INVESTIGATIONS IN THE FIELD OF TETRACYCLINES

LIII. Some Transformations of Tetracycloxides and N-Desmethyltetracyclines*

A. I. Gurevich, M. G. Karapetyan, and M. N. Kolosov

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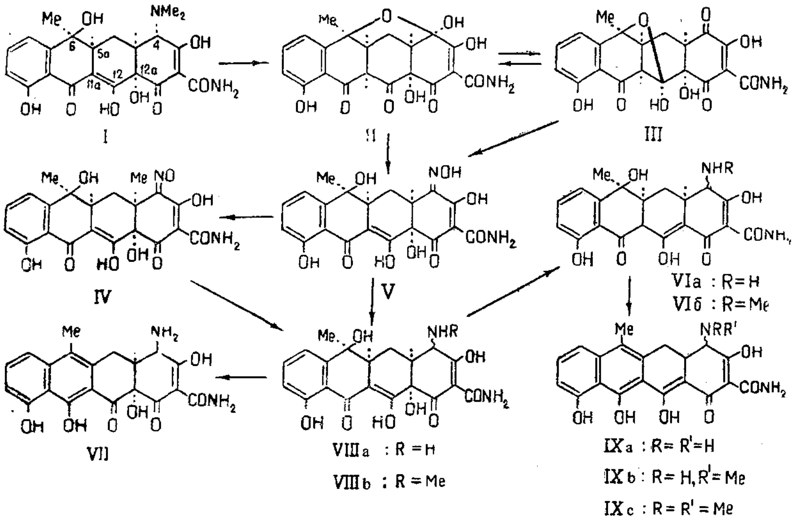
Under the action of N-chlorosuccinimide in an aqueous medium, tetracycline (I) undergoes deamination with the formation of a 4-oxo derivative, to which the structure of the 4, 6-semiketal (II), called "tetracycloxide" has been ascribed [2].

We have found that this compound exists in two tautomeric forms, 4, 6-oxide (II) and the 6, 12-oxide (III). The tautomer III has UV absorption at a longer wavelength, and in its NMR spectrum the signal of the $H_{(11a)}$ proton is in a stronger field than in the 4, 6-oxide (II) [in deuterioacetone δ is, respectively, 2.93 ppm ($J = 7$ Hz), and 4.21 ppm ($J = 5$ Hz)]. On reaction with hydroxylamine, the two oxides give one and the same oxime (V), and methylation of the latter with dimethyl sulfate forms the methyl nitrone (IV).

The reverse transformation, the introduction of an amino group into position 4, can be effected by reducing the oxime V or the nitrone IV with zinc dust [2, 3]. This gives a mixture of 4-epimeric N-desmethyltetracyclines (VIII) with the 4β-amino compound predominating in them. On further reduction with zinc in acetic acid solution, these amines are converted into the 12a-desoxy compound VI, thereby differing from derivatives of tetracycline (I) for which the dimethylamino group is split off preferentially under these conditions [4] and selective hydrogenolysis of the 12a-OH hydroxyl under the action of Zn takes place only in an ammoniacal medium [5].



The dehydration of N-desmethyl- and N-desmethyldesoxytetracyclines (VIII and VI) takes place with the formation of the 5a, 6-anhydro compounds VII and IX. In these compounds, the amino group and the angular hydroxyl possess a considerably lower reactivity than in the corresponding compounds with a nonaromatic ring C. Thus, N-desmethylanhydrotetracycline (VII) undergoes practically no hydrogenolysis by the action of Zn under various conditions, and the N-desmethyl-12a-desoxyanhydrotetracyclines (IXa and b) react with methyl iodide with difficulty even in such a polar solvent as dimethylformamide. The latter reaction gives a low yield of desoxyanhydrotetracycline (IXc), the further transformation of which into the methiodide takes place very slowly.

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*For part LII, see [1].

EXPERIMENTAL

All the IR spectra were measured in mulls with paraffin oil. The UV spectra were taken in 0.01 N solutions of HCl or NaOH in methanol and are denoted, respectively, by λ_{max}^{acid} and λ_{max}^{alkali} (i, inflection). Chromatography was carried out in a 0.5-mm nonfixed layer of silica gel of the "vodnaya kremnevaya kislota" [aqueous silicic acid type]. (activity grade III) or on "slow" paper impregnated with Trilon B in the butan-1-ol–4% aqueous NH_3 (upper phase) system.

