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FORMATION OF 2-METHYL-3-FORMYLFURAN FROM REDUCED STREPTOMYCIN

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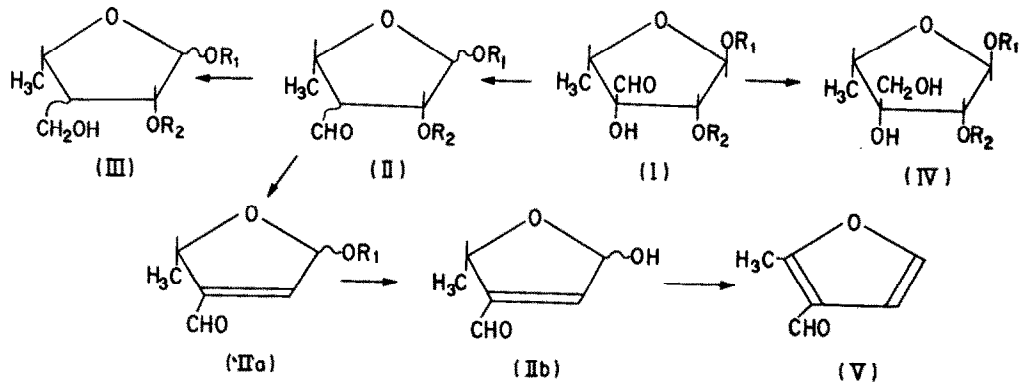
The action of aluminum amalgam (Al-Hg) (1) or a controlled-potential mercury cathode (2) on streptomycin (I), in an aqueous acidic medium, produces dihydrodeoxystreptomycin (III) in high yield, in contrast to catalytic hydrogen or sodium borohydride, whose action gives dihydrostreptomycin (IV) (3). A reaction intermediate of the structure II has been postulated to be involved in the reduction of I to III, based on the results of electrochemical studies (2). We have recently shown (4) that solutions of I treated with Al-Hg contain a proportion of a new reduction product beside III. The proportion of the former reaches about 25% of added I at an early stage of the reaction and then slowly decreases, whereas that of III steadily increases, suggesting the role of the new reduction product as the precursor of III. Although this product was not successfully isolated, various experimental facts indicated it is the presupposed intermediate II. One important line of evidence was the quantitative formation of 2-methyl-3-formylfuran (V) from this product, by steam distillation of a solution containing it at pH 2 to 4 (4).



(R_1OH = streptidine, R_2OH = 2-deoxy-2-methylamino-L-glucose)

The following experiments served to determine the course of the reaction from II to V. Stirring aqueous I sesquisulfate with liquid Zn-Hg at 35°C for 20 hrs, at pH 2.7, converted 70% of I into II without production of III. This reactivity of Zn-Hg compared with Al-Hg will be discussed elsewhere from an electrochemical standpoint. The reduced solution obtained was kept at different temperatures after pH adjustment and was studied by t.l.c. (Table I). Four different spots positive to 2,4-dinitrophenylhydrazine reagent were observed. Unreduced I did not interfere. Two of the spots were due to II and V, and the other two were assumed to be represent intermediates (A and B). The results of Table I seemed to suggest a reaction sequence II→A→B→V, for which the individual rate constants are k_1, k_2 and k_3; the effect of pH on the results may then be interpreted as arising from the variation of the relative order of these constants, i.e., $k_1 < k_2 < k_3$ at pH 2.6 and $k_1 > k_2 > k_3$ at pH 6.9. Accordingly, II in the reduced solution was subjected at 25°C to three successive pH adjustments and standing, i.e., (a) pH 6.9, 90 min, (b) pH 3.0, 5 min and (c) pH 2.2, 20 min, examining the solution at each stage of these treatments. The data thus obtained (Table II) showed that II was degraded to V in three separate steps, through A and B. The yield of V by steam distillation of the solution at pH 2 to 4 was unaffected by these treatments. The physicochemical data in Table II suggest A and B are α,β-unsaturated aldehydes. Polarographic waves are those already observed in similar instances (2). A kinetic study by polarography showed that the first reaction, producing A, is catalyzed by hydroxyl ion, but side reactions which do not lead to V becomes appreciable at pH above 7.5, at room temperature. 2-Deoxy-2-methylamino-L-glucose (R_2OH) was isolated from the solution after the first treatment (pH 6.9) and, streptidine (R_1OH), from that after the second (pH 3.0), as their sulfates.

