Tetrahedron Letters,Vol.25,No.37,pp 4151-4152,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

IDENTIFICATION OF AN INTERMEDIATE IN THE REACTION BETWEEN POLYGODIAL AND METHYLAMINE IN BIOMIMETIC CONDITIONS

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Abstract.- The intermediate 2 has been identified, by spectral means, in the course of the reaction in biomimetic conditions between polygodial (1) and methylamine leading to the pyrrole derivative 3.

In a recent paper[1] the bio-activity on the taste sense exhibited by polygodial (*1*) has been related to the ability of this compound to form adducts with $-NH_2$ groups, rather than -SH groups as previously reported[2a,b]. This view was suggested *inter alia* by the fact that *1* reacts with methylamine under biomimetic conditions (phosphate buffer, pH 9) affording the pyrrole derivative *3*, while the tasteless 9α-isomer of *1* is unreactive under the same conditions[1].

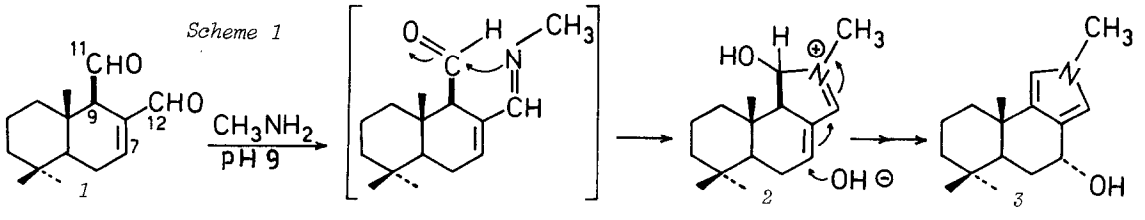
Following the U.V. spectral changes[3] during the reaction of *1* with CH_3NH_2 it is possible to monitor the immediate formation of an adduct (λ_{max} 276 nm) which slowly disappears in the course of the reaction. We whish to report now evidence establishing structure *2* for this intermediate.

The polar nature of *2* was indicated by the observation that extraction of the reaction mixture with cyclohexane leaves in the aqueous phase only the 276 nm absorbing substance which survives for few minutes and therefore cannot be isolated. The U.V. absorption, in connection with the observed solubility, suggests the presence of a positively charged conjugated azomethine chromophore in *2*[4].

Monitoring of the reaction by ^{1}H-NMR (500 MHz) provided additional evidence leading to structure *2*. In a typical experiment, 2 mg of *1*[5] were dissolved in a mixture of 4 ml of 0.1 M phosphate buffer (prepared in D_2O; pD 9) and 1.5 ml CD_3CN; to this solution an excess (3 mg) of $CH_3NH_2 \cdot HCl$ was added . The mixture was stirred at room temperature and 0.5 ml portions were drawn off at 10 ∿ 15 min intervals and monitored by NMR[6]. Representative spectra are reported in fig. 1.

Since the 0-3.5 δ zone was over-crowded, only the diagnostic 3.5-9.5 δ zone was considered. In this part of the spectrum, apart from the $-NCH_3$ groups resonating at δ 3.49 for *2* and 3.54 for *3*, three separate sets of signals appear, whose relative ratio changes during the time: the resonances due to polygodial *1* (Fig.1a), those due to the final product *3* (Fig.1c) and three signals (ratio 1:1:1) at δ 5.65 (d, J=6.6 Hz), 7.18 (m) and 8.56 (s) which were assigned to the

