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AN UNUSUAL REACTION OF TERRAMYCIN WITH METHYL IODIDE[1]

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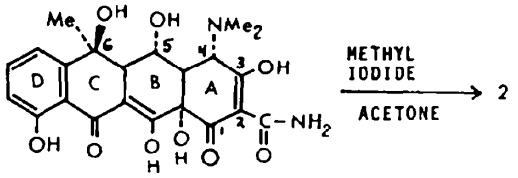
Abstract—An unusual fragmentation reaction was observed when terramycin is treated with MeI in acetone at room temp. The reaction proceeds with quaternization, loss of trimethylamine, fission of bonds 4a,5 and 12,12a with formation of an aldehydo-lactone derived from rings B, C and D. Additionally some transformations of this lactone are described.

The chemistry of terramycin (1) is both interesting and complex.[4] One interesting observation[5] is the formation of tetramethylammonium iodide when terramycin is treated in acetone solution with methyl iodide at room temperature. A number of studies have reported the formation of tarry or otherwise unrecognizable materials.[5] Thus the investigation of the reaction in greater detail was of considerable interest.

The investigation. In this investigation an acetone solution of terramycin was treated with excess methyl iodide at room temperature. Over several days crystals of tetramethylammonium iodide separated. By utilization of solubility properties and recrystallization techniques it was possible to isolate terramycin hydroiodide and an unknown product 2. Elemental analysis of this compound (2) indicated the absence of nitrogen. The IR



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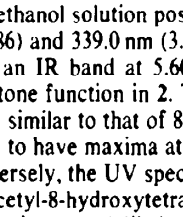
spectrum of 2 contained absorption bands at 5.60, 5.84, 6.04, 6.20 and 6.32 μ. The band at 5.84 varied in intensity when the spectrum was run in solution, whereas this band was of normal CO intensity when a solid state spectrum in potassium bromide was run. The UV spectrum for the acidic ethanol solution possessed maxima at 267.5 nm ($\log \epsilon = 3.86$) and 339.0 nm (3.67).

The presence of an IR band at 5.60 μ suggested the presence of a γ-lactone function in 2. The UV spectrum was seen to be very similar to that of 8-hydroxytetralone which was known[4a] to have maxima at 260 nm (3.94) and 335 nm (3.44). Conversely, the UV spectrum of 2 differed from those of 2-acetyl-8-hydroxytetralone and of terramycin itself. Thus it seemed likely that compound 2 contain the system:

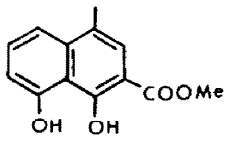


2

but not the enolizable β-dicarbonyl system present in 2-acetyl-8-hydroxytetralone and terramycin. Finally, the absence of nitrogen from the molecule was suggestive of a reaction path other than simple β-elimination of a proton with loss of the dimethylamino group, for this latter reaction course would not readily account for loss of the amide nitrogen.

In order to shed more light on the nature of the Hofmann degradation reaction of terramycin and to elucidate the structure of lactone 2, this compound was treated with methanolic hydrogen chloride. When the reaction mixture was worked up at the end of one hour a second lactone (3) was isolated. While the absorption band attributed to the γ-lactone function in 2 was still present in 3 (at 5.62 μ), the band of varying intensity noted at 5.84 μ in the spectrum of 2 was missing in both the solution and the solid state spectra of 3. The ultraviolet spectrum of 3, which exhibited maxima at 268.0 nm (3.86) and 338.5 nm (3.67), was essentially identical with that of 2. A molecular weight determination using the method of isothermal distillation[6] yielded a value of 296. This, together with elementary analytical data and a Zeisel methoxyl determination, suggested the formula $C_{13}H_{10}O_4(-OCH_3)_2$ for 3. As a consequence, the analytical data for 2 could be taken to correspond to the formula $C_{13}H_{10}O_5$. From this and from the disappearance of a CO absorption band in the formation of 3 from 2 it seemed reasonable to conclude that 3 was a dimethyl acetal or ketal of 2.

