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A NEW PREPARATION OF FURO-2,3b FURANS, AND CONFORMATIONAL STUDIES BY 2D NMR.

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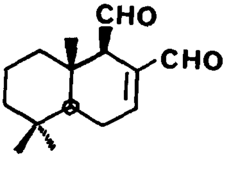
Summary : *Perhydro furo-2,3-b furan derivatives have been prepared by iodocyclisation of unsaturated lactols. Structure and conformation have been studied by high resolution "COSY" 2D NMR.*

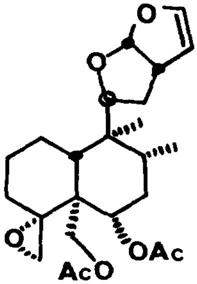
The partially hydrogenated furo-2,3-b furan or furo-2,3-b pyran ring system is embodied in a large number of natural products, most of which display interesting biological activity ranging from bacteriostatic, antifungal, and pungent properties, through those which are highly toxic or carcinogenic (2), and finally to the insect antifeedants (3,4).

Our attention, as chemists, was particularly drawn to the important antifeedants Polygodial (5) and Clerodine (4), which, in spite of their very different structures, can be conceptually related by envisaging that hydrolysis of the furo-2,3-b furan precursor leads to an unsaturated dialdehyde. A similar situation also holds in comparing Azadirachtin (3) and Warbuganal (6).

The synthesis of furo-2,3-b furans has been the object of surprisingly few studies, and is a worthwhile objective in view of the large possible number of stereoisomers (7-8).

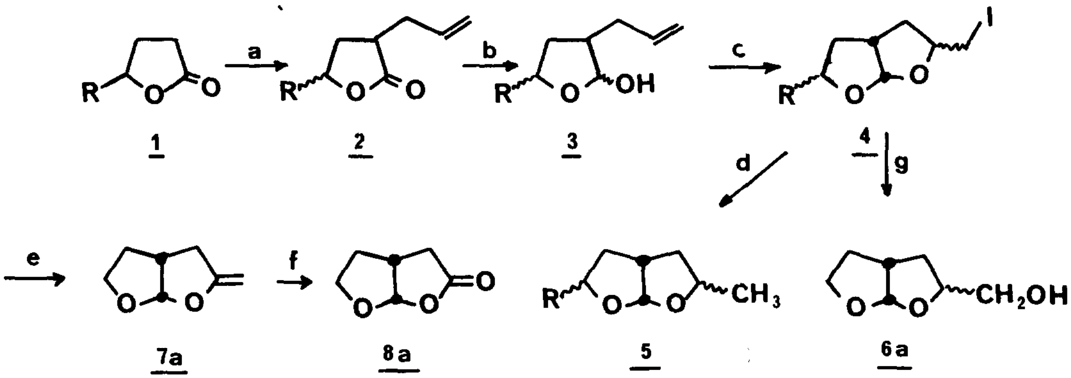


Polygodial



Clerodine

The iodo-lactonisation reaction is well documented and has been proved to be very efficient and stereospecific (9). Extension to γ-unsaturated alcohols, ethers, esters, carbonates encouraged us to examine its possible application to the cyclisation of an unsaturated lactol (scheme I).



Scheme I a : R=-H b : R=-CH_3

Reagents : a: LDA, THF, HMPT, allylbromide, -78°C ; b: DIBAL, Toluene, -60°C ; c: I_2, CH_3CN, $NaHCO_3$, -15 °C, 3 hrs ; d : $LiAlH_4$, ether reflux 4 hrs.; e: DBU, benzene, reflux 12 hrs (10) ; f: O_3,CH_2Cl_2, -78°C, Me_2S ; g: $AgNO_3$, H_2O, THF (1/4), 1.2 equ., 60°C, 4 hrs.

Compound 2 was prepared by a standard procedure. Reduction of 2a (R=H) or 2b (R=-CH_3) with diisobutyl aluminium hydride at -60°C in toluene gave 3a or 3b which inturn could be converted without purification to 4a or 4b in 60% yield by cyclisation in acetonitrile in the presence of 1,1 eq. of iodine and solid $NaHCO_3$. Attémped cyclisation in aqueous medium led to reoxidation of the lactols 3 and regeneration of lactone 2 (10).

