

Transformation of Fusidic Acid into Adrenocortical Hormone Analogues Containing the Fusidane Framework

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THE antibiotic fusidic acid (Ia)¹ is an attractive starting material for synthesis of steroid hormone analogues of unusual stereochemistry because its ring system, stereochemically, deviates fundamentally from that of other tetracyclic triterpenes and sterols.^{1d,e} Whereas a number of fusidic acid derivatives related to androstanes have already been prepared^{1b,1d,2-5} derivatives containing a pregnane side-chain have not previously been described. We now report a degradation of 24,25-dihydrofusidic acid (Ib)^{1b} which in a simple and

convenient manner leads to such compounds.

Heating (Ib) to 140—150° for about 3 hr. in a mixture of anhydrous lithium chloride and dimethylformamide gave a mixture of compounds, four of which have been isolated and identified. The main component, isolated in about 60% yield, is a carboxylic acid, C₂₉H₄₆O₄, m.p. 181—182°, $[\alpha]_D^{20}$ -89.8°, λ_{\max} 209 m μ (ϵ 12,600) and 252 m μ (ϵ 7750)* which could be assigned structure (IIa) for the following reasons: (a) The i.r. spectrum (KBr) of its sodium salt contains no carbonyl bands

* All new compounds gave satisfactory microanalyses. Optical rotations were measured in CHCl₃, and u.v. spectra in 96% EtOH solution. N.m.r. spectra were obtained with a Varian A-60 spectrometer, CDCl₃ being used as solvent and tetramethylsilane as internal reference.

apart from the carboxylate band at 1575 cm^{-1} , and the u.v. spectrum therefore indicates the presence of two conjugated C=C double bonds. (b) Ozonolysis of the corresponding methyl ester (IIb), $\text{C}_{30}\text{H}_{48}\text{O}_4$, m.p. $129\text{--}130^\circ$, $[\alpha]_D^{20} -76.6^\circ$, $\lambda_{\text{max}} 209\text{ m}\mu$ ($\epsilon 13,200$) and $252\text{ m}\mu$ ($\epsilon 6600$), obtained on esterification with diazomethane, gave 4-methylpentanal in high yield indicating the presence of a 20,22-double bond. (c) The n.m.r. spectrum of (IIb) shows that only one vinylic proton is present [triplet centred at $\delta = 5.80$ (CH-22)], and this second double bond must consequently be fully substituted (13, 17). The fact that the signal at $\delta = 3.02$ (CH-13)¹⁴ in the spectrum of (Ic) is absent in that of (IIb) is consistent with this conclusion. (d) A *trans*-relationship of the carboxylic group and the hydrogen at C-22 is strongly suggested by the fact that the chemical shift of the signal due to the C-22 proton corresponds well to that of the signal due to the vinylic proton in methyl angelate ($\delta = 5.92$), whereas in the spectrum of methyl tiglate this signal appears at $\delta = 6.73$.⁶

