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DERIVATIVES OF α-TETRONIC ACID

A.G. Long and A.F. Turner

Glaxo Research Ltd., Greenford,
Middx., England.

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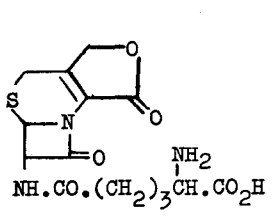
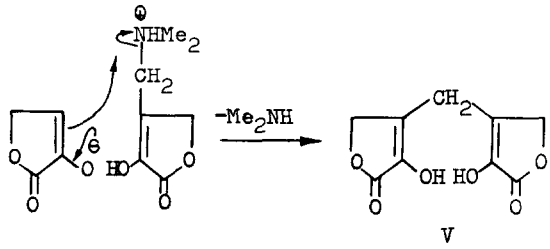
ABRAHAM and NEWTON[1] obtained the lactone (I) from cephalosporin C. We have studied simpler lactones of this type. We made our compounds from the Mannich bases derived from pyruvic acid, formaldehyde and certain secondary amines:[2] for instance, piperidine sulphate gave the α-tetronic acid derivative (III), from which the free base (IV) was obtained by treatment with barium hydroxide. We expected such Mannich bases to undergo substitution of the type advanced here to account for formation of the methylene derivative (V), $C_9H_8O_6$, a by-product[2] (the "$C_{15}H_{14}O_{10}$-Acid") in the preparation of the hydrochloride (II).



I



V

[1] E.P. Abraham and G.G.F. Newton, Biochem.J. 79, 377 (1961).

[2] C. Mannich and Bauroth, Ber 57, 1108 (1924).

Treatment of the base hydrochloride (II) with sodium thioacetate or hydrosulphide in refluxing methanol (conditions intended[3] to curtail generation of sulphide ion in the equilibrium $2HS^{=} \rightleftharpoons H_2S + S^{=}$) yielded the sulphide (VI) (a compound previously obtained[1] by degradation of cephalosporin C) and aqueous mother liquors that contained substances giving violet colours with sodium nitroprusside. Continuous extraction with ether yielded one (VIII) of these; it was isolated as its lead salt and generated therefrom by means of hydrogen sulphide. This method was inefficient and capricious; no greater success attended reduction with zinc in acetic acid of the crude disulphide (VII) obtained by the action on the base hydrochloride (II) of sodium disulphide in isopropanol. Diazomethane converted the mercaptan (VIII) into an ether, probably (IX).

Benzyl mercaptan in refluxing methanol containing sodium methoxide converted the salt (II) into the thioether (X), which was methylated by diazomethane to give the enol ether (XI), and acetylated with acetic anhydride and pyridine to the acetate (XII). Fusion of the thioether (X) with ammonium acetate produced the pale orange enamine (XIII); acid-catalysed hydrolysis reversed this change. Raney nickel in benzene converted the enamine into the derivative of β-methyl-α-tetronic acid (XIV), also obtained by fusing β-

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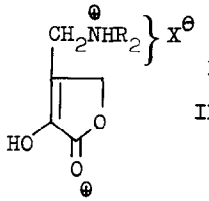
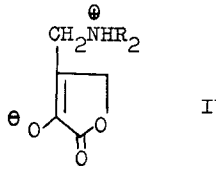
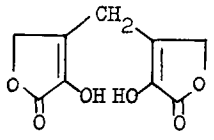
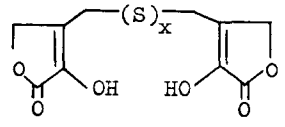
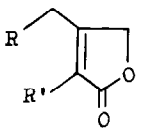
[3] A. Schöberl and A. Wagner, in Methoden der Organischen Chemie, Volume 9, p.7. Georg Thieme Verlag, Stuttgart (1955).

methyl-α-tetronic acid (XV)[4] with ammonium acetate. This enamine has been detected[1] in the products from the degradation of cephalosporin C.

Table 1. Properties of Some α-Tetronic Acids.[a]

		M.p.	λmax.[b]	ε
	II; R=Me, X=Cl	See reference 2		
	III; R_2N=piperidino X≡½SO_4^-	125-128° (decomp.)	233-234 mμ 259-267	6,100 3,500
	IV[c]; R_2N=piperidino	128-131°	235 266-267	6,600 5,700
	V[d]	230° 238-241° (decomp.)	237 277	11,700 15,200
	VI[e]; x=1	127,147°	236 279	14,800 20,300
	VII; x=2	120-129° (crude)		
	VIII; R=SH, R'=OH	Gum	242 278	6,500 3,500
	IX; R=SH, R'=OMe	Oil	231	6,300
	X; R=SCH_2Ph, R'=OH	80-81°	232 277	19,800 10,500
	XI; R=SCH_2Ph; R'=OMe	Oil	<220	
	XII; R=SCH_2Ph, R'=OAc	63-64°	<220	
	XIII; R=SCH_2Ph, R'=NH_2	84-86°	266[f]	10,600
	XIV; R=H, R'=NH_2	145°	255 <220	7,600
	XV; R=H, R'=OH	See references 1 and 4		

[4] F.Fleck, A. Rossi, M. Hinder, and H.Schinz, Helv.Chim. Acta 33, 130 (1950).

Our attempts failed to produce either dihydrothiazines by cyclization of the mercapto-compound (VIII) with aldehydes and ammonia,[5] or thiazines by treatment of the α-tetronic acids (II) or (XIV) with thioacetamide.[6] (Cyclizations of the first type might yield, after neutralization, Δ^4-dihydrothiazines; Δ^3-structures have been postulated,[5] but without spectroscopic confirmation).

