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SYNTHESIS OF 12a-DEOXY-5a,6-ANHYDROTETRACYCLINE. THE FIRST TOTAL SYNTHESIS OF THE NATURALLY OCCURRING TETRACYCLINE (1)

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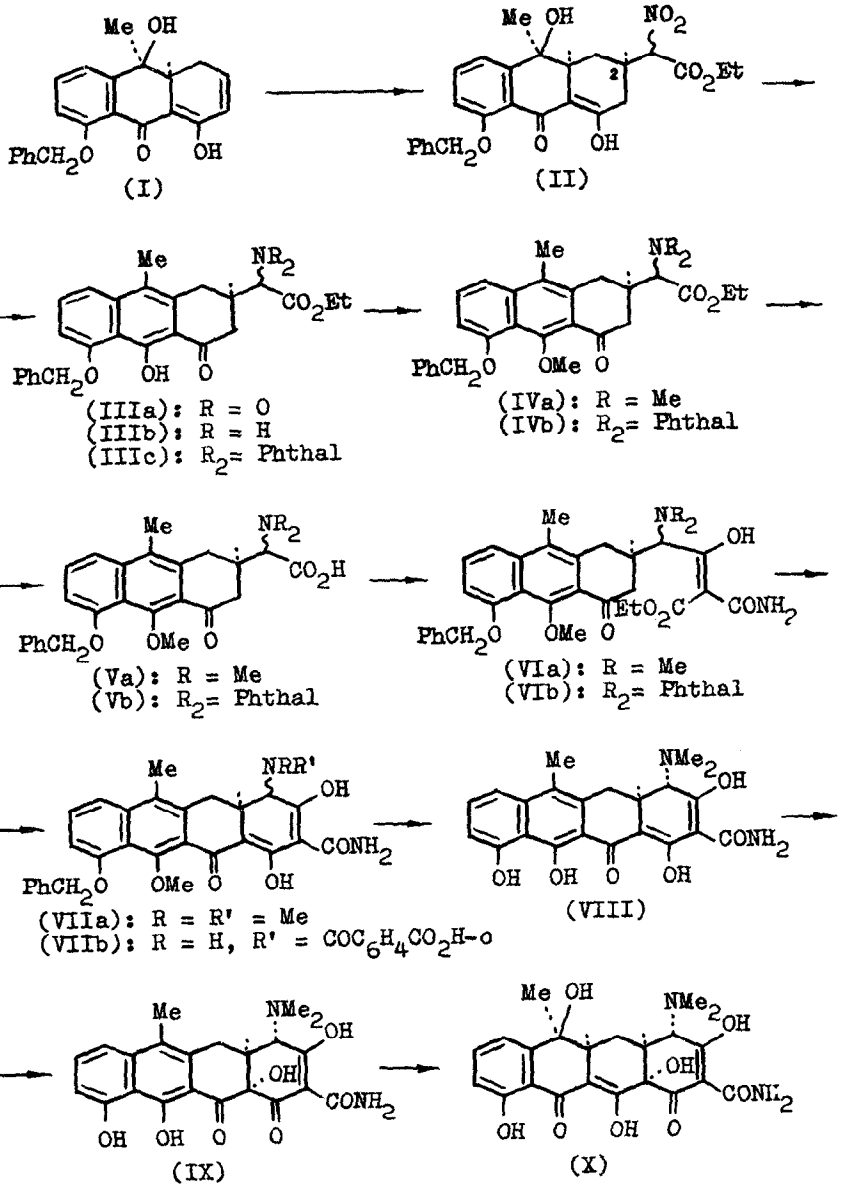
IN the process of studies on hydronaphthacene compounds, closely related to anhydrotetracyclines, we have synthesized (±)-12a-deoxy-5a,6-anhydrotetracycline (VIII). Since we had 12a-hydroxylated the (-)-component of racemate (VIII) into 5a,6-anhydrotetracycline (IX) (2) that had earlier been 5a,6-hydrated into tetracycline (X) by Schach von Wittenau (3) this accomplishes the first total synthesis of a naturally occurring tetracycline antibiotic, and, namely, tetracycline (X), itself.

The starting point in the synthesis was the dienediolone (I) prepared in 6 stages from juglone (4). Its condensation with the triethylammonium salt of ethyl nitroacetate in tetrahydrofuran gave a mixture of C_2-epimeric adducts (II) (IIa: m.p. 134-135°, from EtOH; λ_{max}(here and further in EtOH) 278, 340 mμ (lg ε 3.77, 4.17); ν_{max}(here and further in Nujol)


Me OH
PhCH2O O OH
(I)
Me OH NO2
CO2Et
PhCH2O O OH
(II)
Me NR2
CO2Et
PhCH2O OH O
(IIIa): R = O
(IIIb): R = H
(IIIc): R2= Phthal
Me NR2
CO2Et
PhCH2O OMe O
(IVa): R = Me
(IVb): R2= Phthal
Me NR2
CO2H
PhCH2O OMe O
(Va): R = Me
(Vb): R2= Phthal
Me NR2 OH
EtO2C CONH2
PhCH2O OMe O
(VIa): R = Me
(VIb): R2= Phthal
Me NRR' OH
CONH2
PhCH2O OMe O OH
(VIIa): R = R' = Me
(VIIb): R = H, R' = COC6H4CO2H-o
Me NMe2 OH
CONH2
OH OH O OH
(VIII)
Me NMe2 OH
OH
CONH2
OH OH O O
(IX)
Me OH NMe2 OH
OH
CONH2
OH O OH O
(X)

