**Tetrahedron Letters No.19, pp. 1427-1431, 1965. Pergamon Press Ltd.
Printed in Great Britain.**

# THE SYNTHESIS OF TETRAHYMANOL

Y. Tsuda, A. Morimoto, T. Sano, Y. Inubushi

Faculty of Pharmaceutical Sciences, Osaka University,

Toyonaka, Osaka, Japan.

and

F. B. Mallory, J. T. Gordon

Department of Chemistry, Bryn Mawr College,

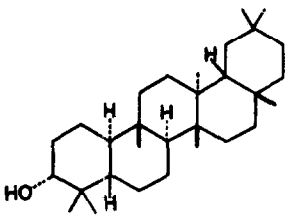
Bryn Mawr, Pa., U. S. A.

(Recieved **21 March 1965** )

TETRAHYMANOL is the first pentacyclic triterpenoid alcohol isolated from an organism of the animal kingdom. This isolation was accomplished by Mallory et al. from a protozoan, Tetrahymena pyriformis, and the structure (I) has been tentatively suggested by them[1].

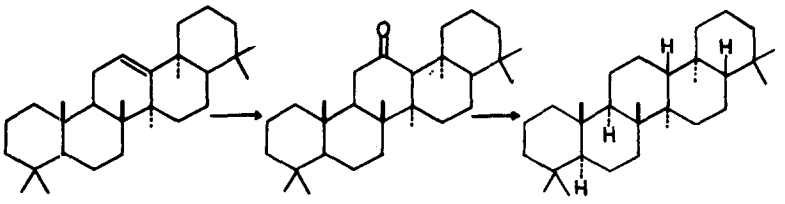
However, the high melting points of the compound and its derivatives prompted us to suspect that it could be a compound possessing a highly symmetrical carbon skelton such as that of gammacerane. Since the symmetrical hydrocarbon, gammacerane (IV), $C_{30}H_{52}$, was not known, we prepared it by the route indicated in Fig. I, and found it to have a melting point of 290° (in an open capillary, and > 300° on kofler hot stage).

Reduction of tetrahymanone was then carried out at Bryn Mawr and the resulting hydrocarbon, tetrahymane, mp. 290° (open capillary) was found to be



(I)

Fig. I



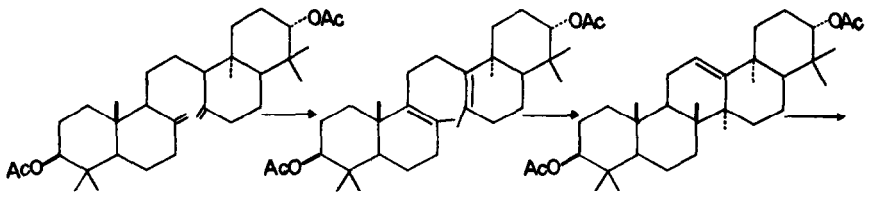
(II) (III) (IV)

identical with gammacerane by comparisons of infrared spectra (in KBr). Hence the structure of tetrahymanol, in conjunction with n.m.r. evidences[1], must be revised to gammaceran-3β-ol (XIII). This was now verified by the following synthesis (Fig. II).

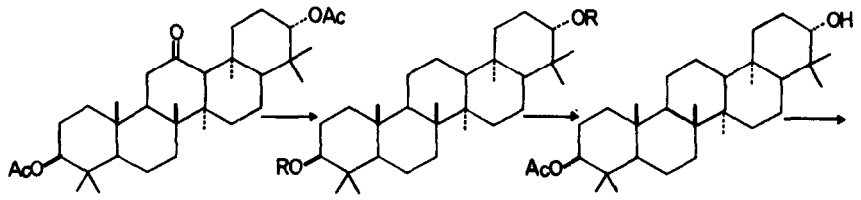
The key intermediate (XII) has already been described by Jeger et al.[2], but we have prepared it by an alternative method, i. e. by the partial hydrolysis of the diacetate (X) and oxidation of the resulting acetoxy-alcohol (XI) and several steps are modified.