Footnotes to Table 1

a All the compounds in the Table gave elementary analyses and infrared spectra in agreement with the structures put forward.

b Of ethanolic solutions, unless otherwise stated; the second pairs of λ max. and ε values were recorded with solutions 0.05N in sodium hydroxide (for enols) or 0.05N or 0.1N in hydrochloric acid (for enamines).

c The values for (III) and (IV) are for aqueous solutions, without additions. We attribute the band at the longer wavelength to the betaine form, the content of which is reduced in the salt (III). These compounds, in solution in D_2O, gave the same bands on nuclear magnetic resonance diagrams. These findings indicate that solutions of (III) contain the zwitter-ion (IV) and the bisulphate ion $HSO_4^{\ominus}$

d See ref. 7.

e Ref. 1.

f The absorption of this compound was the same in solutions 0.1N in sodium hydroxide or hydrochloric acid, but the intensity was reduced in solutions 0.5N in hydrochloric acid. This enamine behaved as a neutral compound during electrophoresis at 12 volts/cm. with M-formic acid as buffer.

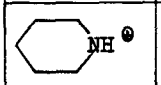
5 F. Asinger, M. Thiel et al., Annalen 610, 1, 17 (1957).

6 M. Suquet, Ann.Chim. (France), 8, 545 (1953).

7 Cf. S. Havre and G. Olsen, Acta Chem.Scand. 8, 47 (1954).

Table 2 collates the effects on the ultraviolet absorption of various substituents at the α- and β-positions of the butenolide system (VIII to XV). The λλ max. are averages; the other figures are average ε values $\times 10^{-3}$.

Table 2. Effects of Substituents in the Lactone (VIII to XV)

R \ R'	H	OAc	OH	$O^{\ominus}$	NH_2	$^{\oplus}NH_3$
H	217 mμ[8] 15.4	<220 mμ	232 mμ[1] 8	265 mμ[1] 6.5	256 mμ 7.6	<220 mμ
			234 mμ 6.1	266 mμ 5.7		
SH			243 mμ 6.5	278 mμ 3.5		
-S- (thio-ether)		<220 mμ	234 mμ 18	278 mμ 15	266 mμ 11	<220 mμ

The lactone (I) has λ max. 257 mμ (ε 8,000) (H_2O); attempts[1] have been made to explain the absorption of compounds of this type, but they have not taken account of the concerted effects of the groups R and R' in the chromophores of such butenolides. The maximum shifts to longer wavelengths as the capacity of R' as an electron-donor increases and as the group RCH_2- becomes better fitted to accommodate a negative charge; such behaviour is in keeping with chromophores of type (XVI).

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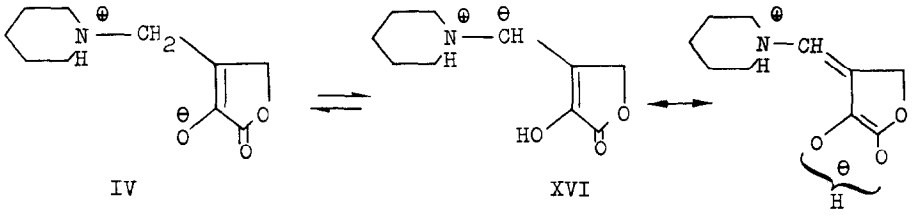
[8] L. Dorfman, Chem.Reviews 53, 90 (1953).



IV XVI

Such structures may contribute little to the ground states of these molecules; accordingly, nuclear magnetic resonance spectroscopy indicated the replacement by deuterium (from D_2O) of only two protons in the amino-sulphide (XIII), and base-catalysed acylation of the enol (X) occurs on oxygen rather than carbon (however, the possibility of a rearrangement cannot be ignored). The thio-ethers offer further possibilities, as the result of d-orbital resonance; consequently, Δ^4-dihydrothiazole[9] has λ max. 251 mμ, whereas the maxima of its Δ^2- and Δ^3- isomers lie at 230-232 mμ. We can therefore attribute the absorption of derivatives of cephalosporin C to structures (in the excited state) such as (XVII) and (XVIII) (we owe the latter to a suggestion by Professor D.H.R. Barton, F.R.S.), and, less probably, to systems such as (XIX). This explanation accords with a statement that the absorption of such compounds does not depend on attachment at the 4-position of a carboxyl group.[10]

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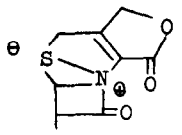
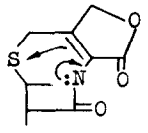
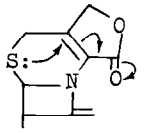
[9] F. Asinger and R. Gluck, Annalen 649, 103 (1961); cf. G. Cilento, Chem. Reviews 60, 147 (1960).

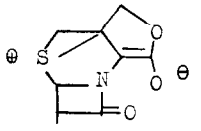
[10] R.R. Chauvette, E.H. Flynn, B.G. Jackson, E.R. Lavagrino, R.M. Morin, R.A. Mueller, R.P. Pioch, R.W. Roeske, C.W. Ryan, J.L. Spencer, and E. von Heymingen, J.Amer.Chem.Soc. 84, 3401 (1962).



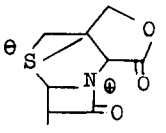
XVII







XIX



XVIII