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# SYNTHESIS OF A DEMETHYLTETRACYCLINE ANALOG

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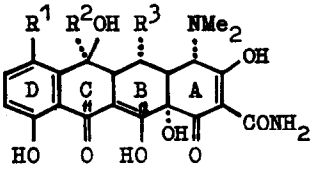
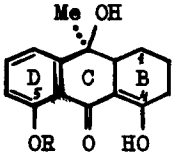
The hypothesis has been advanced that the principal active center of the tetracycline molecule (I) is the $C_{11}$-$C_{12}$ diketone system of the CB rings (1,2,3). This has found considerable support lately in the fact that the DCB tricycline (II; R=H) we had synthesized (4) proved to be highly potent against a number of microorganisms (data of I.D.Ryabova). Since practically the same activity was manifested also by the $O_5$ ether (II; R=$CH_2Ph$) (5) one may assume that in contrast to the $C_{11}$-$C_{12}$ diketone system, the phenol hydroxyl in ring D of the tetracyclines (I) is probably not necessary for manifestation of their antibiotic activity.

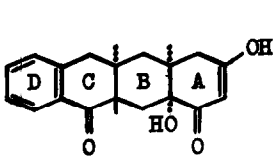



(I)

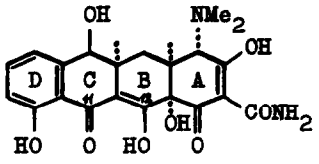



(II)

In order to obtain further backing for the β-diketone hypothesis, we undertook the synthesis of the hydronaphthacene hydroxytriketone (III). This compound, while structurally related to the natural antibiotic demethyltetracycline (IV), lacks the β-diketone system of the CB rings and therefore in conformity with the above hypothesis should be devoid of biological activity.

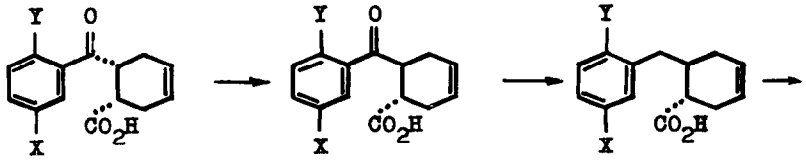



(III)

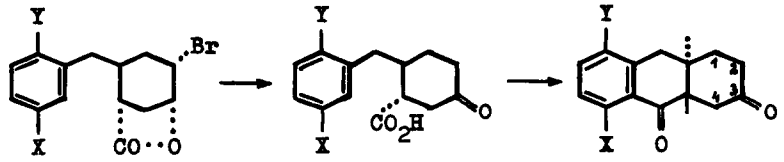



(IV)

The hydroxytriketone (III) was synthesized as follows. Condensation of cis-$\Delta^4$-tetrahydrophthalic anhydride with the corresponding arylmagnesium halide gave the cis-keto acids (V) [(Va) -m.p. 136-137° (from toluene), $\lambda_{max}$ 240 mμ (lg ε 4.00), $\nu_{max}$ 1677, 1704, 3050 $cm^{-1}$; (Vb) -m.p. 116-117° (from 50% methanol), $\lambda_{max}$ 214, 291 mμ (lg ε 4.23, 3.26), $\nu_{max}$ 1593, 1682, 1698, 3040 $cm^{-1}$]. Treated with alkali, these acids isomerized into the trans-keto acids (VI) [(VIa) -m.p. 146-147° (from toluene), $\lambda_{max}$ 241 mμ (lg ε 4.35), $\nu_{max}$ 1681, 1714, 3050 $cm^{-1}$; (VIb) -m.p. 137-139° (from 50% methanol), $\lambda_{max}$ 216, 300 mμ (lg ε 4.21, 3.21), $\nu_{max}$ 1605, 1691, 1704, 3040 $cm^{-1}$].



(Va):X=Y=H (VIa):X=Y=H (VIIa):X=Y=H
(Vb):X=OMe, Y=Cl (VIb):X=OMe, Y=Cl (VIIb):X=OMe, Y=Cl

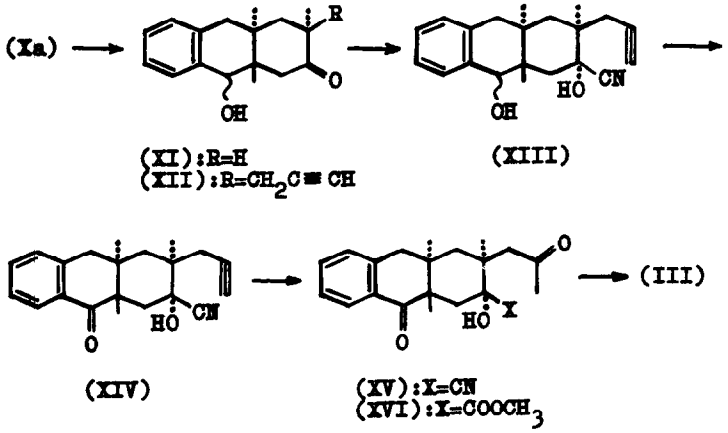


(VIIIa):X=Y=H (IXa):X=Y=H (Xa):X=Y=H
(VIIIb):X=OMe, Y=Cl (IXb):X=OMe, Y=Cl (Xb):X=OMe, Y=Cl

