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THE SYNTHESIS OF 11,12a-DIDEOXY-4-DEDIMETHYLAMINO-5a,6-ANHYDROTETRACYCLINES [*]

A.I.Gurevich, M.G.Karapetyan, M.N.Kolosov, V.G.Korobko,
V.V.Onoprienko and M.M.Shemyakin

Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow, USSR

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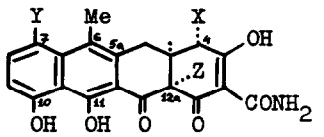
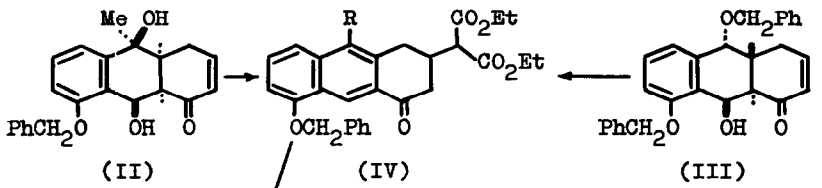
THE development of methods for the C_6-hydroxylation of 7-chloro-5a,6-anhydrotetracycline (I; X = NMe_2, Y = Cl, Z = OH) [1] and the C_{12a}-hydroxylation of various 12a-deoxytetracyclines, in particular (I; X = Y = Z = H) [2], has placed the 5a,6-anhydrotetracyclines (I) in the position of key intermediates in the total synthesis of naturally occurring tetracycline antibiotics. We therefore undertook a synthetic study of anhydrotetracyclines, beginning with the synthesis of 11,12a-dideoxy-4-dedimethylamino-5a,6-anhydrotetracyclines (XI) which is reported in this paper.

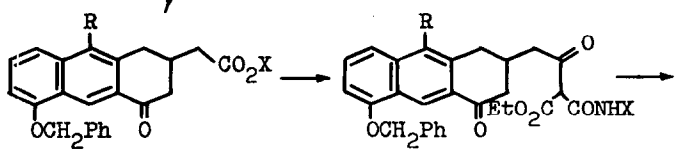


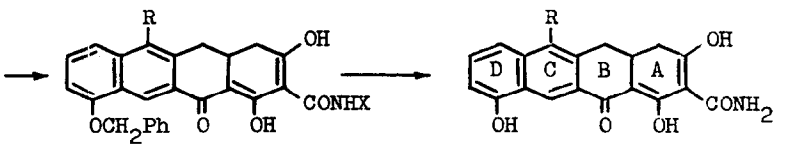
(I)

[*] Part XXXIX in "Studies in the Tetracycline Series".

Michael condensation of the unsaturated ketones (II) [3] and (III) [4] with ethyl sodiomalonate followed by dehydration with alcoholic H_2SO_4 afforded the keto-diesters (IV) (yield 65 - 80%). Direct saponification of these esters proved unsatisfactory, the reverse Michael reaction taking place in the presence of alkali. Hence the keto-acids (V) were obtained by $NaBH_4$ reduction of the keto-diesters (IV) followed by hydrolysis, decarboxylation and H_2CrO_4 oxidation (total yield of (V) up to 70%).







(IVa) - (XIa): R = H, (IVb) - (XIb): R = Me

Ring A was at first constructed by the method of Woodward et al. [5], utilizing the following convenient modification. The keto-acids (V) were converted by the action of Et_3N and $COCl_2$ at -70° to the mixed anhydrides (VI) and the latter, without isolation, were condensed with $EtOMgCH(CO_2Et)CONHBu^t$ to the ester-amides (VII) (yield 60 - 75%). The best condensation agent for cyclizing the latter to compounds (IX) (or their tautomers) was found to be sodium methylsulfinylmethylide in dimethylsulfoxide (Corey's reagent [6]); NaH, $NaNH_2$ and Na (1 μ particles) proving much inferior. Under optimal conditions (4 moles CH_3SOCH_2Na, 1.5 - 3 hr. at 120°) the yield of the tetracyclic compounds (IX) reached a value of 80%. Vigorous treatment with strong mineral acids (for instance 35% HBr in glacial acetic acid at 100°) was required to remove the N- and O-protective groups from (IX), otherwise only the O_{10}-benzyl group was eliminated. This route was therefore unsuitable for preparing the phenoltriketocarboxamides (XI), such drastic conditions causing further degradation of the molecule.