When the reaction of 2 with methanolic hydrogen chloride was allowed to proceed for a total of 7 hr none of lactone 3 was isolable, but instead there were obtained two new compounds, 4 and 5. The less soluble 5 was isolated directly from the crude product by crystallization, while compound 4 was obtained pure by partition chromatography of the mother liquors from 5 using powdered cellulose. Compound 4 exhibited no CO absorption below 6μ. The UV spectrum contained maxima at 218 nm (4.33), 249 nm (4.69), 290 nm (3.41), 303 nm (3.54), 316 nm (3.60), 365 nm (3.93) and at 378 nm (3.90). This was noted to be almost identical to the spectrum reported[4a] for 1,8-dihydroxy-2-naphthoic acid (245 nm (4.72), 288 nm (3.49), 301 nm (3.50), 314 nm (3.68), 360 nm (3.94), 372 nm (3.91)). When one considers the complexity of these spectra, the similarity becomes even more significant. A C-H analysis corresponded to $C_{13}H_{12}O_4$ and a Zeisel OMe determination pointed to the presence of one OMe group. The accumulated evidence suggested that 4 was in reality methyl 1,8-dihydroxy-4-methyl-2-naphthoate.



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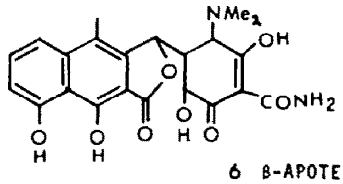
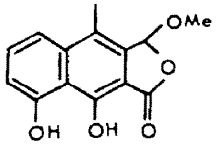
Compound **5** absorbed at 5.76 μ in the IR and possessed a complex UV spectrum (220 nm (4.39), 245 nm (4.69), 3.07 nm (3.61), 319 nm (3.71), 355 nm (3.91), 370 nm (3.96)) very similar to that reported[4a] for β-apoterramycin (**6**) (248 nm (4.78), 308 nm (3.76), 320 nm (3.79), 361 nm (3.96), 375 nm (3.95)). These data were highly suggestive of the naphthalide system.



6 β-APOTERRAMYCIN

Virtually any other type of CO function at the 2-position of the 1,8-dihydroxynapthalenic system would absorb above 6 μ. The C–H analysis, which pointed to $C_{14}H_{12}O_5$, and a Zeisel OMe determination, which indicated the presence of one OMe group, together with the spectral data all suggested:



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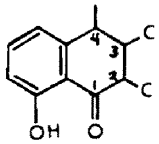
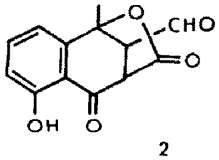
as the structure of **5**.

Given the data thus far considered it was possible to reach a conclusion regarding the structure of **2**. The formation of **5** from **2** along with the similarity of the UV spectrum (of **2**) to that of 8-hydroxytetralone required the presence of the 8-hydroxy-4-methyl-1-tetralone system bearing single carbon substituents at carbons 2 and 3. Also, the C atom at position 2 seemed most likely to be at the same oxidation state as in **5** (i.e. a carboxyl group)



and to be involved in the lactone grouping known to be present in **2**. The 2-carboxyl group could then be bonded with only carbon 4 for a carboxaldehyde function was needed at position 3 to account for the reactive carbonyl in **2** absorbing at 5.84 μ. A lactol structure involving the carboxaldehyde group was excluded by the C–H analysis in conjunction with the non-naphthalenoid nature of **2**. The uniquely defined structure for **2** was thus



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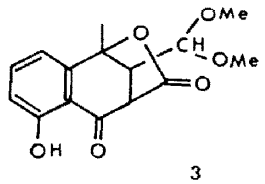
while that for **3** was:



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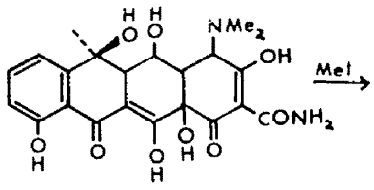
The structures of **2**, **3**, **4** and **5** having been elucidated it remained to consider the mechanism of formation of these compounds. It is readily apparent that the formation of **2** from terramycin with methyl iodide is not explicable on the basis of an ordinary Hofmann elimination. However, elimination of trimethylamine with β-eliminations of the C-5 carbinol group to yield an aldehyde function not only would account for the presence of this group in lactone **2** but also seems reasonable *per se*. Similar β-eliminations of carbinol groups are common in the analogous acidic dehydration of 1,3-diols.[7] The intermediate (**8**) thus formed can readily aromatize by β-diketone fission occasioned by intramolecular attack of the tertiary OH group of ring C on the CO group of ring B:



