Tetrahedron Letters No. 30, pp. 2167-2171, 1963. Pergamon Press Ltd.
Printed in Great Britain.

THE STRUCTURE OF TAXININE, A NITROGEN-FREE COMPOUND OCCURRING IN TAXUS CUSPIDATA.

K. Ueda, S. Uyeo, and Y. Yamamoto
Faculty of Pharmaceutical Sciences, Kyoto University
Kyoto, Japan
Y. Maki.
Gifu College of Pharmacy, Gifu, Japan

(Received 30 September 1963)

Lythgoe and his collaborators[1,2] recently advanced the structure (Ia) or (Ib) for O-cinnamoyltaxicin-I, a nitrogen-free compound derived from taxine occurring in Taxus baccata, and Nakanishi and his associates[3] proposed a closely related structure (II) for taxinine[4], $C_{35}H_{42}O_9$, obtained from Taxus cuspidata*.

We now wish to present evidence which requests revision of the structure for taxinine to (III)**.

As previously reported, the lithium aluminum hydride reduction of taxinine afforded taxinol[5], $C_{20}H_{32}O_5$, which

---

* As pointed out by Lythgoe et.al., physical and chemical properties of taxinine are very similar to those of O-cinnamoyltaxicin-II triacetate. The identity of these compounds, however, awaits direct comparison which has not been undertaken so far due to unavailability of O-cinnamoyltaxicin-II triacetate to us.

** Very recently Professor Nakanishi has kindly informed us in a personal communication that he now accepts structure (III) for taxinine.

still contains a carbonyl group, but no conjugated double bond. Comparative studies of the functional groups of taxinine and taxinol led us to the conclusion that the latter is a product formed by reduction of only the double bond conjugated with the carbonyl group together with hydrogenolysis of the ester functions in the former compound. Since no other change could be expected by this treatment, taxinol was chosen as a useful starting point for detailed investigation.

Ozonolysis of tetraacetyltaxinol[6] gave tetraacetyl-oxonortaxinol[7], $C_{27}H_{38}O_{10}$ (IV), m.p. 215°. The n.m.r. spectrum measured at 60 Mc/sec in deuteriochloroform showed a one-proton doublet (J=6.0 c.p.s.) at 6.34τwhich is ascribed to the proton on α-carbon of the carbonyl group formed by ozonolysis of the exocyclic methylene, indicating, in accord with the formulation (IV) and not with an alternative structure which can be derived from structure (II) for taxinine, that the proton is spin-coupled to only one proton, viz., the carbon atom carrying the secondary acetate, exhibiting a one-proton quartet centred at 4.44 τ(J_1=6.0 c.p.s., J_2=2.2 c.p.s.). The other ajacent carbon (asterisked in IV) atom must be fully substituted.

Zemplén methanolysis[8] of IV gave a substance, $C_{24}H_{36}O_8$, (V), m.p. 242°, $[\alpha]_D$ +2.2° ($CHCl_3$) which showed in the ultraviolet absorption spectrum a maximum at 219mμ (ε 8,300) and in the infrared spectrum bands at 1645 and 1068 cm^{-1} suggesting the presence of an enol-ether grouping. Ready saponification of the methoxyl group and resistance to the catalytic recuction of the double bond also supported the presence of a grouping such as $-\overset{|}{C}=\overset{|}{C}-OCH_3$ in the molecule.

In agreement with these findings, in the n.m.r. spectrum of V the one-proton doublet which was at 6.34τ in the spectrum of IV has disappeared, and a new three-proton peak at 6.60τ from the methoxyl was observed. Furthermore no olefinic proton signal was observed indicating that the enolic double bond was tetrasubtituted as represented by the formula (V).

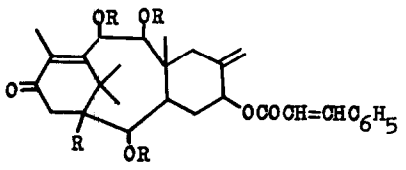
A possibility that the methoxyl peak came from a solvent of crystallisation could be ruled out by the unchanged n.m.r. spectrum after prolonged drying in vacuo at 120° and also by the fact that its monoacetyl derivative, $C_{26}H_{38}O_9$, m.p. 176°, $[\alpha]_D$ -15° ($CHCl_3$) exhibited a singlet at 6.55τ for the methoxyl protons and no vinyl proton signal which would be required of a II-type structure.

