INVESTIGATIONS IN THE FIELD OF TETRACYCLINES

LV. SYNTHESIS OF 4N-DESMETHYL-12a-DEOXY-5a, 6-ANHYDROTETRACYCLINES*

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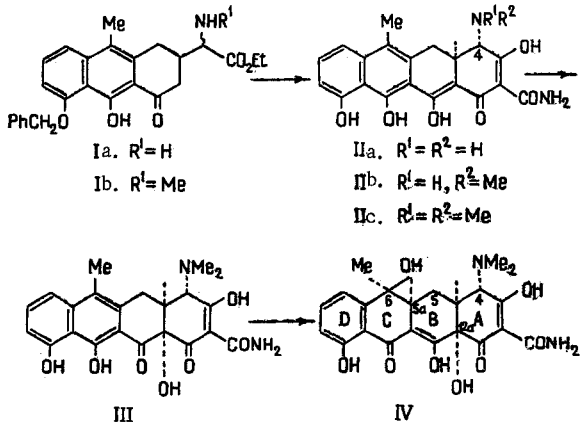
We and other workers have previously effected the N-methylation of the (+)-compounds (IIa) and (IIb) to form deoxyanhydrotetracycline (IIc) and the stereodirected 12aα-hydroxylation of (IIc) to (III) [2], and also the rehydration of 5a,6-anhydrotetracycline (III) to tetracycline (IV) [3].

The present paper describes the transformation of the synthetic amino esters (Ia) and (Ib) [4] into the (±)-N-desmethyldeoxyanhydrotetracyclines (IIa) and (IIb), which is the final stage in the complete synthesis of the antibiotic tetracycline (IV).



During a model synthesis of a 4-unsubstituted analog of compound (II), we had previously established that the presence of a phenolic hydroxyl in ring C prevents the closure of ring A [5]. Consequently, in order to obtain compounds (II) from the hydroxy amino esters (I) it was necessary first to block both active functional groups – the amine and the phenolic groups.

For this purpose, the hydroxy amino ester (Ia) in the form of the N-phthaloyl derivative was methylated with methyl iodide in the presence of Ag_2O, and the resulting methoxy phthaloylamino ester (Va) was hydrolyzed to the corresponding o-carboxybenzoylamino acid (VIb), which was then dehydrated by heating in diglyme. The phthaloylamino acid (VIa) formed was converted into the chloride by the action of PCl_5 + $HCONMe_2$. Acylation of the latter with ethoxymagnesiomalonamic ester gave a mixture of the 1'-epimeric keto amido esters (VIIa); it was subsequently found that a more convenient method for obtaining the same acid chloride is the action of PCl_5 + $HCONMe_2$ directly on the carboxybenzoylamino acid (VIb).

* For preliminary communications, see [1].

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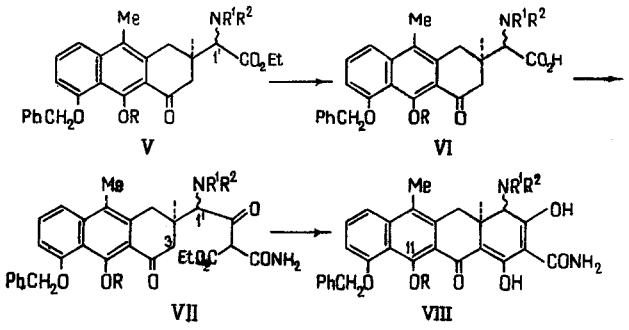

a: R=Me, R^1+R^2 = Phthal; b: R=Me, R^1=H, R^2= o-$COC_6H_4CO_2H$; c: $R=CH_2Ph$, R^1=Me, R^2 = BOC.

The cyclization of the keto amido ester (VIIa) by heating it with sodium methylsulfinylmethylide led to the 4-epimeric tetracyclic compounds (VIIIb). The severe acid hydrolysis of both stereoisomers of (VIIIb), as a result of the splitting out of the O_{10}-benzyl, O_{11}-methyl, and N_4-carboxybenzoyl groups, gave low yields of the (±)-compound (IIa), identified by direct comparison with (+)-N-desdimethyl-12a-deoxy-5a,-6-anhydrotetracycline, obtained by the degradation of natural tetracycline [2].