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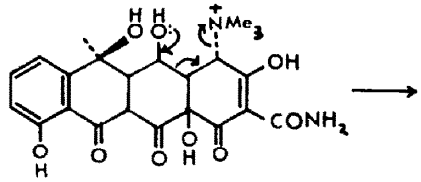

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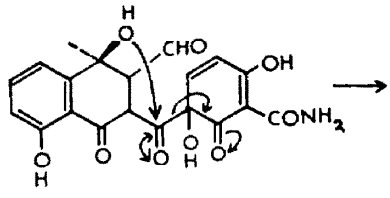

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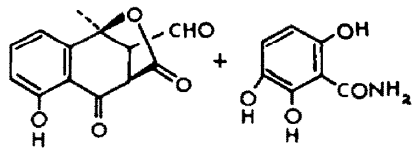

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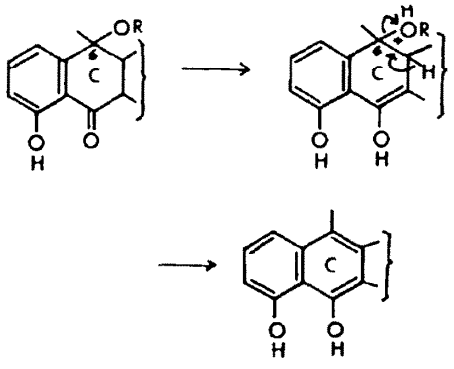
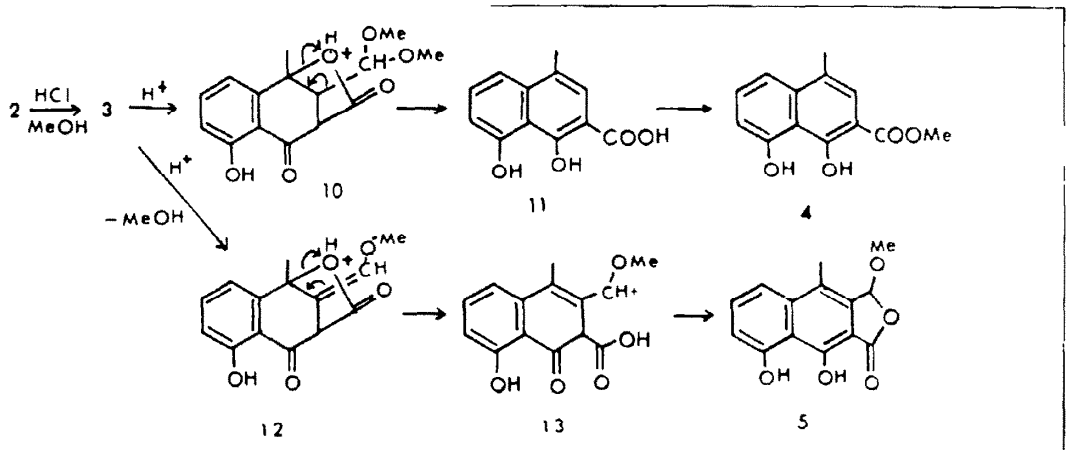
The formation of **3**, **4** and **5**, from **2** is also readily understood. It is reasonable that reaction of **2** with methanolic hydrogen chloride under fairly drastic conditions led merely to the acetal (**3**) and failed to aromatize ring B wth concomitant fission of the lactone grouping, as did occur under still more drastic conditions. In

the facile acid aromatization of other terramycin derivatives the transition state, corresponding to fission of the C-6 C–O bond of ring C and loss of the 5a proton, can partake of some of the aromatic resonance energy of the product, since enolization of the ring C CO group can preceed fission of this tertiary C–O bond.



In contrast, in neither **2** nor **3** can enolization of the keto group precede destruction of the bicyclic ring system (Bredt's rule) and aromatization energy is not available in the lactone fission step.