A second proof for the position of the exocyclic methylene in taxinine was provided by the n.m.r. spectrum of acetyldehydroisopropylidenetaxinol (VI), $C_{25}H_{36}O_6$, m.p. 193°, obtained by acetylation of dehydroisopropylidenetaxinol[6], and its dihydro derivative (VII), $C_{25}H_{38}O_6$, m.p. 235°. Compound (VI) showed a one-proton singlet slightly broadened by weak coupling at 6.11τ for the proton which is on an α-carbon of a carbonyl and at the same time allylic to the double bond, while in the dihydro derivative (VII) the signal for this proton was shifted to higher field and exhibited a doublet (J=5.5 c.p.s.) at 6.61τ in conformity with the formulae (VI) and (VII), respectively. These spectroscopic data require partial structure $-CH(OH)-\overset{O}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}=CH_2$ for taxinol, and therefore also for taxinine.

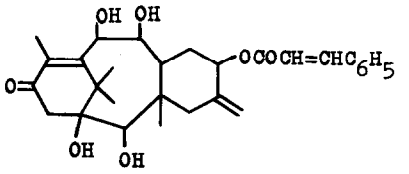
In combination with our experimental findings as to the

other moieties of the molecule which are in good agreement with those reported by Nakanishi et.al.[3] the results obtained above strongly support the structure (III) for taxinine.

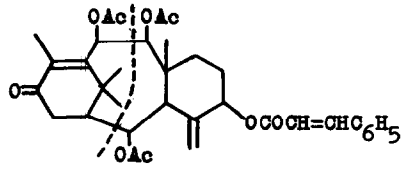
It should be noted that in the revised structure (III) the genesis of the molecule could be from two identical C_{10} units as indicated by the dotted line in III., and it is worth pointing out that this group of compounds may be related to quassin[9] type which are also devisible into two similar C_{10} units.



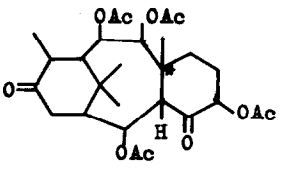
(Ia) R=OH ; R=H
(II) R=H ; R=Ac



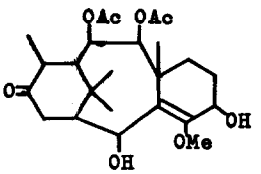
(Ib)



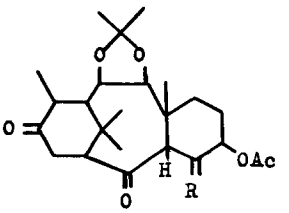
(III)



(IV)



(V)



(VI) R=CH_2

(VII) R=CH_3 (double bond saturated)

We are grateful to the Mead Johnson Research Center, Evansville, Indiana, U.S.A. and the Shionogi Research Laboratory, Osaka, Japan for the n.m.r. spectra.

REFERENCES

(1) J. N. Baxter, B. Lythgoe, B. Scales, R. M. Scrowston & S. Trippett, J. Chem. Soc. 2964 (1962).

(2) B. W. Langley, B. Lythgoe, B. Scales, R. M. Scrowston, S. Trippett & D. Wray, ibid. 2972 (1962).

(3) (a) M. Kurono, S. Konuma, K. Sasaki & K. Nakanishi, Abstracts, 16th Annual Meeting of the Chemical Society of Japan., Tokyo, 1963, p. 81. (b) K. Nakanishi, M. Kurono, S. Konuma, M. Ohashi, M. C. Woods, K. Sasaki, Abstracts, 7th Symposium on the Chemistry of Natural Products, Fukuoka, Japan, 1963, p. 219.

(4) T. Takahashi, J. Pharm. Soc. Japan 51, 401 (1931).

(5) T. Takahashi, K. Ueda, R. Oishi & K. Minamoto, Chem. and Pharm. Bull. (Japan) 6, 728 (1958).

(6) S. Uyeo, K. Ueda, Y. Yamamoto, N. Hazama, & Y. Maki, J. Pharm. Soc. Japan 82, 1081 (1962).

(7) M. Kurono, Y. Nakahira, S. Konuma, K. Sasaki, & K. Nakanishi, Abstracts, 5th Symposium on the Chemistry of Natural Products, Sendai, Japan, 1961, p. 21-1.

(8) G. Zemplén, A. Gerecs, & I. Hadácsy, Ber. 69, 1827 (1936).

(9) Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos and C. Podešva, Tetrahedron 18, 1433 (1962); and references therein.