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I. G. Bolesov, M. N. Kolosov, Academician M. M. Shemyakin

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chemical structures (I) and (II)

Figure 1: chemical structures (I) and (II)

Abstract

Full Text

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SYNTHESIS OF AN ANALOG OF DEMETHYLTETRACYCLINE

In the course of studies devoted to the investigation of routes for the synthesis of tetracyclines and their analogs, and also to elucidating the dependence between structure and antimicrobial activity in this series of compounds, we have carried out the synthesis of the hydronaphthacene oxytriketone (I), structurally related to the natural antibiotic demethyltetracycline (II).

By condensation of trans-benzoylacrylic acid with butadiene (100°, 15 min.), trans-2β-benzoylcyclohexene-4-carboxylic acid (III) was obtained (yield 95%; m.p. 146–147° (from toluene); $\lambda_{\max}$ 241 mμ (lg ε 4.35); $\nu_{\max}$ 1681, 1714, 3050 cm^{-1}*. Found, %: C 73.12; H 6.34. $C_{14}H_{14}O_3$. Calculated, %: C 73.02; H 6.12), which was then reduced by the Clemmensen method (8 hr. under reflux) to trans-2β-benzylcyclohexene-4-carboxylic acid (IV) (yield 69%; m.p. 132–133° (from alcohol); $\lambda_{\max}$ 210, 248, 254, 259, 265, 269 mμ (lg ε 3.97, 2.34, 2.39, 2.46, 2.37, 2.32); $\nu_{\max}$ 1705, 3040 cm^{-1}. Found, %: C 77.71; H 7.48. $C_{14}H_{16}O_2$. Calculated, %: C 77.74; H 7.45). The unsaturated acid (IV), by bromination in CH_2Cl_2 at −60°, was converted into 2β-benzyl-4α,5β-dibromocyclohexanecarboxylic acid (V) (yield 82%; m.p. 145–146° (from 50% alcohol); $\lambda_{\max}$ 209, 248, 253, 259, 265, 269 mμ (lg ε 3.94, 2.29, 2.29, 2.29, 2.28, 2.19); $\nu_{\max}$ 1707, 3027 cm^{-1}. Found, %: C 44.73; H 4.47; Br 42.38. $C_{14}H_{16}Br_2O_2$. Calculated, %: C 44.70; H 4.28; Br 42.49), which was further dehydrobrominated with 0.7 *N* KOH (100°, 1.5 hr.) to trans-2β-benzylcyclohexanone-5-carboxylic acid (VII) (yield 89%; m.p. 110° (from a benzene–hexane mixture); $\lambda_{\max}$ 209, 248, 253, 259, 265, 269 mμ (lg ε 3.96, 2.21, 2.31, 2.39, 2.28, 2.23); $\nu_{\max}$ 1692, 1740 cm^{-1}. Found, %: C 72.43; H 6.97. $C_{14}H_{16}O_3$. Calculated, %: C 72.39; H 6.94). The position of the keto group in compound (VII) follows from the fact that this keto acid is also formed (yield 77%) by the action of 0.36 *N* KOH (100°, 2 hr.) on the lactone of 4α-bromo-2β-benzylcyclohexanol-5α-carboxylic acid (VIII) (m.p. 82–83° (from alcohol); $\lambda_{\max}$ 210, 248, 253, 259, 265, 269 mμ (lg ε 4.12, 2.33, 2.43, 2.51, 2.39, 2.33); $\nu_{\max}$ 1781 cm^{-1}. Found, %: C 56.88; H 5.23; Br 27.07. $C_{14}H_{15}BrO_2$. Calculated, %: C 56.96; H 5.12; Br 27.08), which reaction scheme with compounds (III)-(VIII)