The fission of the lactone function to yield **4** and **5** may be reasonably formulated as follows:



It is to be noted that 2,3,6-trihydroxybenzamide (**9**) is expected as the second product of the methyl iodide reaction of terramycin. This product was not isolated although air-sensitive material possibly containing this compound was observed.

The significance of the methyl iodide reaction affording aldehyde-lactone **2** by C–C fission rather than by elimination of hydrogen in a normal Hofmann fashion is consistent with the transoid stereochemical disposition of the C_{4a}–C_5 and C_4–N bonds. However, in view of the known [4d] facile epimerization of C-4 trimethylammonium derivatives of tetracyclines, the reaction is really not a test of stereochemistry and is more of intrinsic than stereochemical interest.

EXPERIMENTAL

Formation of lactone **2**. Terramycin (50 g) was dissolved in 3500 ml analytical grade acetone and to this soln was added 200 ml MeI. The mixture was kept in a stoppered 4 l dark brown vessel. At the end of several days crystals of tetramethylammonium iodide began to separate. The mixture was allowed to stand at room temp for a least 10 days. The best yield of **2** was obtained when the reaction was run for 14 days. One run which lasted 50 days gave a lower yield of product. At the end of the reaction period the soln was filtered free of 7.1 g tetramethylammonium iodide. The filtrate was concentrated *in vacuo* to leave a tan glass. This was dissolved in 300 ml acetone and then treated with 1500 ml dry ether to give a yellow ppt which was removed by centrifugation. The ether ppt fraction weighed 41.6 g. The ether filtrate was concentrated under vacuum to leave 14.08 g of brownish-yellow solid which was dissolved in 150 ml acetone and treated with 1600 ml benzene. The ppt which formed was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with three 70 ml portions of hot EtOAc and the remaining solid was taken up in 20 ml hot acetone. Crystalline **2** separated from all four extracts on cooling. The mother liquors yielded more **2** on concentration. The lactone was recrystallized from EtOAc containing a little acetone. Slow crystallization by evaporation of solvent from a saturated solution at room temp proved most effective. The yield of product averaged 1.5 g; the highest yield was 2.9 g (12.7%). The ether precipitated fraction isolated from short runs could be redissolved in acetone and treated with MeI to yield more **2**.

Lactone **2** decomposed at 148° turning green. The IR spectrum of **2** in dioxane showed maxima at 5.60, 5.85 m, 6.04, 6.20 and 6.32 μ. The spectrum gave much more detail in the 7–14 μ region but was very similar at shorter wavelengths except that the CO absorption band at 5.84 μ was considerably more intense. The UV spectrum in 0.001 N HCl in EtOH exhibited maxima at 267.5 (log ϵ = 3.86) and 339.0 (3.67) nm. The lactone was sublimed in high vacuum before analysis.

(Found: C, 63.62; H, 4.30. Calc. for $C_{13}H_{10}O_5$: C, 63.41; H, 4.09%).

Lactone **2** readily formed a yellow 2,4-dinitrophenylhydrazone, m.p. 257–8° after extraction with boiling EtOH and recrystallization from EtOAc.

(Found: N, 12.90. Calc. for $C_{19}H_{14}O_8N_4$: N, 13.14%).

Isolation of terramycin hydroiodide from the reaction mixture. The ether precipitated fraction was stirred with 200 ml hot distilled water on the steam-bath until only a dark tar remained undissolved. The tar was removed by filtration and the hot filtrate was extracted with EtOAc until the extracts were colorless. The residual aqueous phase, which was still warm, slowly separated crystalline material. This product was recrystallized from MeOH to yield pure orange terramycin hydroiodide, decomposing over a wide temp range above 200°. The IR spectrum showed absorption bands at 6.10, 6.20 and at 6.30 μ. The UV spectrum had peaks at 270.5 (4.17) and 361.0 nm (4.05). When this compound was dissolved in a minimum of cold water

and was treated with sat aq $NaHCO_3$ a ppt formed. This yellow solid was shown by IR comparison in KBr to be terramycin.

(Found: C, 44.92; H, 4.16; N, 4.86; I, 21.42; (N)Me, 4.89. Calc. for $C_{22}H_{25}N_2O_9I$: C, 44.91; H, 4.28; N, 4.76; I, 21.57; (N)Me, 5.11%).