4a(R=-H) appeared to be a mixture of the two possible isomers whose ratio could be improved to 75/25 by modification of the reaction conditions : lower temperature (-15°C) and longer reaction time (3h). The structural assignments were performed without separation, by 2D NMR. The high resolution "COSY-45" spectrum (11) of 4a displayed on figure 1, clearly indicates the proton-proton correlation in both isomers. A complete measurement of the coupling constant values was also made in order to assign the stereochemistry of substituents and the conformation of this kind of molecule. From the results reported in Table 1, it can be seen that in the major isomer 4at the iodomethyl group is trans relative to

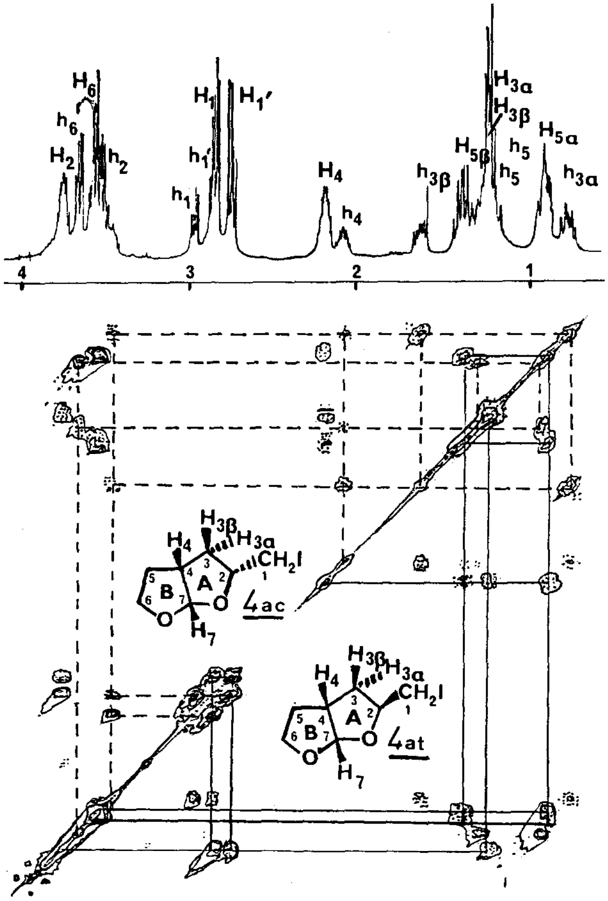


Figure 1

400MHz "COSY 45" spectrum (10) of 4ac + 4at mixtures in C_6D_6 Data size 1Kx2K. Spectrum width : 2KHz. Correlation between H_7 and H_4 in 4at is not shown. Capital letters refers to major isomer 4at. Small letters to minor isomer 4ac for which correlations are drawn in dotted lines. Chemical shifts of H_7=5.87 δ, h_7=5.80 δ.

	12	1'2	23_α	23_β	$3_\alpha 4$	$3_\beta 4$	45_α	45_β	47
4at	6.0	4.5	5.1	10.0	1.2	9.5	3.5	9.5	5.7
4ac	6.5	4.5	8.4	5.2	8.2	8.7	0	8.5	5.5

	$5_\alpha 6_\alpha$	$5_\alpha 6_\beta$	$5_\beta 6_\alpha$	$5_\beta 6_\beta$	$3_\alpha 3_\beta$	$5_\alpha 5_\beta$	$6_\alpha 6_\beta$	11'
4at	7.5^a	7.5^a	6.0^a	10.0^a	12.5	12	12	10.5
4ac	b	9.0	b	b	12.0	12.5	b	10.0

Table 1 : J values in Hertz assigned from "COSY 45" and single frequency decoupling experiments in C_6D_6 and $CDCl_3$.

a= approximate values due to second order effect

b= no possible measurement comming from strong signal overlap.

ring B. Ring A display a conformation in which the two protons $H_{3\alpha}$ and H_4 are almost orthogonal corresponding to a very small coupling constant $J_{H3\alpha}H_4$. The minor isomer 4ac, in which the iodomethyl group is cis, displays a different conformation as reflected by a drastic change in the $J_{H3\alpha-H4}$ value. This has to be related to the well known "N" and "S" conformations in the ribose series (12).

Some model reactions have been performed on compound 4a which was easily transformed to compounds 5a, 6a, (mixture of isomers) 7a (14) and 8a (14)) in good yields. 4b(R=$-CH_3$) could be easily converted to a mixture of the three possible isomers 5b (60/20/20), Scheme 1.

Further uses of this reaction which has some analogy in the organoselenium induced spiroketal formation recently described by Ley and coworkers(13), will be reported in due course.

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(14) ^1H 250 MHz, NMR data : 7a ($CDCl_3$) : 1.8 and 2.08 δ, complex m., H_5 and $H_{5'}$; 2.5, b.m. H_3 ; 2.90, d.t., $H_{3'}$; 2.95, m, H_4 ; 3.90 d(J=3Hz) H_1 ; 4.05, t,d H_6 (2H) ; 4.35 d(J=3Hz) H'_1 ; 5.95 d(J =6Hz) H_7

8a ($CDCl_3$) : 1.8 and 2.2 m, H_5 and $H_{5'}$; 2.45 dd(J=18, J=4Hz) $H_{3\alpha}$; 3.90, dd(J=18,J=10Hz) $H_{3\beta}$; 3.18, m, H_4 3.95, m, 4.10, m, H_6 $H_{6'}$; 6.10, d(J =6Hz), H_7.

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