In view of the low yield of the (±)-desdimethyldeoxyanhydrotetracycline (IIa) in the hydrolysis of the 4-N-carboxybenzoyl-11-methoxy compounds (VIIIb), we then undertook the synthesis of the 4-N-benzyloxycarbonyl-11-benzyloxy compound (VIIIc), in which the N_4 and O_{11} protective groupings are capable of hydrogenolysis. By the action of benzyl bromide in the presence of NaH in dimethyl sulfoxide, the N-benzyloxycarbonyl derivative of the hydroxy amino ester (Ib) was converted into the 10-benzyl ether (Vc). In contrast to the 1'-phthaloylamino ester (Va), which is readily hydrolyzed by 0.1 N KOH at 20°C, the saponification of its methylbenzyloxycarbonyl analog (Vc) took place under more severe conditions (60°C) and was accompanied by partial 1'-epimerization and the splitting off of the BOC group, in consequence of which it was necessary to rebenzyloxycarbonylate, and two stereoisomeric acids (VIc) were isolated. Then the construction of ring A was effected by the same method as in the preceding case. The two acids (VIc) gave the same mixture of 1'-epimeric keto amino esters (VIIc) and, from them, a mixture of 4-epimeric hydronaphthacene compounds (VIIIc). The hydrogenolysis of the chromatographically less mobile stereoisomer of (VIIIc) in the presence of Pd gave a satisfactory yield of (±)-N-desmethyl-12a-deoxy-5a,6-anhydrotetracycline (IIb), identified by direct comparison with the (±)-isomer obtained from natural tetracycline [2].

EXPERIMENTAL

All the UV spectra were taken in 96% ethanol, and the IR spectra in mulls with paraffin oil (*i* denotes an inflection). Chromatography was performed in a 0.5-mm nonfixed layer of silica gel of "hydrated silicic acid" grade (activity grade III) and Al_2O_3 (activity grade II). The analytical results for all the compounds corresponded to the calculated figures.

1. Ethyl Ester of N-Phthaloyl(5-benzyloxy-10-methoxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)glycine (Va). A solution of 0.57 g of the phthaloyl derivative of the amino hydroxy ester (Ia) [4] in 10 ml of dimethylformamide was treated with 5 ml of methyl iodide and 0.7 g of silver oxide. The mixture was stirred at 20°C for 40 min, and was then diluted with 150 ml of benzene and filtered, and the filtrate was washed repeatedly with water and with saturated NaCl solution and was dried with Na_2SO_4 and evaporated. The residue was chromatographed on Al_2O_3 in the ethyl acetate–heptane (1 : 1) system, the zone with R_f 0.6-0.7 being isolated. The yield of the phthaloylamino methoxy ester $C_{35}H_{31}NO_7$ (Va) was 0.51 g (84%), mp 166-167°C (from benzene); λ_{max}221, 263, 307, 320, 375 nm (log ε 4.48; 4.74; 3.93; 3.76; 3.96); ν_{max} 1785, 1753, 1735, 1715, 1692, 1662, 1580 cm^{-1}.

2. N-(o-Carboxybenzoyl)-α-(5-benzyloxy-10-methoxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)-glycine (VIb). A solution of 180 mg of the phthaloylamino ester (Va) in 20 ml of tetrahydrofuran was treated with 10 ml of 0.18 N KOH. The mixture was left for 12 h at room temperature and was then acidified with 1 ml of acetic acid, and 70 ml of ethyl acetate was added. The aqueous layer was separated off and the ethyl acetate solution was washed with water and with saturated NaCl solution, dried with Na_2SO_4, and evaporated. The residue was triturated with ether and the residue of the diacid $C_{33}H_{29}NO_8$ (VIb) was filtered off. Yield

120 mg (67%); mp 176-178°C (decomp.); λ_{max} 222, 262, 308, 323, 375 nm (log ε 4.42; 4.60; 3.76; 3.60; 3.84); ν_{max} 3380, 3310, 1745, 1694, 1676, 1615, 1590 cm^{-1}.

3. N-Phthaloyl-α-(5-benzyloxy-10-methoxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)glycine (VIa). A solution of 0.75 g of the diacid (VIb) in 50 ml of diglyme was heated at 140°C for 1.5 h, and then the solvent was distilled off at 50°C/0.05 mm and the residue was dissolved in tetrahydrofuran and chromatographed on silica gel in the ethyl acetate–heptane (2:1) system. The zone with R_f 0.7-0.8 yielded 260 mg (36%) of the phthaloylamino acid $C_{33}H_{27}NO_7$ (VIa); mp 202-204°C (from nitromethane); λ_{max} 222, 262, 307, 318, 374 nm (log ε 4.63; 4.72; 3.81; 3.71; 3.92); ν_{max} 3480, 3360, 1778, 1727, 1610, 1580 cm^{-1}.