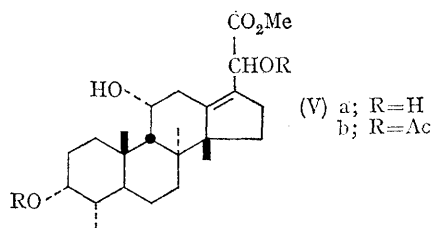
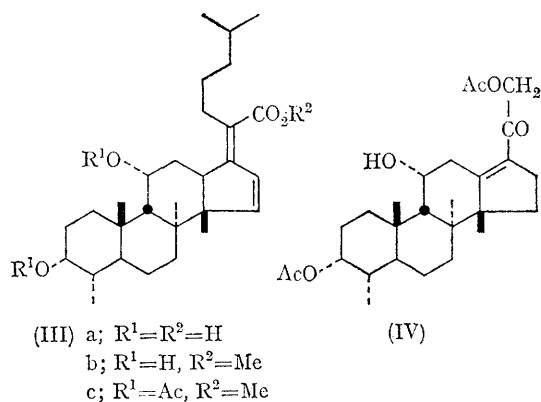
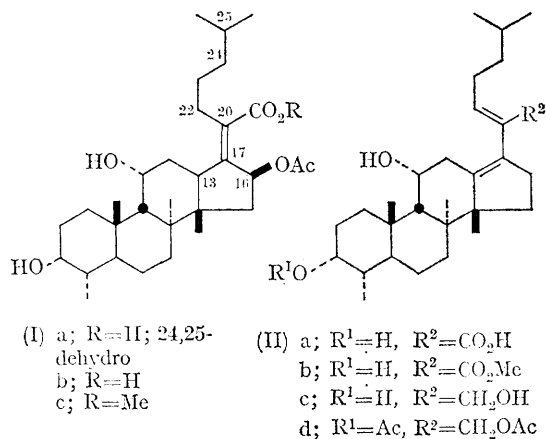
An isomeric carboxylic acid, $\text{C}_{29}\text{H}_{46}\text{O}_4$, m.p. $193\text{--}197^\circ$, $[\alpha]_D^{20} +131.1^\circ$, $\lambda_{\text{max}} 268.5\text{ m}\mu$ ($\epsilon 15,700$), formed in about 20% yield, could be assigned structure (IIIa) since acetylation (acetic anhydride/toluene-*p*-sulphonic acid) of the corresponding methyl ester (IIIb), $\text{C}_{30}\text{H}_{48}\text{O}_4$, m.p. $157\text{--}158^\circ$, $[\alpha]_D^{20} +115.1^\circ$, $\lambda_{\text{max}} 271\text{ m}\mu$ ($\epsilon 16,700$) afforded a diacetate $\text{C}_{34}\text{H}_{48}\text{O}_6$, m.p. $196\text{--}197^\circ$, $[\alpha]_D^{20} +71.3^\circ$, $\lambda_{\text{max}} 271\text{ m}\mu$ ($\epsilon 17,000$) identical with the $\alpha\beta$, $\gamma\delta$ -diunsaturated ester (IIIc) previously prepared in an unambiguous way in connection with the structural work.^{14,7} In addition to (IIa) and (IIIa) two neutral compounds were obtained in poor yield by the reaction. These have been identified as the known compounds 16-deacetyl-24,25-dihydrofusidolactone and 16-*epi*-deacetyl-24,25-dihydrofusidolactone.^{1b,4}

The presence of a free carboxylic acid group in the starting material seems to be a prerequisite for the reaction since methyl 24,25-dihydrofusidate (Ic)^{1b} could be recovered unchanged after a similar treatment.

LiAlH_4 reduction of (IIb) afforded the triol (IIc), $\text{C}_{29}\text{H}_{48}\text{O}_3$, m.p. $96\text{--}97^\circ$, $\lambda_{\text{max}} 238\text{ m}\mu$ ($\epsilon 7150$), converted by acetylation (acetic anhydride/pyridine) into an amorphous, but chromatographically pure 3,21-diacetate (IIId). Ozonolysis of the latter followed by cleavage of the ozonide with Zn-acetic acid gave finally the ketol acetate (IV) $\text{C}_{27}\text{H}_{40}\text{O}_6$, m.p. $117\text{--}118^\circ$, $[\alpha]_D^{20} -14.6^\circ$, $\lambda_{\text{max}} 262\text{ m}\mu$ ($\epsilon 12,300$).

It is evident that this sequence of reactions by a proper choice of starting materials will permit the preparation of compounds with a substitution

pattern corresponding to that of adrenocortical steroids but containing the fusidane framework.



Ozonolysis of (IIb) followed by reductive work-up (Zn-acetic acid) gave in addition to 4-methylpentanal a mixture of compounds from which the two C-20 epimeric triols (Va), $\text{C}_{24}\text{H}_{38}\text{O}_4$, m.p. $197\text{--}198^\circ$, $\lambda_{\text{max}} 208\text{ m}\mu$ ($\epsilon 7100$) and m.p. $208\text{--}210^\circ$, $\lambda_{\text{max}} 210\text{ m}\mu$ ($\epsilon 6650$), respectively, could be isolated by chromatography. They were further

characterized by acetylation to the corresponding 3,20-diacetates (Vb), $C_{28}H_{42}O_7$, m.p. 152—153°,

$[\alpha]_D^{20} -182^\circ$ and m.p. 140—141°, $[\alpha]_D^{20} -14.5^\circ$, respectively.

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