

ON THE STRUCTURE OF AILANTHONE

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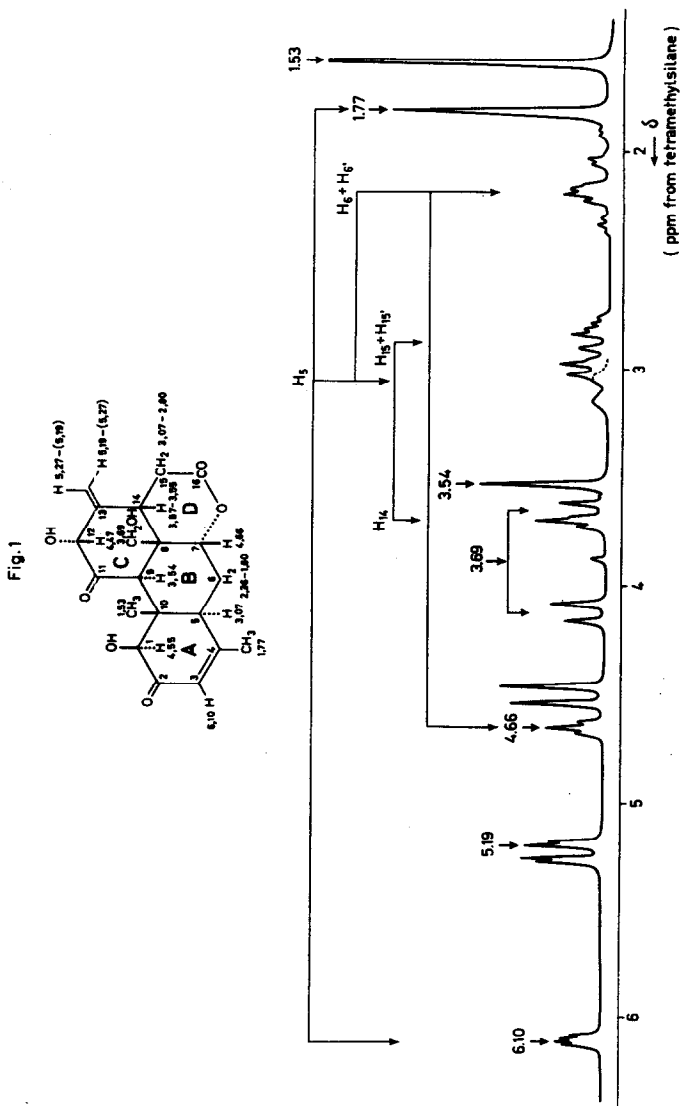
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In a previous communication (1), the isolation and the fundamental chemistry of Ailanthone, $C_{20}H_{24}O_7 \cdot H_2O$, the principal bitter component (+) of Ailanthus glandulosa Desf., were described. In the meantime we have accumulated, by means of chemical (++) and 100 Mc nuclear magnetic double resonance (NMDR) methods, sufficient evidence to propose the formula shown in fig. 1 for Ailanthone.

Ailanthone (I) is an optically active ($[\alpha]_D^{20} = +24^\circ$, c=1% in EtOH) hydroxylactone, easily hydrolyzed in alkaline solution which upon acetylation (Ac_2O in pyridine) gives a triacetate (II, $C_{26}H_{30}O_{10}$, m.p. 227-8 $^\circ$) easily reduced (PtO_2 in glacial AcOH) to a tetrahydroderivate (III, $C_{26}H_{34}O_{10}$, m.p. 274-5 $^\circ$).

(+) Studies on the other substances ($C_{22}H_{30}O_7$, m.p. 264-5 $^\circ$; $C_{20}H_{28}O_6$, m.p. 253-5 $^\circ$; $C_{22}H_{28}O_8$, m.p. 262-3 $^\circ$) isolated from the same source will be reported elsewhere.

(++) Satisfactory elemental analyses were obtained for all new compounds encountered in this work.



Catalytic reduction of (I) leads to a tetrahydrolac-
tone (IV, $C_{20}H_{28}O_7$, m.p. 256-9°) which is acetylated to give (III).
The molecular formula of (I), the presence of a tetracyclic system
and two double bonds in the molecule are demonstrated by elemen-
tal analysis and catalytic hydrogenation data as well as by full
interpretation (table 1) of its 100 Mc NMR spectrum (Fig. 1).

Reaction of (I) with 2, 4-dinitrophenylhydrazine led
to a product whose nitrogen content requires the presence in Ailan-
thone of two C=O groups, one of which lies in a α , β -unsaturated,
six-membered ring, as confirmed by the characteristic U-V absorp-
tion (λ max. = 240 m μ , $\log \epsilon = 4, 02$) (2) and the strong I.R.
band at 1675 cm^{-1} , shifting to 1725 cm^{-1} after catalytic hydrogena-
tion. The second ketonic function is probably in an unconjugated,
unstrained system since the I.R. spectrum of (I) potassium salt
shows the persistence of the 1740 cm^{-1} band, also present in (I);
since Bi_2O_3 in AcOH oxidizes (IV) to a diosphenol (U.V. evidence),
at least one of the carbonyls bears an α -hydroxyl, thus corroborat-
ing NMR deductions (table 1).

