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SYNTHESIS OF 6-THIATETRACYCLINE, A HIGHLY ACTIVE ANALOGUE OF THE ANTIBIOTIC TETRACYCLINE

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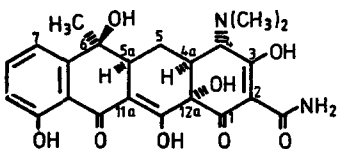
Summary: 6-Thiatetracycline, an analogue of the antibiotic tetracycline, has been synthesized from 2-chloro-5-methoxy-thiophenol in a 10 step synthesis.

The tetracyclines are a family of broad spectrum antibiotics, which, since the isolation of the first member of the family, chlorotetracycline, by Duggar in 1947 (1), have been used extensively by the medical profession for nearly 3 decades. Based on the natural tetracyclines, the parent substance of which is tetracycline, 1, a large number of tetracyclines have been synthetized by variation of the substituents at positions C_5, C_6 and C_7. Several total syntheses have been published by Woodward's, Shemyakin's and Muxfeldt's groups (2).

We decided to probe a new concept in order to prepare a class of possibly antimicrobial active tetracyclines. Our idea was to investigate substitution of one of the carbon atoms in the ring system with a heteroatom and we decided to prepare 6-thiatetracycline, 2, which required its total synthesis. We chose to follow the general strategy of Muxfeldt (3-5) and report herewith the successful synthesis of 2 (6).



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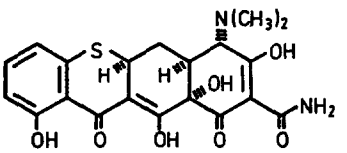
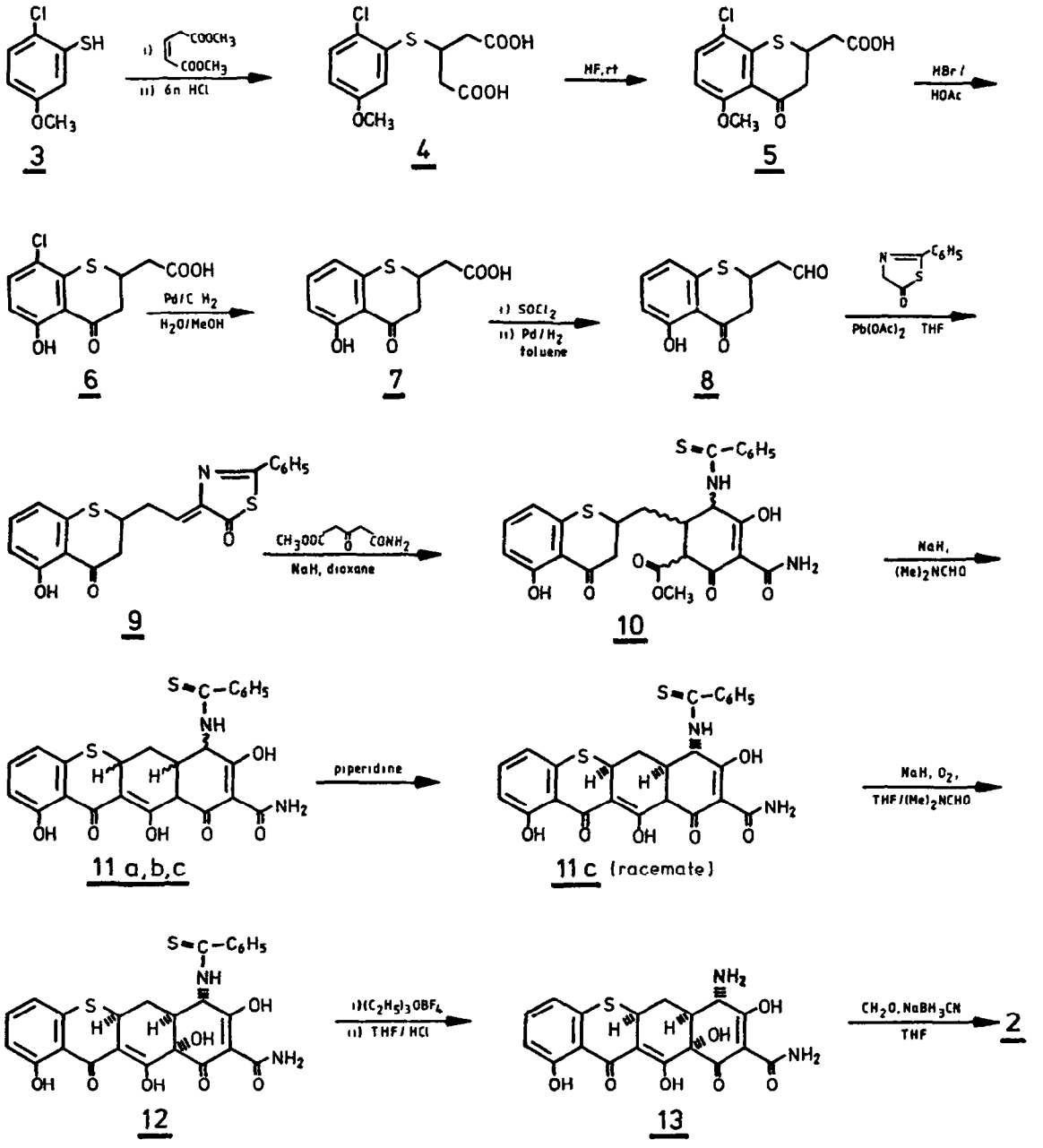


2

2-Chloro-5-methoxy-thiophenol, 3, was synthesized from 2-chloro-5-methoxy-aniline (7) by the xanthogenate method (8) in 63 % yield. Addition of dimethyl glutaconate and saponification provided the dicarboxylic acid 4 (mp 133-135°C) in 82 % yield. Cyclization in liquid hydrogen fluoride led to carboxylic acid 5 (mp 167-168°C) in 96 % yield. The chloro atom functions as a blocking group; the diacid with H at this position cyclizes primarily at this position.