1. **4,6-Tetracycloxide (II) and 6,12-tetracycloxide (III).** A solution of 3.2 g of the hydrochloride of tetracycline (I) in 150 ml of water and 0.6 ml of concentrated HCl was treated with 2.1 g of N-chlorosuccinimide, and the mixture was stirred at 20° C for 40 min and was extracted with ethyl acetate. This gave 2.1 g of a mixture of the oxide II and III (1 : 3) which was separated by chromatography on silica gel in the ethyl acetate–benzene (1 : 2) system.

The 4,6 oxide (II): R_f 0.47; mp 193–197° C; λ_{max}^{acid}, mμ: 258, 337 ($\log \varepsilon$ 4.34, 3.64); ν_{max}, cm^{-1}: 3490, 3380, 3300–3200, 1723, 1655–1640, 1586, 1545; $[\alpha]_{589}^{26}$ −104°, $[\alpha]_{380}$ −2400°, $[\alpha]_{360}$ −4200°, $[\alpha]_{312}$ +3900°, $[\alpha]_{290}$ +1570°, $[\alpha]_{262}$ +22 400°, $[\alpha]_{235}$ − 18 700° (c 0.1; MeOH).

Found, %: C 57.2; H 4.8; N 3.0. Calculated for $C_{20}H_{17}NO_9$, %: C 57.8; H 4.1; N 3.4.

The 6,12-oxide (III): R_f 0.24; mp 188–192° C; λ_{max}^{acid}, mμ: 267, 347 ($\log \varepsilon$ 4.27, 3.64); ν_{max}, cm^{-1}: 3450–3200, 1765, 1675, 1660, 1635, 1585, 1545; $[\alpha]_{589}^{26}$ −84°, $[\alpha]_{370}$ −1530°, $[\alpha]_{337}$ −6870°, $[\alpha]_{300}$ +2440°, $[\alpha]_{290}$ +2280°, $[\alpha]_{262}$ + +14 500°, $[\alpha]_{243}$ −6870°, $[\alpha]_{230}$ 0° (c 0.1; MeOH).

Found, %: C 58.2; H 4.9; N 3.4. Calculated for $C_{20}H_{17}NO_9$, %: C 57.8; H 4.1; N 3.4.

On treatment with hydroxylamine at pH 8.5, both oxides formed the oxime V (see [2]), R_f 0.41 [on silica gel in the ethyl acetate–benzene (1 : 1) system]; decomp. p. 217–220° C; λ_{max}^{acid}, mμ: 277, 308, 360 ($\log \varepsilon$ 4.09, 4.25, 4.18); ν_{max}, cm^{-1}, 3450–3200, 1638, 1620, 1585, 1570; $[\alpha]_{589}^{26}$ −540°, $[\alpha]_{342}$ −12 700°, $[\alpha]_{310}$ +23 500°, $[\alpha]_{282}$ −380°, $[\alpha]_{265}$ + +380°, $[\alpha]_{255}$ +255°, $[\alpha]_{245}$ +700°, $[\alpha]_{220}$ −12 700° (c 0.2; MeOH).

2. **N-Oxide of 4-desdimethylamino-4-methyliminotetracycline (IV).** With stirring, 1.15 g of dimethyl sulfate was added to a suspension of 1.9 g of the oxime V in 36 ml of water, and the mixture was brought to pH 10 with 1 N KOH. After 2 hr, the solution was acidified with 2 N HCl to pH 2, the precipitate that had deposited was filtered off, and the mother solution was extracted with ethyl acetate. The total yield of the nitrone IV was 1.78 g (90%); mp 198–203° C; R_f 0.50 [on silica gel in the ethyl acetate–benzene (1 : 1) system]. λ_{max}^{acid}, mμ: 267, 330 i, 335 ($\log \varepsilon$ 4.15, 4.29, 4.29); λ_{max}^{alkali}, mμ: 260, 372 ($\log \varepsilon$ 4.16, 4.21); ν_{max}, cm^{-1}: 3400, 1651, 1618, 1582; $[\alpha]_{589}^{26}$ −660°, $[\alpha]_{375}$ −8070°, $[\alpha]_{323}$ + +22 000°, $[\alpha]_{283}$ −5000°, $[\alpha]_{263}$ +5000, $[\alpha]_{243}$ +8000°, $[\alpha]_{220}$ −1000° (c 0.1; MeOH).

