INVESTIGATIONS IN THE FIELD OF TETRACYCLINES

XLIII. Partial Synthesis of Anhydrotetracycline

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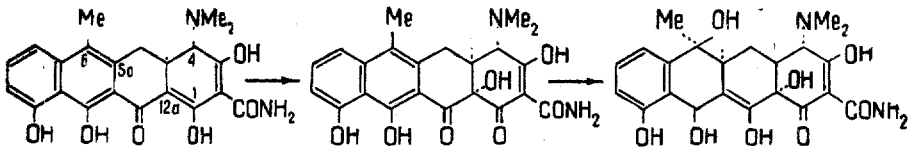
Anhydrotetracyclines, which are the first products of the acid degradation of the tetracycline antibiotics, are of great interest as direct biosynthetic representatives of the natural tetracyclines [1] and as intermediates for the complete synthesis of the antibiotics of this group [2]. In view of this, we have undertaken the partial synthesis of 5a, 6-anhydrotetracycline (II), starting from the known [3] 12a-deoxy-5a, 6-anhydrotetracycline (I).



I II III

The 12a-hydroxylation of the deoxyanhydro compound (I) was effected by catalytic oxidation with oxygen at 20° C in the presence of platinum (from PtO_2, prepared by a published method [4]), $MnCl_2$ or $CeCl_3$ (cf. [5, 6]). The best results were obtained with a platinum catalyst (350 mg/mmole) in anhydrous tetrahydrofuran (70 ml/mole) containing triethylamine (15 mmole/mmole). The hydroxylations lasted 6-8 hr. After purification of the reaction product by countercurrent distribution [120 transfers in the system ethyl acetate-heptane (4:1), citrate-phosphate buffer with pH 8.0] a substance was isolated with mp (micro) 225°-228° C (decomp., from benzene) $[\alpha]_{578}^{20}$ + 50 ± 5°, $[\alpha]_{546}^{20}$ −5 ± 5° (c 0.3; dimethylformamide); on descending chromatography on Whatman No. 2 paper impregnated with Trilon B, R_f 0.87 [in the acetic acid-butanol-water (1:4:5) system] and R_f 0.56 [in the butanol-4% aqueous ammonia (2:3) system]; in 0.01 N methanolic HCl, λ_{max}: 223, 273, 298 inflexion, 310 (inflexion), 324 (inflexion), 427 mμ (log ε 4.49, 4.74, 3.90, 3.72, 3.37, 3.94); ν_{max}^{KBr} 1510, 1573, 1626, 1648, 3320, 3380 cm^{-1}.

A direct comparison of this substance with the anhydrotetracycline obtained by the acid dehydration of natural tetracycline [7] showed their complete identity. Thus, in contrast to the 12a-hydroxylation of 12a-deoxytetracycline described previously [5], the conversion of (I) into (II) is not accompanied by the epimerization of the asymmetric center at C_4, but leads to the "natural" configuration of ring A.

Since anhydrotetracycline (II) has recently been rehydrated to tetracycline [], the conversion that we have effected also forms a partial synthesis of the main antibiotic of this group, tetracycline (III).

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