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chemical structures

Figure 1: chemical structures

Abstract

Full Text

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CONSTRUCTION OF THE DCB SYSTEM OF TETRACYCLINES

In recent years, the groups of Muxfeldt ([1]), Buza ([2]), and Woodward ([3]) have carried out syntheses of hydronaphthacene compounds of the type of 5a,6-anhydro- and 6-deoxytetracyclines, which are close analogs and degradation products of the highly active antibiotics of the tetracycline group (I). However, the preparation of these compounds, which possess a simplified structure of ring C and therefore are considerably more stable, has still not opened a route to the natural tetracyclines themselves. One of the principal problems in the synthesis of these antibiotics remains, as before, the construction of the tricyclic DCB system, which is the most labile and at the same time the biologically most important part of their molecule. Early attempts to create such a system were not successful ([4]), and only recently have ways of solving this problem appeared as a result of the partial synthesis of tetracycline (I) from anhydroaureomycin ([5]). The present communication describes another approach to the construction of the ring system DCB of tetracyclines—by the synthesis of oxydiketones of types (II) and (III).

(I)

(IIa): $R = H$ (IIIa): $R = H$

(IIb): $R = CH_2Ph$ (IIIb): $R = CH_2Ph$

The starting material for the synthesis of these compounds was acetoxyketodiol (V), which had previously been obtained by Inhoffen and co-workers ([4]) in an attempt to synthesize dioxydiketone (IIIa), and the method for its preparation was modified by us, which made it possible to increase its yield from juglone to 50%. Before condensation with $MeMgJ$, it seemed advisable to protect both free hydroxyl groups in this diol with some readily removable grouping, for example a ketal grouping, and therefore we converted diol (V), by the action of a 0.5% acetone solution of H_2SO_4, into the 5,10-acetonide (IV) (yield

95%). The substance obtained was readily hydrolyzed by dilute HCl to the starting compound, but unexpectedly proved inert toward Grignard reagent in tetrahydrofuran or boiling ether, although with $LiAlH_4$ it reacted in the usual manner with formation of diol (IX). Since saponification of the acetoxy group in acetoxyketoacetonide (IV) also proceeded with great difficulty, we concluded that deactivation of the 9-keto group was caused by its interaction with the 4-acetoxyl, which, being in a quasi-axial position, is spatially close to C_9. We therefore decided to remove the acetyl group and to block the hydroxyls in positions 4 and 10 with an isopropylidene residue, since we had previously found ([6]) that simple ether groups, in contrast to acetal groups, not only do not hinder but even facilitate the addition of $MeMgJ$ and $LiAlH_4$ to the carbonyl shielded by them. For this purpose diol (V) was alkylated with MeJ and $PhCH_2Br$ in acetone in the presence of K_2CO_3, and the resulting 5-alkoxy-10-hydroxy-4-acetates (VI) (yield 60%) were saponified with 0.5 N aqueous methanolic KOH to 5-alkoxy-4,10-diols (VII) (yield 80%), which were then converted by the action of a 0.1 N acetone solution of H_2SO_4 into the isopropylidene derivatives (VIII) (yield 90%). As expected, the interaction of 4,10-acetonides (VIII) with $MeMgJ$ proceeded normally, giving, in 75% yield, the methylcarbinols (XII)

For the further conversion of compounds (XII) into 4,10-diketones (II) and (III), it was first necessary to remove the isopropylidene protection from hydroxyls 4 and 10.

[Reaction scheme with compounds: (IV); (V): R = H; (VIa): R = Me; (VIb): R = CH_2Ph; (VIIa): R = Me; (VIIb): R = CH_2Ph; (VIIIa): R = Me; (VIIIb): R = CH_2Ph; (IX); (X); (XIa): R = Me; (XIb): R = CH_2Ph; (XIIa): R = Me; (XIIb): R = CH_2Ph.]

protection. However, the m-dioxane grouping of compounds (XII) proved to be so resistant to acids that it underwent hydrolysis only under conditions ($0.05N$ $H_2SO_4, 80^\circ$) under which dehydration of the molecule occurred to give derivatives of 10-methylanthrol-1 (XI).

[Reaction scheme with compounds: (XIIIa): R = Me; (XIIIb): R = CH_2Ph; (XIVa): R = Me; (XIVb): R = CH_2Ph; (XV); (XVIa): R = H; (XVIb): R = Me; (XVII); (XVIIIa): R = Me; (XVIIIb): R = CH_2Ph; (XIXa): R = Me; (XIXb): R = CH_2Ph; (XXa): R = H; (XXb): R = Me; (XXI); (XXII); (XXIII); (XXIV).]