4. Ethyl Ester of N-Benzyloxycarbonyl-(5-benzyloxy-10-hydroxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)sarcosine. To a solution of 1.78 g of the amino ester (Ib) [4] and 5.6 ml of triethylamine in 35 ml of tetrahydrofuran at 20°C was added a solution of 2.04 g of benzyloxycarbonyl chloride in 15 ml of tetrahydrofuran. The mixture was left at 20°C for 20 h and was then evaporated, and the residue was dissolved in 80 ml of ethyl acetate and the resulting solution was washed with water, dried with Na_2SO_4, and evaporated again. The residue was chromatographed on silica gel, being eluted with a mixture of ethyl acetate and petroleum ether (1:3). This gave 0.72 g (42%) of the initial amino ester (Ib) with R_f 0.12, and 1.24 g (53%) of its N-benzyloxycarbonyl derivative $C_{35}H_{35}NO_7$ with R_f 0.38, mp 161-162°C (from benzene); λ_{max} 224, 269, 296, 308, 319, 410 nm (log ε 4.42; 4.58; 3.65; 3.62; 3.48; 3.94); ν_{max} 2700, 1736, 1708, 1618, 1583 cm^{-1}.

5. Ethyl Esters of the Stereoisomeric N-Benzyloxycarbonyl-α-(5,10-dibenzyloxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)sarcosines (Vc). The benzyloxy amino hydroxy ester (1.16 g) obtained in the preceding experiment was dissolved in 8 ml of dimethyl sulfoxide, and 4 ml of benzyl bromide and 0.3 g of 70% sodium hydride were added. The mixture was stirred at 20°C for 2.5 h and was then acidified with 0.6 ml of acetic acid, diluted with 100 ml of benzene, washed repeatedly with water, dried with Na_2SO_4, and evaporated. The residue was chromatographed on Al_2O_3 in the ethyl acetate–benzene (1:9) system. This zone with R_f 0.76 yielded 0.80 g (60%) of the dibenzyloxy ester $C_{42}H_{41}NO_7$ (Vc 1), mp 156-157°C (from ethyl acetate); λ_{max} 225, 263, 308, 320, 375 nm (log ε 4.54; 4.64; 3.84; 3.75; 3.88); ν_{max} 1730, 1698*i*, 1690, 1610, 1582, 1550 cm^{-1}.

The zone with R_f 0.68 gave 0.21 g (16%) of the stereoisomeric dibenzyloxy ester $C_{42}H_{41}NO_7$ (Vc 2), mp 154-155°C (from ethyl acetate); λ_{max} 223, 265, 300*i*, 311, 320, 379 nm (log ε 4.54; 4.58; 3.60; 3.68; 3.60; 3.80); ν_{max} 1732, 1700*i*, 1690, 1610, 1580, 1557 cm^{-1}.

6. The Stereoisomeric N-Benzyloxycarbonyl-α-(5,10-dibenzyloxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)sarcosines (VIc). A solution of 198 mg of the ester (Vc 1) or (Vc 2) in 3 ml of tetrahydrofuran was treated with 0.18 ml of 2.5 N ethanolic KOH. The mixture was heated at 60°C for 1.5 h and was then cooled, treated with 100 mg of benzyloxycarbonyl chloride, and left at 20°C for 20 h, after which it was acidified with 0.3 ml of acetic acid and evaporated. The residue was dissolved in ethyl acetate and chromatographed on silica gel in the ethyl acetate–benzene (1:2) system. The zone with R_f 0.92 yielded 90 mg (47%) of the acid $C_{40}H_{37}NO_7$ (VIc 1) with mp 156-157°C (from ethyl acetate); λ_{max} 225, 264, 299*i*, 310, 322, 378 nm (log ε 4.52; 4.56; 3.59; 3.68; 3.61; 3.79); ν_{max} 1726, 1692, 1609, 1580, 1550 cm^{-1}.

The zone with R_f 0.34 yielded 90 mg (47%) of the diastereomeric acid $C_{40}H_{37}NO_7$ (VIc 2) with mp 172-173°C (from ethyl acetate); λ_{max} 225, 264, 299, 310, 322, 378 nm (log ε 4.56; 4.62; 3.65; 3.72; 3.65; 3.81); ν_{max} 1710*i*, 1692, 1610, 1576, 1550 cm^{-1}.

