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A NOVEL REARRANGEMENT OF 4-DEDIMETHYLAMINO-4-KETO-5a, 6-ANHYDROTETRACYCLINE

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The intermediacy of the fully aromatic compounds, 6-methylpretetramids (1a and 1b) has been well established in the biosynthesis of the tetracycline antibiotics.[1,2] Thus, hydroxylation of 1b at C-12a followed by reductive amination at C-4 and subsequent methylations complete the remaining transformations necessary for anhydrotetracycline generation.[2c]

In the course of recent experiments concerned with the in vitro conversion of 4-hydroxy-6-methyl-pretetramid (1b) to the biointermediate, 4-dedimethylamino-4-keto-5a, 6-anhydrotetracycline (2)[3], an intriguing molecular rearrangement of the latter (2) was discovered.

Upon mild (steam bath) heating and subsequent cooling to r.t., an acetonitrile solution of 2 yielded a new crystalline compound in 86% yield,[4] which was homogenous on tlc (polyamide; n-BuOH/HOAc/H_2O = 60/25/15: the product had an R_f 0.60, while starting material had an R_f 0.65). The composition was determined by high resolution mass spectrometry (observed 397.07997; calcd. for $C_{20}H_{15}NO_8$ 397.07983). The pmr spectrum (DMSO-d_6) revealed significant resonances at δ 4.25 (s, 2H), 7.10 and 7.70 (m, 3H), and 8.5 (br s, 2H). Deuterium exchange resulted in the disappearance of resonances attributed to phenolic and amide protons, leaving eight nonexchangeable protons. A completely decoupled cmr spectrum (DMSO-d_6) displayed twenty separate carbon resonances, only two of which could be attributed to sp^3 carbons.[5] The uv spectrum [λ_{max}^{MeOH} 455(sh), 390, 335, 270, 230 nm] indicated that the chromophore was interrupted at the C-12a position,[6] while the ORD spectrum revealed the complete loss of optical activity. The ir (KBr) showed absorptions at 1675 and 1650 cm^{-1}, the low carbonyl absorption (1675 cm^{-1}) being easily accommodated on the basis of intramolecular hydrogen bonding. The lactone structure 4 is suggested for the rearranged product, based on the above data.

The lactone 4, upon treatment with 1% KOH-MeOH at r.t., gave the tricyclic ketone 5, which was identical with an authentic sample[2b,7] in all respects (tlc, uv in MeOH and in 0.1N-HCl/MeOH, mass spectrum, ir and melting point). An isolable yield of 5 could be obtained directly from the 4-keto compound 2 by treatment with KOtBu in MeOH under N_2, despite the propensity of 2 towards 4a, 12a-dehydration in basic solution.

In view of the above observations and by analogy with earlier tetracycline chemistry[8], we suggest the following mechanism as shown in the scheme. The dependence of product yield on the choice of solvent is in accord with a mechanism involving the keto-ketene species 3. The facile nature of the rearrangement mechanism is attested by an observation that the pmr spectrum of 2 in DMSO-d_6 underwent a remarkably clean change to that of 4 within two hours at r.t. Since 2 has been implicated as a biointermediate between 4-hydroxy-6-methylpretetramid (1b) and the tetracyclines by virtue of is transformation by Streptomyces sp. to tetracycline antibiotics, the facile in vitro chemistry of 2 described herein may require some reassessment of the previously postulated pathway, e.g. the steps 1 → 4 → 3 → 2 might be Nature's method of achieving 12a-hydroxylation.

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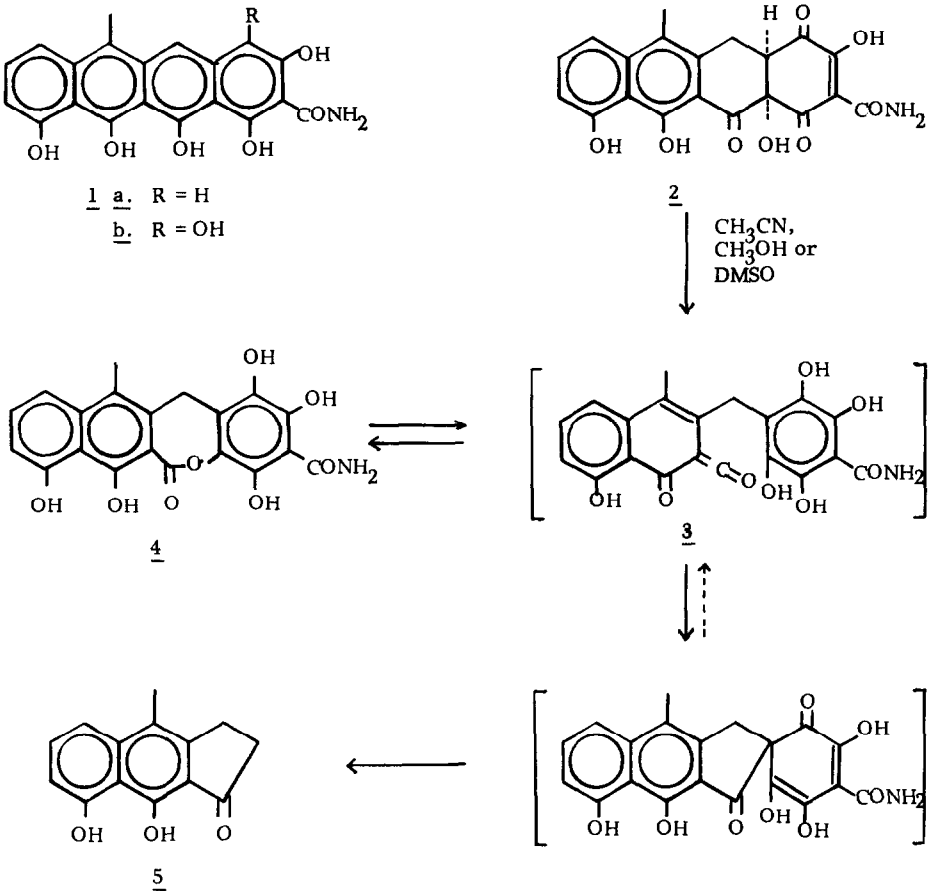
R
OH
CONH2
OH OH OH OH
1 a. R = H
b. R = OH
H O
OH
CONH2
OH OH O OH O
2
CH3CN,
CH3OH or
DMSO
OH
OH
CONH2
O
OH OH O OH
4
OH
OH
CONH2
O
OH O OH OH
3
O
OH
CONH2
OH OH O OH OH
OH OH O
5

SCHEME

4. The same product was obtained in 40% yield from similar treatment in MeOH.

5. CMR: 14.33, 26.05, 101.62, 109.43, 110.21, 113.15, 116.36, 118.51, 126.71, 129.45, 130.43, 133.43, 136.09, 136.38, 140.98, 147.81, 154.76, 154.94, 163.65, 172.03. Chemical shifts are expressed as ppm downfield from TMS.

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