In connection with this, it became necessary to use, for blocking 4-OH and 10-OH, some more labile grouping, and we assumed that the role of such a protective grouping could be played by an orthoacetate bridge, which should close between O_4 and O_{10} upon removal of a proton from 10-oxy-4-acetates (VI). Indeed, on condensation of compounds (VIa) and (VIb) with MeMgJ in tetrahydrofuran, we succeeded in obtaining (evidently through the stage of formation of anions (X)) 5-alkoxy-10-acetoxy-9-methyl-4,9-diols (XIIIa) (yield 50%) and (XIIIb) (yield 75%).

The position of the acetoxy group in these compounds was established by oxida-

Fig. 1. UV absorption spectra

Figure 2: Fig. 1. UV absorption spectra

tion of (XIII) with $CrO_3 \cdot 2Py$ to acetoxyketones (XIV), the structure of which was proved spectroscopically. The configuration of the asymmetric center 9 was clarified as a result of correlation with the ketol (XXIV) synthesized by us earlier ([7]), which was carried out as follows. On saponification of acetoxydiol (XIIIb) with 0.03 N aqueous methanolic KOH, triol (XVIIIb) is obtained (yield 85%); the most reactive hydroxy group in it is 4-OH, and therefore on its direct oxidation (for example, with MnO_2 or CrO_3 in pyridine) 10-hydroxy-4-ketone (XVII) is formed.

However, if triol (XVIIIb) is first monoacetylated with Ac_2O in pyridine and then oxidized with CrO_3, 4-acetoxy-10-ketone (XIXb) is formed (yield 70%), structurally isomeric with the above-mentioned compound (XIV). Being a β-acetoxyketone, it is readily deacetoxylated by 1 N EtONa at 20° to compound (XV) (yield 95%), whose UV spectrum shows the presence of a linearly conjugated dienone chromophore, which excludes the presence of a double bond in position 4a,9a. Catalytic reduction of dienone (XV) (Pd/C in methyl cellosolve) leads to saturation of the double bonds of ring B and hydrogenolysis of the benzyl group, with formation of ketophenol (XXa).

Fig. 1. UV absorption spectra: 1 –(XIVb), 2 –(XIXb), 6 –(IIa); determined in 95% alcohol. 3 –(XXIII), 4 –(XXII), 5 –(IIb), 7 –(IIIb); determined in CH_2Cl_2

Direct methylation of the latter proceeds unsatisfactorily, but after reduction with $LiAlH_4$ to triol (XVIa) the phenolic hydroxyl is smoothly alkylated with MeJ in the presence of K_2CO_3, and on oxidation with CrO_3 methoxyketol (XXb) is formed. The same compound is obtained on hydrogenation of methoxyketol (XXIV), whose 9βOH,9aαH-configuration was proved by us earlier. Thus, the hydroxyl of ring C in ketol (XXb) and in the genetically related compounds, as also in natural tetracyclines, is in the trans position to the neighboring angular H atom.

Having effected conversion of the 9-keto group into a methylcarbinol group, we proceeded to create a diketone system in rings C and B. For this purpose we investigated the oxidation reactions of ketodiol (XVII), Δ^2-triol (XVIIIb), and its saturated analog (XXI), formed on hydrogenation of the unsaturated ketodiol (XVII) in the presence of skeletal Ni. It was found that such oxidizing agents as CrO_3 in AcOH, $CrO_3 \cdot 2Py$, and t-$BuCrO_4$ are unsuitable for converting the 4,10-ketol and 4,10-diol groupings of compounds (XVII), (XVIIIb), and (XXI) into the 4,10-diketone grouping; satisfactory results are obtained only when using Jones chromic mixture ([8]) and carrying out the reaction in acetone at 0–20°. Under these conditions ketodiol (XVII) and triol (XVIIIb) give, in 55% yield, the unsaturated diketone (XXIII), and from triol (XXI) the saturated diketone

(XXII) is formed in the same yield.

It is interesting that, although oxidation by this method proceeds in the presence of H_2SO_4, which strongly catalyzes prototropy, and despite the fact that the reaction products are β-diketones, very prone to enolization, they are nevertheless obtained in the form of almost pure keto forms. On recrystallization, chromatography, or storage in solution these diketones pass into more stable tautomers, which, judging from their UV spectra (see Fig. 1), are 10-keto-4-en-4-ols (IIb) and (IIIb).