7. Ethyl Esters of the Stereoisomeric [N-Phthaloyl-α-(5-benzyloxy-10-methoxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthyl)glycyl]malonamic acids (VIIa). a. At −70°C, 310 mg of phosphorus pentachloride was added to a solution of 400 mg of the carboxybenzoylamino acid (VIb), 150 mg of triethylamine, and 1.07 g of dimethylformamide in 20 ml of absolute tetrahydrofuran. The mixture was stirred at −70°C for 30 min and then at room temperature for 1 h, after which it was evaporated in vacuum and the residue was dried at 40°C/0.1 mm for 1 h. Then it was dissolved in 30 ml of absolute tetrahydrofuran and added over 10 min to a solution of ethoxymagnesiomalonamic ester in tetrahydrofuran (44 ml, 0.08 M) cooled to −70°C. The mixture was stirred at −70°C for 30 min and at 20°C for 1 h and was then acidified with 2 ml of acetic acid, diluted with 80 ml of ethyl acetate, washed with water and with saturated NaCl solution, dried with Na_2SO_4, and evaporated. The residue was chromatographed on silica gel in the ethyl acetate–petroleum ether (1:1) system. The zone with R_f 0.56 yielded 145 mg (29%) of the keto amido ester (VIIa 1);

λ_{max} 221, 263, 306*i*, 320*i*, 378 nm (log ε 5.01; 4.79; 4.10; 3.93; 3.97); ν_{max} 3450, 3350, 2700, 1778, 1722, 1672, 1614, 1585*i*, 1568 cm^{-1}.

The zone with R_f 0.32 yielded 60 mg (12%) of the stereoisomeric keto amido ester (VIIa 2); λ_{max} 222, 264, 307*i*, 321*i*, 378 nm (log ε 4.67; 4.35; 3.88; 3.76; 3.68); ν_{max} 3430, 3340, 2700, 1778, 1720, 1672, 1613, 1583*i*, 1558 cm^{-1}.

b. From 630 mg of the phthaloylamino acid (VIa) by the action of 115 mg of triethylamine and 238 mg of phosphorus pentachloride, and then 13 ml of a 0.62 M tetrahydrofuran solution of ethoxymagnesiomalonamic ester, under the conditions of the preceding experiment, we obtained 200 mg (26%) of the stereoisomeric keto amido esters (VIIa) and 270 mg (44%) of the initial acid (VIa).

8. Ethyl Esters of the Stereoisomeric [N-Benzyloxycarbonyl-α-(5,10-dibenzyloxy-9-methyl-4-oxo-1,2,3,4-tetrahydro-2-anthryl)sarcosyl]malonamic acids (VIIc). The benzyloxycarbonylamino acid (VIc 1) or (VIc 2) (344 mg in 20 ml of absolute tetrahydrofuran) was converted into the chloride by the action of 113 mg of triethylamine, 0.6 ml of dimethylformamide, and 117 mg of phosphorus pentachloride and was then condensed with ethoxymagnesiomalonamic ester (3.9 ml of a 0.62 M solution in tetrahydrofuran). The reaction was performed by the method of experiment 7a, but the acid chloride was dried for only 30 min at 20°C/0.1 mm. After chromatography on silica gel in the ethyl acetate–petroleum ether (2:3) system, the zone with R_f 0.89 yielded 137 mg (32%) of the keto amido ester (VIIc 1), mp 153-154°C (from ethyl acetate); λ_{max} 225*i*, 264, 298, 309, 322, 382 nm (log ε 4.24; 4.16; 3.47; 3.46; 3.37; 3.41); ν_{max} 1735, 1705*i*, 1697, 1615, 1605, 1583, 1555 cm^{-1}.

The zone with R_f 0.25 gave 86 mg (20%) of the stereoisomeric keto amido ester (VIIc 2), with mp 170-175°C (from ethyl acetate); λ_{max} 225*i*, 264, 298, 309, 322, 382 nm (log ε 4.50; 4.54; 3.66; 3.71; 3.62; 3.76); ν_{max} 1716*i*, 1705*i*, 1700*i*, 1695, 1680*i*, 1615, 1583, 1555 cm^{-1}.

9. Stereoisomeric 10-Benzyloxy-2-carbamoyl-4-(o-carboxybenzoylamino)-1,3-dihydroxy-11-methoxy-6-methyl-12-oxo-4,4a,5,12-tetrahydronaphthacenes (VIIIa). a. In a current of argon at 120°C, a solution of 145 mg of the keto amido ester (VIIa 1) in 1.5 ml of dimethyl sulfoxide was added to a solution of the sodium methylsulfinylmethylide prepared from 36 mg of 70% sodium hydride and 1 ml of dimethyl sulfoxide. The mixture was heated at 120°C for 2 h, cooled, acidified with 0.1 ml of acetic acid, diluted with 30 ml of ethyl acetate, washed repeatedly with water, dried with Na_2SO_4, and evaporated, and the residue was chromatographed on silica gel in the ethyl acetate–petroleum ether (1:1) system. The zone with R_f 0.18 yielded 35 mg (24%) of compound (VIIIa 1), mp 173-180°C (micro); λ_{max} 224, 266, 297, 310, 320, 388 nm (log ε 4.67, 4.57; 3.94; 3.91; 3.84; 4.02); ν_{max} 3350, 2700, 1712, 1695, 1680, 1662, 1615, 1603, 1583, 1557 cm^{-1}.

