro*.

Upon treatment with benzylamine in benzene at room temperature, 19-O-acetonyldamavaricin C (**1**) was converted into the isomer (**2**) [$C_{40}H_{51}NO_{14}\cdot H_2O$;* amorphous orange powder, m.p. 162~163°C; $\lambda_{max}^{MeOH}$ 270(29,600), 333(9,470) and 422(4,700) nm] by an intramolecular aldol condensation without dehydration (Scheme 1).

The n.m.r. spectra of **1** and the aldol compound **2** showed that the typical AB pattern of the acetonyl $CH_2$ protons at $\delta$4.37 (d, J=16.4 Hz) and $\delta$4.84 (d, J=16.4 Hz) in **1** was replaced in **2** by two sharp singlets observed at $\delta$4.84 and $\delta$5.65. The latter disappeared by adding $D_2O$, indicating that compound **2** is an aldol form of **1**. Furthermore, the vinyl proton at C-15, observed as a broad singlet at $\delta$6.07 in **1**, was shifted to higher field at $\delta$4.96 in **2**, indicating that the carbonyl group at C-17 in **1** was absent in **2** due to the intramolecular aldol condensation.

In the mass spectrum of **2**, the molecular ion peak was not detected but dehydration peaks at *m/e* 751 ($M-H_2O$), 733 ($M-2H_2O$), 715 ($M-3H_2O$) and 697 ($M-4H_2O$) suggested

Scheme 1



* Microanalysis agree with the molecular formula assigned.

Scheme 2

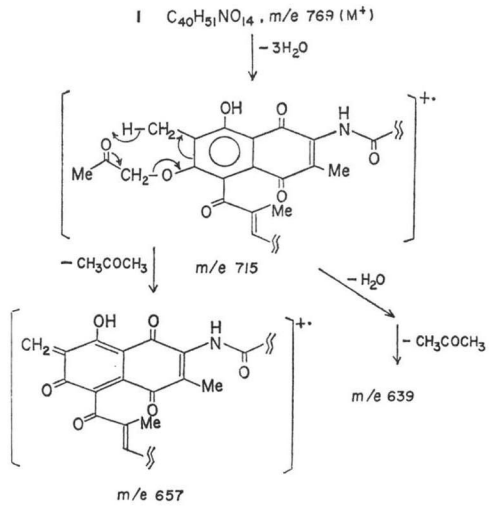
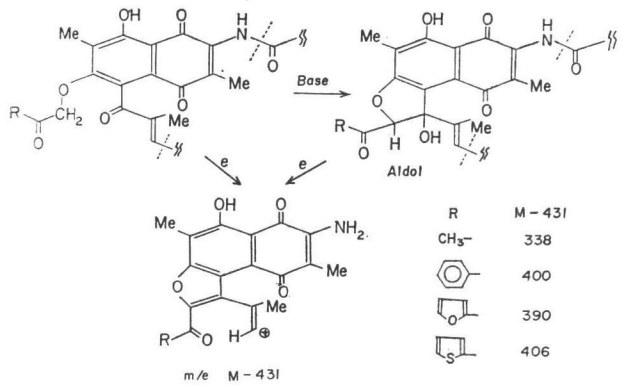



Table 1. Antibacterial activity ($\mu$g/ml) of various aldol compounds *in vitro*.

| No. | R* | *St. aureus* FDA209P | *M. tuberculosis* $H_{37}Rv$ | *E. coli* |
|---|---|---|---|---|
| **2** | $CH_3-$ | 0.2 | 50 | >100 |
| **3** | $CH_3CH_2-$ | 10 | 10 | >100 |
| **4** |  | 2 | 50 | >100 |
| **5** |  | 10 | 10 | >100 |
| **6** |  | 5 | 10 | >100 |
| **7** |  | 2 | 20 | >100 |
| **8** |  | 5 | 10 | >100 |

* R refers to the structure shown in Scheme 3.

Scheme 3




the facile loss of a tertiary hydroxyl group at the C-17 position in **2**. Furthermore, intense peaks due to deacetonation observed at *m/e* 657 and 639 in **1** were undetectable in the aldol compound **2**. The deacetonation may result from a vinylogous McLAFFERTY rearrangement, as shown in Scheme 2.

Other than the aldol compound **2**, a series of analogous aldol compounds was prepared by the same reaction procedure.

Table 1 shows that various aldol compounds have an inhibitory activity against *Staphylococcus aureus* FDA209P and *Mycobacterium tuberculosis* H37Rv *in vitro*, but are inactive below 100 $\mu$g/ml against *Escherichia coli in vitro*.

Preliminary investigations of other biological activities such as antitumor activity *in vitro* and the inhibition of RSV RNA-directed DNA polymerase (reverse transcriptase) are now in progress and will be published elsewhere.[2]

KAZUYA SASAKI
TAKANOBU NAITO
TOSHIYUKI SATOMI
YOSHIO MOMOKI

Research Laboratory
Kaken Chemical Co., Ltd.
2-28-8 Honkomagome
Bunkyo-ku, Tokyo 113, Japan

(Received April 28, 1975)

## References

1) SASAKI, K.; T. NAITO, T. SATOMI & K. ONODERA: Chemical modification of streptovaricin C. I. 19-O-Substituted damavaricin C. J. Antibiotics 29: 147~154, 1976
2) ONODERA, K. & K. SASAKI: manuscript in preparation