For this reason we abandoned Woodward's method and devised a new route for ring A formation. This method which does not involve acid treatment is applicable not only for the synthesis of 5a,6-anhydrotetracyclines, but also for direct preparation of the tetracyclines, themselves, bypassing the anhydro stage. Condensation of the mixed anhydrides (VI) with the ethoxymagnesium derivative of ethyl malonamate gave the N-unsubstituted ester-amides (VIII) in 80% yield. The products were then cyclized by CH_3SOCH_2Na (5 moles; 120°, 30 min.) to

the tetracyclic triketocarboxamides (X) (yield up to 70%). Hydrogenolysis of the latter compounds in the presence of Pd in tetrahydrofuran solution afforded the ultimate 11,12a-dideoxy-4-dedimethylamino-5a,6-anhydrotetracyclines (XI) in 85 - 90% yield.

The constants of the compounds synthesized are summarized in the Table. The analytical data correspond to the required values.

TABLE

Comp. No.	M.P. °C	UV Spectra in EtOH	
		λ max mμ	lg ε
IVa	114-115	263, 309, 320, 372	4.57, 3.69, 3.58, 3.64
IVb	128-130	261, 308, 319, 372	4.63, 3.76, 3.66, 3.76
Va	163-165	261, 307, 320, 370	4.47, 3.70, 3.59, 3.57
Vb	193-194	260, 309, 320, 372	4.60, 3.74, 3.64, 3.74
VIIa	147-149	263, 308, 320, 372	4.54, 3.70, 3.59, 3.60
VIIb	170-171	262, 308, 320, 372	4.66, 3.73, 3.62, 3.69
VIIIa	168-170	264, 308, 320, 372	4.62, 3.70, 3.61, 3.63
VIIIb	151-152	262, 308, 320, 373	4.89, 3.98, 3.88, 3.92
IXa	161-163	245, 259, 314*, 384	4.41, 4.47, 3.89, 4.59
IXb	193-195	247, 262, 316, 382	4.30, 4.34, 3.76, 4.39
Xa	210-212	245, 259, 314*, 382	4.36, 4.39, 3.86, 4.52
Xb	218-220	246, 260, 316, 382	4.40, 4.43, 3.93, 4.56
XIa	>250 dec.	246, 261, 320, 383	4.41, 4.46, 3.99, 4.54
XIb	>255 dec.	246, 261, 320, 382	4.35, 4.37, 3.91, 4.46

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REFERENCES

1. A.I.Scott, C.T.Bedford, J.Am.Chem.Soc., 84, 2271 (1962).

2. H.Muxfeldt, G.Buhr, R.Bangert, Angew.Chem., 74, 213 (1962).

3. M.N.Kolosov, S.A.Popravko, M.M.Shemyakin, Dokl.Acad. Nauk SSSR, 150, 1285 (1963).

4. A.I.Gurevich, M.G.Karapetyan, M.N.Kolosov, V.G.Korobko, V.V.Onoprienko, M.M.Shemyakin, Dokl.Acad.Nauk SSSR, 155, 139 (1964).

5. L.H.Conover, K.Butler, J.D.Johnston, J.J.Korst, R.B. Woodward, J.Am.Chem.Soc., 84, 3222 (1962); R.B.Woodward, Pure a. Appl.Chem., 6, 561 (1963).

6. E.J.Corey, M.Chaykovsky, J.Am.Chem.Soc., 84, 866 (1962).