b. From 60 mg of the keto amido ester (VIIa 2) by the analogous cyclization (1 h at 120°C), 36 mg (60%) of the stereoisomeric compound (VIIIa 2) was obtained with R_f 0.23 (in the same system), mp 185-190°C (micro); λ_{max} 224, 266, 297, 310, 319, 388 nm (log ε 4.66; 4.49; 3.98; 3.94; 3.93; 4.17); ν_{max} 3350, 2650, 1726, 1670, 1613, 1560 cm^{-1}.

10. Stereoisomeric 10,11-Dibenzyloxy-4-N-benzyloxycarbonyl-N-methylamino-2-carbamoyl-1,3-dihydroxy-6-methyl-12-oxo-4,4a,5,12-tetrahydronaphthacenes (VIIIc). The cyclization of 1.17 g of the keto amido ester (VIIc 1) or (VIIc 2) in 12 ml of dimethyl sulfoxide was effected by heating it with the sodium methylsulfinylmethylide obtained from 290 mg of 70% sodium hydride and 8 ml of dimethyl sulfoxide (3 h at 120°C). The reaction mixture was treated as in experiment 9a and chromatographed on silica gel in the ethyl acetate–petroleum ether (2:3) system. The zone with R_f 0.31 yielded 144 mg (13%) of compound (VIIIc 1), $C_{43}H_{38}N_2O_8$; λ_{max} 264, 295*i*, 310*i*, 320*i*, 368 nm (log ε 4.33; 4.00; 3.95; 3.85; 3.81); ν_{max} 3400–3300, 1710, 1705, 1650, 1610–1600, 1580 cm^{-1}.

The zone with R_f 0.16 yielded 59 mg (5%) of the stereoisomeric compound (VIIIc 2), $C_{43}H_{38}N_2O_8$; λ_{max} 272, 295*i*, 310*i*, 320*i*, 425 nm (log ε 4.00; 3.70; 3.63; 3.55; 3.45); ν_{max} 3400–3300, 1710, 1700, 1650, 1610, 1590, 1580 cm^{-1}.

11. 4-Amino-1, 3, 9, 10-tetrahydroxy-6-methyl-12-oxo-4,4a,5,12-tetrahydronaphthacene (4-N-Desdimethyl-12a-deoxy-5a,6-anhydrotetracycline) (IIa). A solution of 50 mg of compound (VIIIa 1) or (VIIIa 2) in 3 ml of acetic acid and 5 ml of 48% HBr was heated at 110°C for 40 min, diluted with water, and extracted with ethyl acetate. The extract was treated in the usual way and evaporated, and the residue was chromatographed on silica gel in the ethyl acetate–petroleum ether (3:1) system. The zone with R_f 0.54 yielded

2 mg (7%) of (±)-desdimethyldeoxyanhydrotetracycline (IIa), chromatographically and spectrally (UV, IR, and mass spectra) identical with the (+)-compound (IIa) obtained by the degradation of tetracycline (see [2]).

12. 1, 3, 9, 10-Tetrahydroxy-6-methyl-4-methylamino-12-oxo-4,4a,5,12-tetrahydronaphthacene (4-N-Desmethyl-12a-deoxy-5a,6-anhydrotetracycline) (IIb). Compound (VIIIc 2) (50 mg) in 5 ml of ethanol was hydrogenated over Pd (from 30 mg of PdO) until 3 moles of H_2 had been absorbed, and it was then chromatographed on silica gel in the ethyl acetate–petroleum ether (4:1) system. The zone with R_f 0.58 yielded 19 mg (68%) of (±)-desmethyldeoxyanhydrotetracycline (IIb), chromatographically and spectrally (UV, IR, and mass spectra) identical with the (+)-compound (IIb) obtained from natural tetracycline (see [2]).

The IR spectra were taken by L. B. Senyavina, and the mass-spectrometric measurements were performed by B. V. Rozynov.

SUMMARY

The synthesis of 4-N-desdimethyl- (IIa) and 4-N-desmethyl-12a-deoxy-5a,6-anhydrotetracycline (IIb) has been effected.

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