3400, 1752, 1615, 1593, 1561, 1376 cm^{-1}. IIb: m.p. 140-141°, from EtOH; λ_{max} 277, 340 mμ (lg ε 3.76, 4.16); ν_{max} 3490, 1742, 1610, 1593, 1560, 1376 cm^{-1}). On treatment with 0.4 N alcoholic HCl at 80° the adducts are dehydrated into the nitro-compound (IIIa)(m.p. 126-128°, from EtOH; λ_{max} 221, 269, 297, 309, 321, 408 mμ (lg ε 4.50, 4.65, 3.69, 3.65, 3.50, 3.98); ν_{max} 2680, 1750, 1616, 1577, 1380 cm^{-1}), which is smoothly reduced by zinc dust in acetic acid to the amino ester (IIIb)(m.p. 138-140°, from EtOH; λ_{max} 223, 269, 297, 309, 322, 408 mμ (lg ε 4.62, 4.81, 3.85, 3.80, 3.64, 4.15); ν_{max} 3400, 3340, 2690, 1740, 1615, 1577 cm^{-1}).

In order to synthesize deoxyanhydrotetracycline (VIII) via the dimethylamino derivatives (VIa) and (VIIa) we first methylated the amino ester (IIIb) by MeI + Ag_2O in dimethylformamide to the dimethylamino ester (IVa)(m.p. 106-108°, from EtOH; λ_{max} 222, 262, 307, 318, 373 mμ (lg ε 4.65, 4.72, 3.84, 3.74, 3.96); ν_{max} 1720, 1675, 1609, 1580 cm^{-1}) and saponified the latter to dimethylamino acid (Va)(λ_{max} 223, 268, 307, 318, 366 mμ (lg ε 4.49, 4.43, 3.72, 3.65, 3.72); ν_{max} 3450, 2700, 1684, 1615, 1582 cm^{-1}). However attempts to condense the acid (Va) as the chloride, the isopropyl carbonate (cf. (5)) or the isobutyl carbonate with ethyl ethoxymagnesium malonamate did not yield the desired acylmalonamate (VIa).

We, therefore, acylated the amino ester (IIIb) with carboethoxyphthalimide in tetrahydrofuran to obtain the phthaloyl derivative (IIIc)(m.p. 176-178°, from EtOH; λ_{max} 222, 269, 297, 308, 322, 407 mμ (lg ε 4.60, 4.78, 3.52, 3.50, 3.18, 3.87); ν_{max} 1780, 1750, 1720, 1618, 1580 cm^{-1}) which was then methylated by MeI + Ag_2O to (IVb)(m.p. 166-167°, from benzene; λ_{max} 221, 263, 307, 320, 375 mμ (lg ε 4.48, 4.74, 3.93, 3.76, 3.96); ν_{max} 1785, 1753, 1735, 1715, 1692, 1612, 1580 cm^{-1}). Saponification of this compound with 0.1 N KOH in aqueous tetrahydrofuran followed by recyclization of the phthalimido

grouping by heating in diglyme at 140° gave the acid (Vb)(m.p. 202-204°, from $MeNO_2$; λ_{max} 222, 262, 307, 318, 374 mμ (lg ε 4.63, 4.72, 3.81, 3.71, 3.92); ν_{max} 3480, 3360, 1778, 1727, 1610, 1580 cm^{-1}), which was then converted into the substituted ethyl N-phthaloylglycylmalonamate (VIb)(λ_{max} 223, 261, 308, 319, 374 mμ (lg ε 4.42, 4.68, 3.75, 3.56, 3.89); ν_{max} 3350, 1780, 1727, 1687, 1665, 1610, 1585 cm^{-1}) by treatment with PCl_5 + $HCONMe_2$ (cf. (6)) in tetrahydrofuran, followed by $EtOMgCH(CO_2Et)CONH_2$. The compound (VIb) was cyclized by means of $MeSOCH_2Na$ in dimethylsulfoxide into the substituted hydronaphthacene (VIIb)(m.p. 170-180°; λ_{max} 224, 266, 297, 310, 320, 388 mμ (lg ε 4.67, 4.57, 3.94, 3.91, 3.84, 4.02); ν_{max} 3350, 2700, 1712, 1695, 1680, 1662, 1615, 1603, 1583 cm^{-1}) and this on hydrolysis with HBr in AcOH and methylation with MeI in tetrahydrofuran gave (±)-12a-deoxy-5a,6-anhydrotetracycline (VIII) identified spectroscopically and chromatographically with the (-)-isomer prepared by degradation of the naturally occurring tetracycline according to the procedure of Green and Boothe (7).

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