Figure 2: reaction scheme with compounds (III)-(VIII)

is obtained in 40% yield on milder dehydrobromination of the dibromo acid (V) by heating it with 5% Na_2CO_3 solution (50°, 2 hr.). The circumstance that in dehydrohalogenation of the bromolactone (VIII) a keto-, and not an epoxy-compound is formed, testifies to the cis-orientation of Br and the lactonized hydroxyl, whence, in turn, follows also the stereochemistry of the dibromo acid (V). Cyclization of the keto acid (VII) with anhydrous HF (20°, 4 hr.) led to 3,10-diketo-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (VI) (yield 77%; m.p. 137-138° (from alcohol); $\lambda_{\max}$248, 292 mμ (lg ε 4.19, 3.25); $\nu_{\max}$1684, 1706 cm^{-1}. Found, %: C 78.53; H 6.59. $C_{14}H_{14}O_2$. Calculated, %: C 78.48; H 6.59.

The instability of this diketone in the presence of bases made its alkylation at position 2 difficult, and therefore octahydroanthracenedione (VI), by the action of $HC(OEt)_3$ in an alcoholic solution of HCl (20°, 40 h), was converted into the 3-diethyl ketal (yield 62%; m.p. 111-112° (from heptane); $\lambda_{\max}$248, 294 mμ (lg ε 4.08; 3.24); $\nu_{\max}$1681 cm^{-1}. Found, %: C 74.95; H 8.32. $C_{18}H_{24}O_3$. Calculated, %: C 74.97; H 8.39), which was then reduced with $LiAlH_4$ in tetrahydrofuran (20°, 12 h) to the diethyl ketal of the ketol (IX) (yield 95%; m.p. 108-110° (from 50% alcohol); $\lambda_{\max}$204, 266, 273 mμ (lg ε 4.06, 2.60, 2.60); $\nu_{\max}$3450 cm^{-1}. Found, %: C 74.86; H 8.94. $C_{18}H_{26}O_3$. Calculated, %: C 74.44; H 9.03), and the latter was hydrolyzed with an aqueous-methanolic 2% HCl solution (20°, 12 h) to 3-keto-10-hydroxy-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (IX) (yield 96%; m.p. 179° (from 60% alcohol); $\lambda_{\max}$203, 266, 273 mμ (lg ε 3.91, 2.33, 2.33); $\nu_{\max}$1720, 3450 cm^{-1}. Found, %: C 77.64; H 7.30. $C_{14}H_{16}O_2$. Calculated, %: C 77.75; H 7.46). By acetylation with Ac_2O in pyridine (20°, 12 h), ketol (IX) was converted into acetate (X) (yield 95%; m.p. 173° (from alcohol); $\lambda_{\max}$203, 266, 273 mμ (lg ε 3.67, 2.69, 2.69); $\nu_{\max}$1728 cm^{-1}. Found, %: C 74.32; H 6.95. $C_{16}H_{18}O_3$. Calculated, %: C 74.39; H 7.02). Attempts to alkylate the latter compound through its pyrrolidine enamine were unsuccessful, but on oxalylation, condensation with propargyl bromide, and solvolysis (heating with $(CO_2Et)_2$ and $BrCH_2C{\equiv}CH$ in an alcoholic solution of EtONa; 78°, 7 h), the acetoxyketone (X) was converted into 3-keto-10-hydroxy-2β-(propyn-2$'$)-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (XI) (yield 26%; m.p. 152-154° (from toluene); $\lambda_{\max}$204, 266, 273 mμ (lg ε 4.07, 2.57, 2.57); $\nu_{\max}$1720, 2120, 3290 cm^{-1}. Found, %: C 80.22; H 7.03. $C_{17}H_{18}O_2$. Calculated, %: C 80.28; H 7.13). The position of the propargyl residue in compound (XI) was proved by hydrogenation in the presence of PdO,

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* All UV spectra were recorded in 96% alcohol; IR spectra, unless a solvent is indicated, were measured in a paste with vaseline oil.

Reaction scheme showing transformations of compounds (VI), (IX) $R = H$, (X) $R = Ac$, (XI), (XII), (XIII), (XIV), (XV) $X = CN$, and (XVI) $X = CO_2CH_3$, leading to (I).