The substitution pattern of the α , β -unsaturated,
six-membered ketonic ring (ring A in formula (I)) follows from
the above observation that one of the flanking groups must be a
secondary alcoholic function (C_1H-OH) ($\delta = 4, 55$) contiguous to a
quaternary saturated carbon (C_{10}), the other being an ethylenic
carbon bearing only one hydrogen ($=C_3-H$) ($\delta = 6, 10$). The allylic
couplings of this latter with a methyl group ($=C_4-CH_3$) ($\delta = 1, 77$)
and with a single proton (C_5-H) ($\delta = 3, 07$) demonstrate the correct-
ness of the formulation of ring A. Now, C_5-H is a broad doub-

let, (+) coupled with the complex multiplet at $\delta = 2, 36-1, 80$ (two protons). Since the largest splitting is consistent with an axial-axial relationship, C_5 must be linked to a methylene group (in position 6), to which an alcoholic function bearing carbon (C_7) is

TABLE 1

Signal	δ	Interpretation
1	6, 10	$O=C-\overset{1}{C}=H$
2	5, 27-5, 19	$C=C\begin{matrix} H \\ \\ H \end{matrix}$
3	4, 66	$O=C-O-\overset{3}{C}-H$
4	4, 55	$O=C-\overset{4}{C}\begin{matrix} \diagup \\ \diagdown \end{matrix}\begin{matrix} OH \\ H \end{matrix}$
5	4, 47	$O=C-\overset{5}{C}\begin{matrix} \diagup \\ \diagdown \end{matrix}\begin{matrix} OH \\ H \end{matrix}$
6	3, 39	$C-CH_2-OH$
7	3, 87-3, 55	$CH-CH_2-$
8	3, 54	$CH-CO-$
9	3, 07	$HC=\overset{9}{C}\begin{matrix} \diagup \\ \diagdown \end{matrix}\begin{matrix} CH \\ CH_3 \end{matrix}-CH_2-$
10	3, 07-2, 80	$CH-CH_2-CO-O-$
11	2, 36-1, 80	$CH-CH_2-\overset{11}{CO}$
12	1, 77	$\begin{matrix} H & CH & H \\ & & \\ C & =C & -CH_3 \end{matrix}$
13	1, 53	$\begin{matrix} C \\ \diagdown \\ C-C-CH_3 \\ \diagup \\ C \end{matrix}$

(+) Only the lower field half of this doublet is visible in fig. 1; irradiation of C_7-H , however, simplifies the neighbouring multiplet, uncovering at the same time the upper field half (see pointed line in fig. 1).

contiguous (NMR evidence, see fig. 1). Since the C_7 H proton resonance ($\delta = 4, 66$) is not lowered upon acetylation, C_7 is engaged in the lactone ring.

The fact that C_7 -H is equally coupled with both hydrogens at C_6 represents strong evidence against the hypothesis of a four-membered ring B; furthermore the presence of an one-proton singlet ($\delta = 3, 54$) throughout the series (I)-(IV) is at this point consistent only with a proton α to a CO (axial). Therefore, ring B must bear a tertiary carbon (C_9 -H), flanked by two quaternary carbons (C_8 and C_{10}) and linked to a carbonyl (C_{11}).

The environment of this latter can be deduced considering that the other proton, belonging, as stated above, to a CH-OH group ($\delta = 4, 47$), is a singlet in (I) and in (II) and becomes a doublet ($\delta = 4, 2$) in (III); the sequence $-\text{CO}-\text{CH}(\text{OH})\text{C}=\text{CH}_2$ is then obvious.

For reasons of chemical shift, the system formed by the one-proton multiplet at $\delta \sim 3, 87-3, 55$, coupled with the two-proton multiplet at $\delta \sim 3, 07-2, 80$ to form an ABC type spectrum, can be explained only by extending the above sequence to $-\text{CO}-\text{CH}(\text{OH})-\text{C}(\text{=CH}_2)-\text{CH}-\text{CH}_2-\text{CO}-\text{O}-\text{C}_7$ or $-\text{CO}-\text{CH}(\text{OH})-\text{C}(\text{=CH}_2)-\text{CH}_2-\text{CH}-\text{CO}-\text{O}-\text{C}_7$. Since, however, C_5 -H shows a strong allylic coupling ($J \sim 3$ cps) with C_3 -H and is axially-axially coupled (see above) with one of the C_6 protons, ring A and B must be trans fused; hence the C_7 -O-bond and the C_{10} , as yet unknown, substituent are axial. As a consequence, for steric reasons, the tertiary carbon contained in both the sequences referred to above cannot be linked to C_{10} but to C_8 and only equatorially. Since the existence of a five-membered lactone ring can be excluded on the basis of the I.R. spectra of all the products investigated,

the tetracyclic system of Ailanthone must be as shown in fig. 1. The rather high δ value for C_{14} -H which lies in the plane of the vinyl bond, is now satisfactorily explained.

In order to explain the relatively high δ value of the quaternary methyl group in Ailanthone, it is now necessary to place it at C_{10} , the B/C junction being trans. (A similar deshielding effect is shown by the 11-keto group on the C_{19} -methyl in steroids) (3). The remaining CH_2OH group (AB quartet centered at $\delta = 3,69$) is obviously placed at C_8 (axial), its chemical shift being in good agreement with the values found in the diterpene (field (4)). The axial nature of C_1 -H is also in good agreement with rather high δ values found for simpler cyclic ketones (5) and for the more similar 2-hydroxy-3-keto- Δ_4 -steroids (6), whilst the equatorial disposition of C_{12} -H is in full agreement with its relatively low δ value (5, 15) in (II), shifting at notably higher fields (doublet at $\delta = 4,2$) in (III).

The presence in other Simaroubaceae of strictly related compounds, such as Quassin (7), Chaparrin (8), Glaucarubin (9) and Simarolide (10) constitutes an additional proof of the correctness of our conclusions (11); moreover, (I) can represent the absolute configuration also, if the biogenetic origin of Ailanthone from triterpenes is assumed (10, 11, 12, 13).

This hypothesis was experimentally checked by feeding, last spring, young Ailanthus plants with labelled acetate and mevalonate: the results obtained will be published in a subsequent paper.

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