3. **4-N-Desdimethyl-12a-deoxytetrahydrocyclines (VIa).** A solution of 0.8 g of the oxime V in 30 ml of 50% acetic acid was treated with 0.8 g of Zn dust, and the mixture was stirred at 20° C for 30 min, filtered, and evaporated. The residue was dissolved in water and neutralized with NaOH to pH 7. This gave 1.05 g of a mixture of the zinc complexes of the amines VIIIa (see [2]), which was dissolved in 40 ml of acetic acid; this solution was treated with 2 g of Zn dust, stirred for 20 hr, filtered, and evaporated. After the usual working up, a mixture of amines (VIa) was obtained. The mixture was chromatographed on silica gel in the ethyl acetate–petroleum ether (4 : 1) system, the zones with R_f 0.35–0.45 and 0.50–0.75 being isolated. The lower zone gave 0.41 g of the 4β-amine (VIa). Yield 65%; R_f 0.38 (on paper); mp 207–213° C; λ_{max}^{acid} (after 2 hr), mμ: 223, 264, 362, 435 ($\log \varepsilon$ 4.45, 4.45, 4.20, 3.48); λ_{max}^{alkali}, mμ: 248, 266, 376, 463, 488 ($\log \varepsilon$ 4.22, 4.23, 4.14, 3.83, 3.78); ν_{max}, cm^{-1}: 3400–3250, 1660, 1650, 1618, 1599, 1589, 1580, 1560, 1545, 1538; $[\alpha]_{589}^{26}$ −340°, $[\alpha]_{380}$ −3400°, $[\alpha]_{340}$ −6750°, $[\alpha]_{282}$ +4230°, $[\alpha]_{268}$ +1630°, $[\alpha]_{255}$ +2440°, $[\alpha]_{248}$ +1630°, $[\alpha]_{232}$ +6750°, $[\alpha]_{220}$ −9750° (c 0.1; MeOH).

The upper zone yielded 0.13 g (17%) of the 4α-amine VIa; R_f 0.36 (on paper); mp 204-209°C; λ_{max}^{acid} (after 2 hr), mμ: 265, 310i, 320, 435 ($\log \varepsilon$ 4.34, 4.12, 4.12, 3.28); λ_{max}^{alkali}, mμ: 240, 266, 374, 460, 485 ($\log \varepsilon$ 4.24, 4.24, 3.95, 3.68, 3.60). ν_{max}, cm^{-1}: 3370–3200, 1659, 1650–1638, 1620, 1615, 1607, 1600, 1588, 1575, 1565, 1550, 1540; $[\alpha]_{589}^{26}$ +112°, $[\alpha]_{465}$ +296°, $[\alpha]_{430}$ +41°, $[\alpha]_{380}$ +600°, $[\alpha]_{340}$ −2660°, $[\alpha]_{300}$ +118°, $[\alpha]_{280}$ 0°, $[\alpha]_{265}$ +1180°, $[\alpha]_{245}$ −2360°, $[\alpha]_{230}$ +1180° (c 0.2; MeOH).

4. **4-N-Desmethyl-12a-deoxytetracycline (VIb).** A solution of 500 mg of the nitrone IV in 15 ml of acetic acid was treated with 1 g of Zn dust. The mixture was stirred at 20° C for 18 hr and was filtered and evaporated, and the

residue was washed with water and chromatographed on silica gel in ethyl acetate. This gave 115 mg (24%) of the methylamino compound VIb; R_f 0.65 (on silica gel in ethyl acetate), 0.40 (on paper); $\lambda_{\max}^{\text{acid}}$, mμ: 262, 345 i, 360 (log ε 4.13, 3.92, 3.98); $\lambda_{\max}^{\text{alkali}}$, mμ: 250 i, 265, 375, 460, 490 (log ε 4.14, 4.17, 4.07, 3.86, 3.78); $\nu_{\max}$, cm^{-1}: 3400–3200, 1673, 1648, 1620, 1590, 1580, 1550; $[\alpha]_{589}^{26}$ −344°, $[\alpha]_{350}$ −3880°, $[\alpha]_{284}$ +4030°, $[\alpha]_{270}$ +2090°, $[\alpha]_{262}$ +2980°, $[\alpha]_{251}$ +2980°, $[\alpha]_{233}$ +4780°, $[\alpha]_{218}$ −5970° (c 0.1; MeOH).

