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THE STRUCTURE OF RYANODINE

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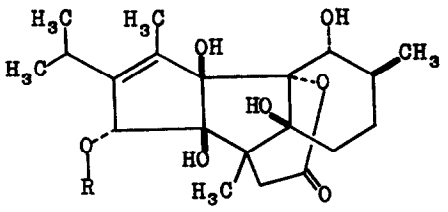
Some time ago we have deduced (1) the structure of anhydroryanodine I, the dehydration product of the insectidical principle ryanodine. Later (2), we have succeeded to determine the structure of trisecoryanodol II, the cleavage product of ryanodol with three moles of periodate. Any structure of ryanodine worthy of consideration must clearly explain the formation of these two derivatives in a plausible manner.

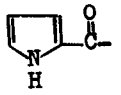
For this reason, we have considered the hemilactal formulae III and IV for ryanodine and ryanodol (3). The rationalization of I and II on the basis of these structures is most simple and plausible but we pointed out (3) that another degradative series, the so-called ''iso-series'' (2), defies explanation by these structures and will be further investigated. The acidity of ryanodol determined in the laboratory of Professor J. M. Los (Amsterdam) (pK_a = 11.4 $\mp$ 0.2) did not seem to exclude III and IV.

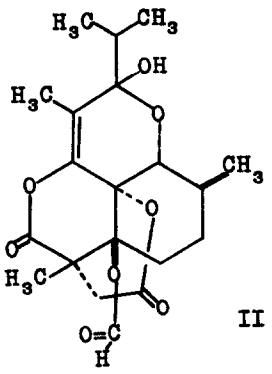
We have now found that there exists one more structural formula for ryanodol V and ryanodine VI which explains the

formation of I and II with equal simplicity. The mechanism of the anhydro reaction is shown by arrows in the formulae V and VI. The genesis of II is represented by the self-explanatory sequence V → VII → VIII → IX → II. The new formulae are capable of simply and convincingly rationalizing the ''iso-series''. We have now been able to obtain proof that this rationalization is correct and this series thus provides clear-cut evidence for the structures V and VI. First of all, we have found by means of analysis of the monoacetonide (m.p. 244-246°. Found: C, 65.37; H, 7.91. Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11; O, 26.51.) that ''isoryanodol'' (2) is a hydrate and an isomer of anhydroryanodol, not of ryanodol. Thus, we formulate the formation of this compound X from ryanodol by thionyl chloride (2) as a simple dehydration of a tertiary alcohol. The monoseco derivative XI (2) obtained by the action of periodate on X shows an infrared spectrum (1751, 1682 cm^{-1}) in agreement with a ketone in a five-membered and another conjugated ketone in a larger ring. The presence of an isopropylidene group in X and XI is shown by N.M.R. (2) and the U.V. spectrum of XI is in agreement with a twisted α,β-unsaturated ketone chromophore (strong end-absorption shoulder at 265 mμ).

The action of sodium carbonate on XI yields (2) compound XII by a simple aldol condensation. The evidence which includes U.V., I.R., N.M.R. and deuteration studies and which proves the presence of an α-isopropylidene cyclopentanone in XII has already been described (2). We have now rigorously proved this simple interpretation by a direct oxidation of



I (R = )



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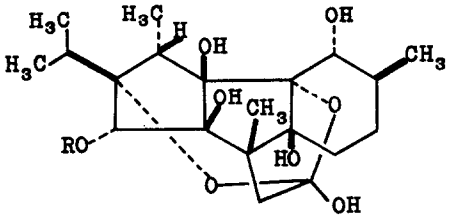
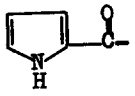


III (R = )

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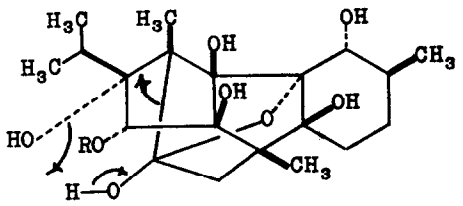
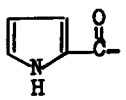
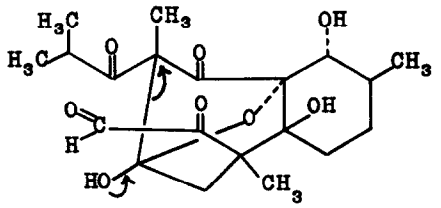


V (R = H)

VI (R = )



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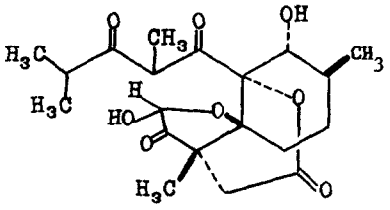

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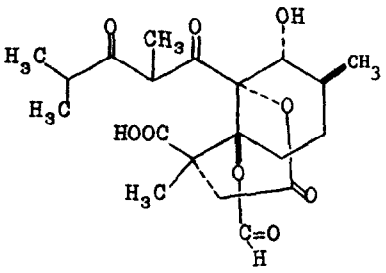

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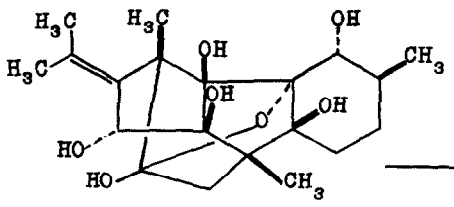
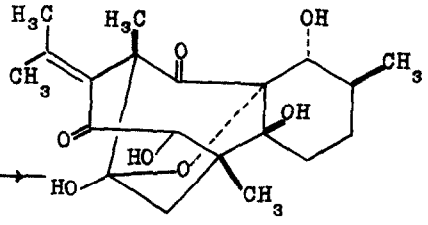


X



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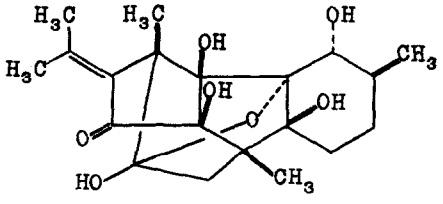

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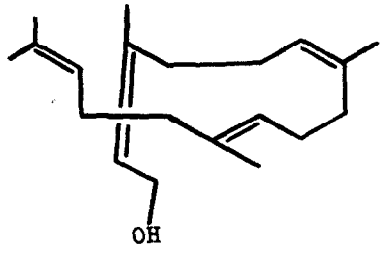

XIII

X into XII with platinum and oxygen. Thus, the ''iso-series'' is not only explained but becomes a strong support of the proposed structure.

Without exception, all the remaining degradative evidence which we have accumulated in our studies is equally readily accommodated (see forthcoming full paper) and an extensive review of this evidence convinced us that the formula VI for ryanodine is proved. Specifically, we should mention that all the difficulties posed by the N.M.R. spectrum of ryanodol have been removed. After prolonged equilibration with deuterated methanol, ryanodol shows the presence of only two hydrogens unshielded by oxygen (N.M.R. (D_5-pyridine): 5.04 (singlet, 1H) and 5.50 τ (doublet, 1H)); the methyl region which appears to show (2) two singlets and three doublets is no longer anomalous.

The new carbon-carbon bond which formula VI contains makes it possible to regard geranyl geraniol XIII, the usual precursor of diterpenoids, as the biogenetic source of ryanodine.

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