Based upon above results, a reaction sequence involving two intermediates IIa and IIb, which correspond to A and B, respectively, was conceived and shown in the scheme. It was substantiated by the isolation of the intermediate B and its identification, which is as follows. The solution after the second of the above successive treatments (pH 3.0, 5 min) was readjusted to pH 6.9 and was repeatedly extracted with ethyl acetate. After concentration in vacuum, the substance in the extract was transferred to the aqueous phase, from which traces of V was removed by extraction

Table I. T.l.c. study of the degradation of II. Silica gel G, C_6H_6-EtOAc 3:2. Visualized with 2,4-dinitrophenylhydrazine in N-HCl, 50% MeOH.

s = strong
m = medium
w = weak

pH	2.6			4.0				6.9					
Temp., °C	50	100		50				25		50			
Time, min.	100	5	10	0	5	15	30	5	60	15	30	Rf value	color
Spot II	s	w	-	s	m	w	-	m	-	-	-	0.00	yellow
A (IIa)	-	-	-	-	w	w	-	w	s	m	w	0.00	orange
B (IIb)	-	-	-	-	-	w	m	-	-	w	m	0.22	orange
V	-	m	s	-	-	-	w	-	-	-	-	0.61	orange

Table II. Data on solutions under stepwise degradation.

Solution	t.l.c.	Absorption, nm	Polarographic waves. $E_{1/2}$ vs.S.C.E.	controlling factor	n^c.
Before (a)	II only	~220(end abspn.)	-1.16 (pH 2.5)[a.]	kinetics	2
After (a)	A only	222 (shoulder)	-0.90 (pH 6.0)[b.]	diffusion	2
After (b)	B only	222 (shoulder)	-1.00 (pH 6.0)[b.]	diffusion	2
After (c)	V only	271 (maximum)	-1.45 (pH 6.0)[b.]	diffusion	-

a. 0.1 M citrate. b. 0.1 M phosphate. c. Number of electrons consumed.

Table III. N.m.r. results on IIb. Solvent: D_2O. 100 MHz.

Integration	1H	1H		1H		3H	
Signal Group	A	B_1	B_2	C_1	C_2	D_1	D_2
Pattern	br.s.	m.	br.s.	m.	q. (J=5.2Hz)	overlapped br.doublets	
Chemical Shift[a.]	6.98	(6.3~6.1)		(5.4~4.8)		(1.5~1.2)	
Spin Decoupling		s.	s.	5.21 →		→ d. (J=3.2Hz)	s.
				5.12 (high power) →		→ s.	s.
				5.02 →		→ s.	d. (J=3.5Hz)
		Decoupled		Irradiated		Decoupled	
Signal due to [of the isomer(s)]	H-2 [1 & 2]	H-1 [1 or 2]	H-1 [2 or 1]	H-4 [1]	H-4 [2]	H-5 [2]	H-5 [1]

a. Chemical shifts are referred to DSS signal.
Chemical shifts of signals under decoupling: B_1 6.30; B_2 6.20; D_1 1.43; D_2 1.34. Abbreviations: br.=broad; m.=multiplet; q.=quartet; t.=triplet; d.=doublet; s.=singlet.

with petroleum ether. Freeze-drying gave a colorless syrup, $[\alpha]_D^{20}$ nearly zero (c = 1, H_2O). It was readily dehydrated to V, within hours at room temperature. The i.r. spectrum (film) showed an α,β-unsaturated aldehyde group ($\nu_{C=O}$ 1685 cm^{-1}), a trisubstituted ethylene group (ν_{C-H} 807 cm^{-1}) and a methyl group. Its u.v. absorption, $\lambda_{max}^{H_2O}$ (nm) 218 (ε 9,400), 322 (ε 26), and polarographic reduction wave, $E_{1/2}$ = -1.00 v. vs. SCE at pH 6.0 (n = 2), are typical of an α,β-unsaturated aldehyde. N.m.r. results (Table III) were consistent with the structure IIb, but also revealed that the substance obtained was very probably an equilibrium mixture of a pair of stereoisomers (1 and 2 in Table III). Long-range interactions aided by the presence of C=C bond within the furanose ring (5) are obvious in the complexed coupling of signals.

A disemicarbazone, $C_8H_{14}O_3N_6$, was obtained from the substance B as yellow plates, m.p. 223°C, $[\alpha]_D^{20}$ +8.7° (c = 0.5, DMSO). The wavelength of its absorption, $\lambda_{max}^{H_2O}$ (nm) 320 (ε 46,100), which is unusually long for a semicarbazone, should be due to a -N=C-C=C-C=N- group and indicates it is the disemicarbazone of the open-chain form of IIb. These accumulated results established the structure of B as 3-C-formyl-2,3,5-trideoxy-L-glycero-pent-2-enofuranose (IIb) and, consequently, that of A as IIa. A reaction sequence similar to this, i.e., the formation of a 2',3'-unsaturated nucleoside by E2 mechanism, and its transition to a furan derivative, has been reported (6). In our case the formation of IIa may be by an E2, or perhaps by an ElcB mechanism, involving a carbanion intermediate. Either of the two reaction which follow it seem catalyzed by hydrogen ion.

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