In contrast to the strategy of Muxfeldt, who cleaved the ether under drastic conditions at the last step, we accomplished the demethylation in the next step. The reaction proceeded smoothly with hydrogen bromide/acetic acid at room temperature to give compound 6 (mp 141-143°C) in 98% yield.

Catalytic hydrogenolysis (which is also possible before the ether cleavage) resulted in carboxylic acid 7 (mp 145-147°C) in 75% yield. Reaction with thionyl chloride gave the carboxylic acid chloride, which was subsequently reduced under Rosenmund conditions to the aldehyde 8 (mp 66-68°C) in 85% yield. Condensation with 2-phenyl-3-thiazolin-5-one (9) led to 9 (mp 139-141°C) in 82% yield. Reaction with methyl 3-oxoglutaramate (4) yielded 10 as a mixture of isomers, which were not isolated but were immediately cyclized after addition of 4 mol sodium hydride and dimethyl formamide to the tetracyclic system 11. Product 11 consists of three stereoisomers (four are theoretically possible) which were separated by column chromatography and their configuration assigned on the basis of NMR and electronic spectra. Two of the isomers show a coupling constant of 13 Hz between C_4 and C_{4a} protons.

This clearly indicates that these protons are trans and diaxial. The coupling constant of 6 Hz for the third isomer implies an equatorial-axial relationship between the C_4 and C_{4a} protons. The nature of the relationship between C_{4a} and C_{5a} protons was determined by comparison of electronic spectra. Two isomers in methanolic sodium borate exhibit an intense absorption maximum at 478 nm (ε = 39,200) with shoulders at 454 and 508 nm, whereas the other compound has λ_{max} = 471 nm (ε = 34,600) and was devoid of shoulders. Inspection of molecular models leads to the conclusion that only the isomers with syn standing C_{4a} and C_{5a} protons can exist in a relatively strain free planar state and therefore exhibit the more intense and more structured absorption at higher wavelength.

Accordingly, we have assigned the isomers as 11a, C_4 - C_{4a} and C_{4a} - C_{5a} protons syn (mp 200-202°C), 11b with C_4 - C_{4a} and C_{4a} - C_{5a} both with anti protons (mp 228°C) and 11c with C_4 - C_{4a} anti, C_{4a} - C_{5a} syn protons (mp 195-196°C). The ratio 11a : 11b : 11c = 7 : 5 : 1.

Only isomer 11c is usable for our further synthesis. It is known from Muxfeldt's work that the isomers with C_4 - C_{4a} syn protons can be transformed into anti isomers on prolonged standing in pyridine solution at room temperature. We found that when our series was maintained in piperidine at 50°C for 1 h, not only did this epimerization occur, but so did epimerization of C_{4a} - C_{5a} anti to its syn analog. We were therefore able to quantitatively transform isomers 11a and 11b into the desired isomer 11c. The total yield of 11c based on 9 is 62%. We assume that this unusual epimerization proceeds by cleavage of the C_{5a}-S bond in a retro-Michael reaction and that subsequent ring closure is apparently thermodynamically more stable with C_{4a} - C_{5a} protons syn.

Introduction of the 12a-hydroxyl function was then achieved by treatment of 11c with sodium hydride and molecular oxygen (10). We obtained 12 (mp 230°C) after chromatography on silica gel in 44% yield (some material, hydroxylated in the 11a position was also isolated, mp 195°C).

Reaction with triethyloxonium tetrafluoborate (11) afforded the thioimino ether, which was hydrolyzed to the hydrochloride of 13 (mp 268-270°C dec.) in

89% yield. Dimethylation of the amino group with formaldehyde and sodium cyanoborohydride (12) proceeded readily and furnished thiatetracycline 2 (mp 225°C) as a racemate in 62% yield upon crystallization from methanol (yellow needles).

UV (EtOH) λ_{max} (ε), 354 (12,100), 252 (27,050); UV (0,1 M methanolic borate) λ_{max} (ε), 376 (13,800), 250 (22,700);

^{1}H NMR (90 MHz, Me_2SO-d_6) δ = 2,54 (-NMe_2, 6 H, s), 3,98 (H_4, d, J = 11 Hz), 4,61 (H_{5a}, dd, J = 9 Hz), 6,72-7,48 (3 aromat. H, m), 8,98, 9,25 (-$CONH_2$, 2s), 11,62 (phenolic OH, s); MS m/e P^+ 432.

6-Thiatetracycline 2 was obtained as its hydrochloride from ethanolic hydrogen chloride, mp 280°C dec.; UV (H_2O) λ_{max} (ε), 351 (13,550), 275 (13,150), 249 (21,200); ^{1}H NMR (90 MHz, Me_2SO-d_6), δ = 2,92 (-NMe_2, 6 H, s), 4,42 (H_4, d, J = 2 Hz), 4,61 (H_{5a}, dd, J = 9 Hz), 6,72-7,48 (3 aromat. H, m), 9,10, 9,62 (-$CONH_2$, 2s), 11,56 (phenolic OH, s).

6-Thiatetracycline 2 is superior in its antibacterial spectrum to all known tetracyclines (13). Its activity will be described in detail in a future report.

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