The compounds obtained (their constants are given in Table 1) are important intermediates for the synthesis of natural tetracyclines and various analogs thereof. Thus, on removal of the benzyl group

and restoration of the 2,3-double bond in the unsaturated diketone (III) by its hydrogenation in the presence of Pd/C at 20° gives, in 60% yield, tricycline (IIa), which completely reproduces the ring system of DCB tetracycline (I); this tricycline has approximately 5% of the activity of tetracycline against a series of microorganisms.

Table 1

Compound	M.p. (or decomp.), °C	λ_{max}^{EtOH}, mμ ($\lg \varepsilon$)	ν_{max}^{Nujol}, cm^{-1}
IIa	137–138	220, 270, 356 (4.15; 3.88; 4.22)	3560, 1593, 1570
II	109–110	266, 342 (3.76; 4.12)	3460, 1599–1595
III	121–122	246, 387 (4.13; 4.26) *	3450, 1653, 1594 *
IV	206–207	228, 263, 317 (4.05; 3.78; 3.31)	1741, 1681
VIa	130–131	223, 253, 310 (4.22; 3.88; 3.41)	3525, 1743, 1698
VI	135–137	224, 253, 308 (4.37; 3.71; 3.44)	3530, 1732, 1696
VIIa	149–150	223, 256, 318 (4.21; 3.81; 3.37)	3270, 1680
VII	171–172	225, 257, 315 (4.45; 3.95; 3.47)	3280, 1686

Compound	M.p. (or decomp.), °C	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{Nujol}, cm^{-1}
VIIIa	189–190	222, 255, 316 (4.54; 4.07; 3.72)	1676
VIII	199–200	223, 255, 313 (4.51; 3.90; 3.51)	1682
IX	148–150	278, 286 (3.38; 3.38)	3340
XIa	58–59	239, 256, 356, 364, 375, 396 (4.60; 5.02; 3.80; 3.75; 3.94; 3.84)	1624, 1569, 1534, 1465, 1045, 888
XI	96–98	239, 256, 355, 363, 374, 394 (4.47; 4.96; 3.74; 3.68; 3.88; 3.80)	1623, 1559, 1531, 1457, 1041, 895
XIIa	201–202	275, 281 (3.29; 3.29)	3458
XII	174–175	275, 281 (3.39; 3.38)	3507
XIIIa	188–189	277, 283 (3.54; 3.53)	3475, 1716 **
XIII	186–188	276, 281 (3.27; 3.27)	3465, 1715 **
XIVa	181–183	276, 281 (3.49; 3.49)	3450, 1722, 1690
XIV	217–218	277, 282 (3.33; 3.33)	3540, 1739, 1685
XV	120–122	284, 337 (3.65; 4.01)	3420, 1660, 1627
XVIa	196–198	277, 282 (3.26; 3.26)	3500, 3250, 2700
XVI	143–144	274, 281 (3.25; 3.25)	3370
XVII	155–156	275, 282 (3.32; 3.33)	3485, 3350, 1659
XVIIIa	149–151	275, 281 (3.36; 3.36)	3490, 3320–3380
XVIII	125–126	275, 282 (3.40; 3.39)	3485, 3600
XIXa	154–156	258, 315 (3.90; 3.72)	3490, 1718, 1690

Compound	M.p. (or decomp.), °C	λ_{max}^{EtOH}, mμ (lg ε)	ν_{max}^{Nujol}, cm^{-1}
XIX	140–141	256, 313 (3.79; 3.61)	3495, 1742, 1681
XX	166–168	258, 319 (3.97; 3.71)	3450, 1673
XXI	121–122	275, 281 (3.39; 3.38)	3415, 3520, 3542
XXII	116–117	260, 320 (4.04; 3.63) *	3600, 3440, 1715–1695, 1669
XXIII	136–138	255, 321, 387 (4.02; 3.77; 3.15) *	3520, 1693, 1664

* In CH_2Cl_2 solution.
** In tetrahydrofuran solution.

tetracycline against a series of microorganisms. On the other hand, α,β-unsaturated ketones (XIV), (XVII), and (XXIII) $\rightleftarrows$ (III) proved capable of adding, by Michael reaction, compounds with an acidic CH group, which makes it possible to introduce into position 2 of their molecule such carbon substituents as are necessary for the further construction of ring A of tetracyclines.

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