Figure 3: Reaction scheme showing transformations of compounds (VI), (IX) $R = H$, (X) $R = Ac$, (XI), (XII), (XIII), (XIV), (XV) $X = CN$, and (XVI) $X = CO_2CH_3$, leading to (I).

followed by reduction with $LiAlH_4$ and dehydrogenation over Pd/C at 300° to 2-*n*-propylanthracene (XII) (m.p. 122-123° (from alcohol), cf. (^{1})), obtained by an independent synthesis from the acetoxyketone (X) by condensation with *n*-propylmagnesium bromide and dehydration-dehydrogenation by heating with Pd/C. As regards the spatial structure of compound (XI), on the basis of the conditions of formation of its three-carbon chain at C_2, it may be assigned the thermodynamically favorable equatorial conformation, i.e., the 2β-configuration.

By hydrocyanation of ketol (XI) with acetone cyanohydrin in a methanolic solution of K_2CO_3 (20°, 3 h), the corresponding oxycyanohydrin was obtained in 57% yield; for it, on the basis of considerations of the preferred axial addition of the cyanide ion (see (^{2})), the 3αOH-configuration (XIII) was postulated (m.p. 183-185° with decomposition (from toluene); $\lambda_{\max}$203, 266, 273 mμ (lg ε 3.89, 2.37, 2.37); $\nu_{\max}$2111, 2242, 3280, 3380 cm^{-1}. Found, %: C 76.50; H 6.84; N 4.92. $C_{18}H_{19}NO_2$. Calculated, %: C 76.84; H 6.81; N 4.98). Oxycyanohydrin (XIII) was oxidized with CrO_3 in acetic acid (20°, 3.5 h) to 10-keto-3α-hydroxy-3β-cyano-2β-(propyn-2′)-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (XIV) (yield 91%; mp 185-186° with decomposition (from 80% methanol); $\lambda_{\max}$ 248, 292 mμ (lg ε 3.94; 3.12); $\nu_{\max}$ 1605, 1680, 2120, 2235, 3300, 3450 cm^{-1}. Found, %: N 4.97. $C_{18}H_{17}NO_2$. Calculated, %: N 5.01), hydration of which with $Hg(OAc)_2$ in acetic acid (20°, 3 h) gave the diketooxynitrile (XV) (yield 85%; mp 162-164°; $\lambda_{\max}$ 248, 291 mμ (lg ε 4.19, 3.18); $\nu_{\max}^{\mathrm{THF}}$ 1605, 1691, 1720, 3300 cm^{-1}). The latter was alcoholyzed with 35% methanolic HCl (16 h at 0°, 48 h at 20°) to 10-keto-3α-hydroxy-3β-carbomethoxy-2β-acetonyl-1,2,3,4,4aβ,9,9aα,10-octahydroanthracene (XVI) ($\lambda_{\max}$ 248, 290 mμ (lg ε 4.11, 3.16); $\nu_{\max}^{\mathrm{THF}}$ 1603, 1688, 1723, 1734, 3500 cm^{-1}), cyclized by the action of MeONa in an alcohol-benzene solution (20°, 2 h) to 1,11-diketo-3,12aα-dihydroxy-1,4,4aα,5,5aα,6,11,11aβ,12,12a-decahydronaphthacene (I) ($\lambda_{\max}$ 251 mμ (lg ε 4.12); $\lambda_{\max}^{0.01N\ \mathrm{KOH}}$ 249, 290 mμ (lg ε 4.00, 4.06); $\nu_{\max}^{\mathrm{THF}}$ 1620, 1660, 1692, 3400 cm^{-1}).

Microbiological tests carried out at our institute by I. D. Ryabova showed that the hydronaphthacene analog (I) of the antibiotic demethyltetracycline (II) synthesized by us does not possess appreciable antibacterial activity. These data confirm the hypothesis advanced earlier, according to which the principal active center of the tetracycline-antibiotic molecule is the 11,12-diketo grouping of rings *CB* (^{3}).

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