α-Onocerin diacetate (V) was quantitatively isomerized to β-onocerin diacetate (VI) by mild treatment with sulphuric acid[3] and VI was further isomerized, in about 40% yield, to γ-onocerin diacetate (VII), mp. 331-334° (lit.[3] mp. 333-336°), by $BF_3$ in $CHCl_3$[4]. The diacetate (VII) was then transformed into the diacetoxy-ketone (VIII) (IR. 1724, 1248 (OAc), 1695cm$^{-1}$ (CO):

Fig. II

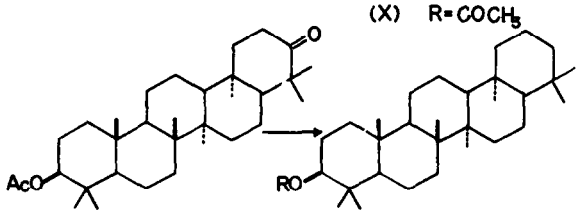



(V) (VI) (VII)




(VIII) (IX) R=H (XI)

(X) R=$COCH_3$




(XII) (XIII) R=H

(XIV) R=$COCH_3$

ORD. $(\phi)_{275m\mu}$=+1557°, $(\phi)_{312m\mu}$=-724°) by hydrogen peroxide oxidation[3].

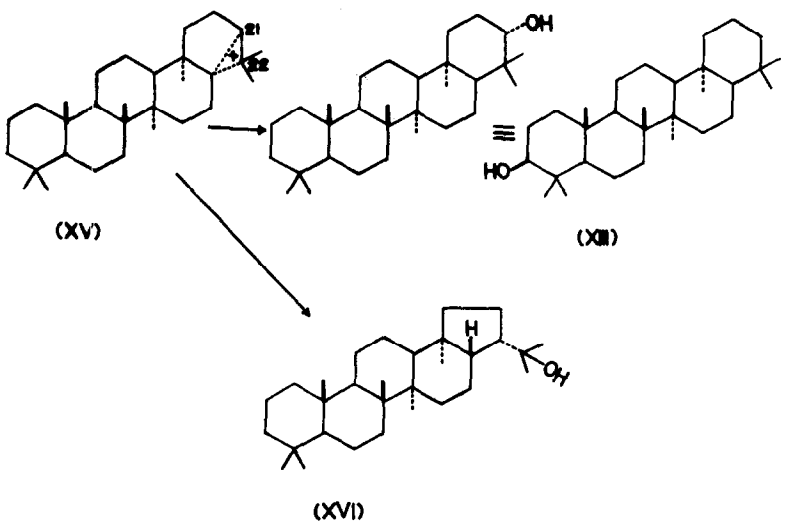
Application of the forced Wolff-Kishner reduction according to Negata's modification[5] to VIII gave gammaceran-3β,21α-diol (IX) in 50% yield. The diacetate (X), mp. > 350° (lit[2] mp. > 355°), of IX was heated under reflux with 2% hydro-

chloric acid in ethanol-chloroform mixture for 30min. to give, in 60% yield, the monoacetate (XI), mp. 321-325°, $C_{32}H_{54}O_3$, (IR.(Nujol). 3322, 3257 (OH) and 1724cm$^{-1}$ (OAc)) which was then oxidized to the known acetoxy-ketone (XII), mp. 269-271° (lit.[2] mp. 267-270°). Wolff-Kishner reduction of XII and purification of the resulting mono-ol (XIII) by acetylation furnished gammaceran-3β-ol acetate (XIV) as colorless needles, mp. 297-299° (open capillary), $C_{32}H_{54}O_2$. This acetate was found to be identical with tetrahymanyl acetate by comparisons of both infrared (in KBr) and n.m.r. spectra.

Hydrolysis of XIV gave gammaceran-3β-ol (XIII), mp. 295-296°, which was also identical with tetrahymanol (IR comparison).

As α-onocerin has already been totally synthesized[6], the above transformation provides the total synthesis of tetrahymanol. The structure thus established for this triterpenoid also provides the first example of a naturally occuring triterpenoid of the gammacerane group.

Fig. 1



Biogenetically tetrahymanol (XIII) should have a close relationship with diplopterol (XVI)[7]. Both alcohols may be derived from the cation (XV) which could originate from squalene by proton induced simple cyclization. Introduction of hydroxide ion to $C_{21}$ would give the former and to $C_{22}$ would give the latter alcohol.

References

1) F. B. Mallory, J. T. Gordon and R. L. Conner, J. Amer. Chem. Soc., 85, 1362 (1963).

2) K. Schaffner, L. Caglioti, D. Arigoni and C. Jeger, Helv. Chim. Acta, 41, 152 (1958).

3) D. H. R. Barton and K. H. Overton, J. Chem. Soc., 2639 (1955).

4) Y. Tsuda, T. Sano, K. Kawaguchi and Y. Inubushi, Tetrahedron Letters, No. 20, 1279 (1964).

5) W. Nagata, and H. Itazaki, Chem. and Ind. 1194 (1964)..

6) G. Stork, J. E. Davies and A. Meisels, J. Amer. Chem. Soc., 85, 3419 (1963).

7) H. Ageta, K. Iwata, and Y. Otake, Chem. Pharm. Bull., (Tokyo) 11, 407 (1963).