Scheme 1



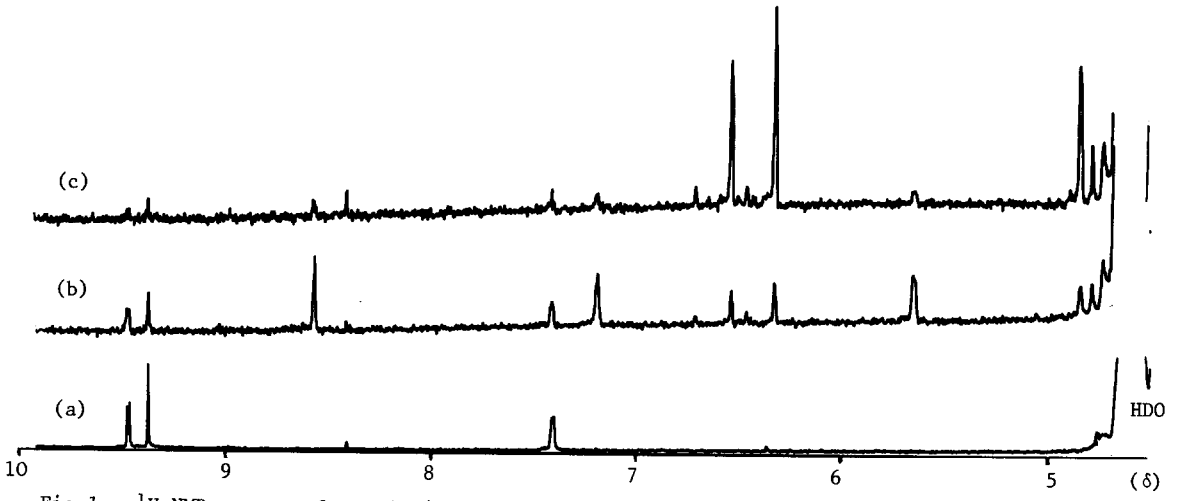


Fig.1 - ^{1}H-NMR spectra for solutions in phosphate buffer -D_2O-CD_3CN (see text; DSS internal standard at δ=0) of (a) polygodial (*1*); (b) 10 min after addition of $CH_3NH_2 \cdot HCl$; (c) 40 min after addition of $CH_3NH_2 \cdot HCl$.

intermediate *2*. In particular, chemical shift arguments allowed to assign the singlet at δ 8.56[7] to the proton on C-12 and the multiplet at δ 7.18 to the olefinic proton on C-7; these signals account for the conjugated chromophore. The third signal (δ 5.65) was assigned to a proton on a carbon atom (C-11) bearing the nitrogen atom and an -OH group both for its chemical shift and on mechanistic grounds (Scheme 1). The Schiff base formation at the less hindered aldehyde group (C-12) and attack on C-11 lead to the intermediate *2*; OH^- nucleophilic attack on C-7 and subsequent dehydration afford *3*.

Although an automatic link between the reactivity of *1* in the *in vitro* selected conditions and its behaviour *in vivo* cannot be simply inferred, it is worth noting that formation of type *2* adducts is possible, in principle, for all the dialdehydes exhibiting antifeedant activity against insects and tasting very hot to humans[8]; on the other hand the tasteless dialdehydes such as the 9α-isomer of *1* or the isosaccalutals[9], cannot afford type *2* adducts, owing to the major distance between the C-9 axial aldehyde and the enal moiety.

Acknowledgements.- This work has been done with the financial support of "Progetto Finalizzato per la Chimica Fine e Secondaria", C.N.R., Roma. We thank Mr. S. De Falco for aid in the experimental work and Prof. G.Jommi for discussion.

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3. Fig. 2 in ref. 1.
4. A.I.Scott, "*Interpretation of the Ultraviolet Spectra of Natural Products*", Pergamon Press, Oxford 1964, p.85.
5. *1* was synthesized according to D.M.Hollinshead, S.C.Howell, S.V.Ley, M.Mahon, N.M.Ratcliffe and P.A.Worthington, *J.C.S.Perkin Trans.I* 1579, 1983.
6. Cyclohexane extraction, as for the U.V. spectra,evidenced in the organic phase the signals due to *1* and *3*, while signals due to *2* and *3* remained in the aqueous phase, although the high dilution prevented the recording of well defined spectra.
7. Cfr. the chemical shift of protons in a similar environment: G.M.Sharma and O.A.Roels, *J. Org.Chem. 38*, 3648, 1973.
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(Received in UK 8 June 1984)