Clemmensen reduction of the trans-acids (VI) led to the unsaturated acids (VII) [(VIIa) -m.p. 132-133° (from alcohol), $\lambda_{max}$ 210, 248, 254, 259, 265, 269 mμ (lgε 3.97, 2.34, 2.39, 2.46, 2.37, 2.32), $\nu_{max}$ 1705, 3040 $cm^{-1}$; (VIIb) -m.p. 119-121° (from 50% methanol), $\lambda_{max}$ 204, 273, 280 mμ (lgε 4.39, 3.39, 3.06), $\nu_{max}$ 1711, 3030 $cm^{-1}$] which on treatment with bromine followed by $Na_2CO_3$ were converted to the bromolactones (VIII) [(VIIIa) -m.p. 82-83° (from alcohol), $\lambda_{max}$ 210, 248, 253, 259, 265, 269 mμ (lgε 4.12, 2.33, 2.43, 2.51, 2.39, 2.33), $\nu_{max}$ 1781 $cm^{-1}$; (VIIIb) -m.p. 156-158° (from chloroform-hexane mixture), $\lambda_{max}$ 207, 230, 282, 290 mμ (lgε 4.34, 4.00, 3.22, 3.19), $\nu_{max}$ 1787 $cm^{-1}$]. The bromolactones were dehydrobrominated with 0.5 N KOH at 100° to give the keto acids (IX) [(IXa) -m.p. 110° (from benzene-hexane mixture), $\lambda_{max}$ 209, 248, 253, 259, 265, 269 mμ (lgε 3.96, 2.21, 2.31, 2.39, 2.28, 2.23), $\nu_{max}$ 1692, 1740, 2600-

3300 $cm^{-1}$; (IXb) -m.p. 107-109° (from hexane-acetone mixture), $\lambda_{max}$ 229, 282, 289 mμ (lgε 4.02, 3.31, 3.26), $\nu_{max}$ 1710, 2600-2700 $cm^{-1}$]. Cyclization of the keto acids with anhydrous HF yielded the diketones (X) [(Xa) -m.p. 137-138° (from alcohol), $\lambda_{max}$ 248, 292 mμ (lgε 4.19, 3.25), $\nu_{max}$ 1684, 1706 $cm^{-1}$; (Xb) -m.p. 160° (from toluene), $\lambda_{max}$ 223, 255, 323 mμ (lgε 4.34, 3.86, 3.58), $\nu_{max}$ 1573, 1682, 1724 $cm^{-1}$].

The instability of the diketones (X) in the presence of bases made difficult their 2-alkylation. Compound (Xa) was therefore treated with $HC(OEt)_3$ to convert it to the 3-monoketal and the latter was reduced with $LiAlH_4$ and then hydrolyzed with 2% HCl to the ketol (XI) [m.p. 179° (from 60% alcohol), $\lambda_{max}$ 203, 266, 273 mμ (lgε 3.91, 2.33, 2.33), $\nu_{max}$ 1720, 3450 $cm^{-1}$].



The acetate of this ketol in alcoholic EtONa by treatment with $(CO_2Et)_2$ and then heating with $BrCH_2C{\equiv}CH$ was alkylated to the acetylenic ketol (XII) [m.p. 152-154° (from toluene), $\lambda_{max}$ 204, 266, 273 mμ (lgε 4.07, 2.57, 2.57), $\nu_{max}$ 1720, 2120, 3290 $cm^{-1}$]. The position of the propargyl group was demonstrated by conversion of the compound to 2-n-propylanthracene. Based on the conditions of formation of compound (XII) the tricarbon chain at $C_2$ was ascribed the thermodynamically preferred equatorial conformation, i.e. the 2β-configuration.

Treatment of ketol (XII) with acetonecyanohydrin in methanolic $K_2CO_3$ afforded the corresponding hydroxycyanohydrin for which, on the basis of a number of analogies [cf.(6)], was postulated the 3α-OH-configuration (XIII) [m.p. 183-185° with decomp. (from toluene), $\lambda_{max}$ 203, 266, 273 mμ (lgε 3.89, 2.37, 2.37), $\nu_{max}$ 2111, 2242, 3280, 3380 $cm^{-1}$]. The hydroxycyanohydrin (XIII) was subjected to $CrO_3$ oxidation in acetic acid, yielding the acetylenic ketocyanohydrin (XIV) [m.p. 185-186° with decomp. (from 80% methanol), $\lambda_{max}$ 248, 292 mμ (lgε 3.94, 3.12), $\nu_{max}$ 1605, 1680, 2120, 2235, 3300, 3450 $cm^{-1}$], of which hydration with $Hg(OAc)_2$ in acetic acid led to the diketocyanohydrin (XV) [m.p. 162-164°, $\lambda_{max}$ 248, 291 mμ (lgε 4.19, 3.18), $\nu_{max}^{THF}$ 1605, 1691, 1720, 3300 $cm^{-1}$]. Compound (XV) was alcoholyzed with 35% methanolic HCl to methyl hydroxydiketocarboxylate (XVI) [$\lambda_{max}$ 248, 290 mμ (lgε 4.11, 3.16), $\nu_{max}^{THF}$ 1603, 1688, 1723, 1734, 3500 $cm^{-1}$]. Cycli-

zation by MeONa in alcohol-benzene solution finally gave the hydroxytriketone (III) [$\lambda_{max}$ 251 mμ (lgε 4.12), $\lambda_{max}^{0.01\ N\ KOH}$ 249, 290 mμ (lgε 4.00, 4.06), $\nu_{max}^{THF}$ 1620, 1660, 1692, 3400 $cm^{-1}$].

Microbiological tests (data of I.D.Ryabova) showed that this hydronaphthacene hydroxytriketone has no noticeable antibacterial activity. This then provides further support for the hypothesis (1,2,3) according to which the principal active center of the tetracycline antibiotics is the $C_{11}$-$C_{12}$ diketone system of the rings CB.

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