5. 4-N-Desdimethyl-12a-deoxy-5a, 6-anhydrotetracyclines (IXa). A) A solution of 167 mg of the 4β-amine (VIa) in 5 ml of 2 N methanolic HCl was heated to boiling for 1 hr and was then evaporated, and the residue was chromatographed on silica gel in the ethyl acetate–petroleum ether (3 : 1) system. This gave 117 mg (73%) of the 4β-amino-5a 6-anhydro compound IXa; R_f 0.54 (on silica gel), 0.40 (on paper), mp 201–205° C; $\lambda_{\max}^{\text{acid}}$, mμ: 224, 275, 298i, 311i, 325, 385i, 435 (log ε 4.45, 4.60, 3.82, 3.71, 3.57, 3.82, 4.04); $\lambda_{\max}^{\text{alkali}}$, mμ: 228, 269, 338, 435 (log ε 4.37, 4.45, 3.60, 3.99); $\nu_{\max}$, cm^{-1}: 3400–3300, 1658, 1634, 1629, 1600, 1586, 1570, 1560, 1550, 1532; $[\alpha]_{589}^{26}$ +1330°, $[\alpha]_{500}$ +9800°, $[\alpha]_{465}$ −5330°, $[\alpha]_{382}$ −20 800°, $[\alpha]_{350}$ 0°, $[\alpha]_{298}$ −8330°, $[\alpha]_{250}$ +8300° (c 0.1; HCONMe_2).

Found, %: mol wt 382 (mass spectrometry). Calculated for $C_{20}H_{18}N_2O_6$: mol wt 382.

B) Under the conditions of the preceding experiment, 52 mg of the 4α-amine (VIa) yielded 21 mg (43%) of the 4α-amino-5a, 6-anhydro compound IXa; R_f 0.53 [on silica gel in the ethyl acetate–petroleum ether (3 : 1) system], 0.40 (on paper); mp 199–203° C; $\lambda_{\max}^{\text{acid}}$, mμ: 222, 273, 298i, 310 i, 324, 390i, 435 (log ε 4.39, 4.53, 3.81, 3.70, 3.57, 3.79, 4.00), $\lambda_{\max}^{\text{alkali}}$, mμ: 228, 270, 338, 434 (log ε 4.32, 4.43, 3.70, 4.06); $\nu_{\max}$, cm^{-1}: 3400–3300, 1670, 1650, 1640, 1632, 1610, 1598, 1580, 1570, 1565, 1550, 1535; $[\alpha]_{589}^{26}$ +123°, $[\alpha]_{500}$ +825°, $[\alpha]_{410}$ 0°, $[\alpha]_{382}$ −2270°, $[\alpha]_{300}$ +2270°, $[\alpha]_{272}$ −2640°, $[\alpha]_{260}$ 0° (c 0.05; HCONMe_2).

6. 4-N-Desmethyl-12a-deoxy-5a, 6-anhydrotetracycline (IXb). The aminoalcohol VIb (50 mg) was dehydrated under the conditions of experiment 5. This gave 26 mg (58%) of the anhydro compound (IXb); R_f 0.78 (on silica gel in ethyl acetate), 0.34 (on paper); mp 209–214° C; $\lambda_{\max}^{\text{acid}}$, mμ: 272, 380 i, 435 (log ε 4.39, 3.59, 3.88); $\lambda_{\max}^{\text{alkali}}$, mμ: 230, 272, 335, 430 (log ε 4.50, 4.66, 3.88, 4.27); $\nu_{\max}$, cm^{-1}: 3380–3300, 1660, 1650, 1630, 1582, 1560, 1550; $[\alpha]_{589}^{26}$ −298°, $[\alpha]_{500}$ −224°, $[\alpha]_{430}$ −2540°, $[\alpha]_{410}$ −2690°, $[\alpha]_{387}$ −4030°, $[\alpha]_{370}$ −600°, $[\alpha]_{352}$ +300°, $[\alpha]_{283}$ −6000°, $[\alpha]_{268}$ +36 000°, $[\alpha]_{250}$ +7500°, $[\alpha]_{226}$ +20 900°, $[\alpha]_{215}$ +15 000° (c 0.1; MeOH).

Found: mol wt 396 (mass spectrometry). Calculated for $C_{21}H_{20}N_2O_6$: mol wt 396.

7. Methylation of the amine IXa. A solution of 20 mg of the 4α-amine IXa and 10 mg of cyclohexene oxide in 2 ml of dimethylformamide was treated with 0.2 ml of methyl iodide, and the mixture was kept at 20° C for 24 hr and evaporated. The residue was chromatographed on silica gel in ethyl acetate, the zone with R_f 0.45–0.65 being isolated. It yielded 2 mg of crude 12a-deoxy-5a, 6-anhydrotetracycline (IXc), which was purified by paper chromatography; R_f 0.59 (on paper); $\lambda_{\max}^{\text{acid}}$, mμ: 223, 273, 327, 381, 438 (log ε 4.52, 4.51, 3.95, 4.13, 4.36).

The IR spectra were taken by L. B. Senyavina. The optical rotatory dispersion was measured by G. A. Kogan and M. I. Struchkova.

CONCLUSIONS

Some properties and transformations of the tetracycloxides and N-desmethyltetracyclines have been studied.

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