Lactone **3**. To 25 ml MeOH containing 7.5 g HCl and cooled in ice was added 353 mg of **2**. The lactone was dissolved by swirling and the soln was immediately allowed to warm to room temp. Having been allowed to stand at room temp for 1 hr, the yellow soln was cooled in ice and poured onto an ice and water mixture (*ca* 75 g) and the whole was EtOAc extracted. The extract was washed thoroughly with water and was dried over Na_2SO_4. Concentration *in vacuo* left a crystalline residue which was dissolved in *ca* 7 ml hot EtOAc, then treated with ligroin to cloudiness and allowed to cool. On cooling, the soln yielded large rhombs, m.p. 171–2°. Recrystallization from EtOAc–ligroin yielded 136 mg pure **3**, m.p. 172°. This compound gave a single fluoroescent spot, R_f 0.76, when paper strip partition chromatographed (using Watman 3MM; ligroin–AcOH–water: 90:10:1, using the organic phase). The IR spectrum in $CHCl_3$ contained bands at 5.62, 6.04, 6.18 and 6.32 μ. A solid state spectrum run in KBr failed to show any other CO bands. The UV spectrum in 0.001 N HCl in EtOH had peaks at 268.0 (3.86) and 338.5 nm (3.67). A molecular weight determination using the method of isothermal distillation[6] (solvent $CHCl_3$) gave a value of 296 as compared with a theoretical value of 292.

(Found: C, 61.45; H, 5.51; MeO, 21.31. Calc. for $C_{15}H_{16}O_6$: C, 61.64; H, 6.52; MeO, 21.24%).

Compound **5**. To 30 ml MeOH containing 10 g HCl and cooled in ice was added 201 mg of **2**. After soln had been effected the mixture was allowed to stand at room temp for 12 hr. In several other runs 7 hr proved adequate; in one run given a still shorter reaction time only **3** was isolated. At the end of the reaction period the mixture was poured onto a mixture of ice and water (*ca* 70 g) and the mixture was EtOAc extracted. The extract was washed once with 2 ml water and was then dried over Na_2SO_4. Concentration *in vacuo* left solid material which on crystallization from EtOAc–ligroin gave **5**, m.p. 180°, in 69 mg yield after recrystallization. This compound gave a single fluorescent spot, R_f 0.08, on paper partition chromatography on Whatman 3MM paper using ligroin–AcOH–water (90:10:1). The IR spectrum of **5** has bands at 2.86, 2.96, 5.76, 6.04 and 6.11 μ. The UV spectrum in 0.001 N HCl in EtOH has maxima at 220 (4.39), 245 (4.69), 307 (3.61), 319 (3.71), 355 (3.91) and 370 nm (3.96). Compound **5** was sublimed under high vacuum before analysis.

(Found: C, 64.41; H, 4.79; OMe, 12.27. Calc. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65; OMe, 11.93%).

Isolation of compound **4**. the filtrates from the isolation of **5** were partially concentrated *in vacuo* and the conc EtOAc soln was subjected to partition chromatography on a slurry packed powdered cellulose (Whatman standard grade) column (18 × 550 mm) using ligroin–AcOH–water (90:10:1). Ten fractions were collected and the first two fractions yielded on concentration crystalline solid. This, after crystallization from EtOAc, melted at 148° and weighed 89 mg. The m.p. was not raised by further recrystallization. After vacuum sublimation for analysis the material melted at 145°. Compound **4** exhibited IR absorption bands at 2.93, 6.01, 6.11, 6.20 and 6.29 μ. It had the following maxima in the UV: 218 (4.33), 249 (4.69), 290 (3.41), 303 (3.54), 316 (3.60), 365 (3.93), 378 nm (3.90). Paper strip partition chromatography yielded only one fluorescent spot, R_f 0.91, using ligroin–AcOH–water (90 : 10 : 1).

(Found: C, 67.45; H, 5.50; OMe, 13.93. Calc. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21; OMe, 13.36%).

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[1]This work was done at Harvard University in 1953–54 by H. E. Zimmerman in collaboration with R. B. Woodward.

[2]Deceased 8 July 1979.

[3]Author to whom correspondence should be addressed at: Department of Chemistry, Universtiy of Wisconsin, Madison, WI 53706, U.S.A.

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