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SYNTHESIS OF NOVEL TETRACYCLINE DERIVATIVES WITH SUBSTITUTION AT THE C-8 POSITION

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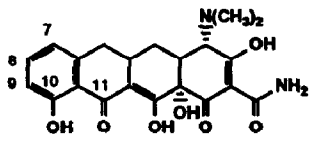
Key Words: 8-Substituted tetracyclines, *ortho*-chloroamines, acid-catalyzed azide rearrangements, 7(or 9)-azidotetracyclines

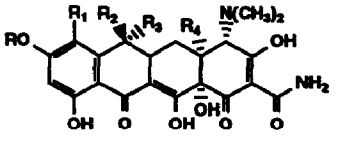
Abstract: The C-8 functionalization of tetracycline derivatives *via* acid-catalyzed rearrangement of 7(or 9)azidotetracyclines is described. These compounds are the first to be prepared from an intact tetracycline nucleus.

The frequent use of the tetracycline antibiotics has caused many bacteria to develop resistance to these agents.[1] In the search for new structural entities that might overcome this problem, we investigated the synthesis of new derivatives using either natural or semisynthetic tetracyclines.

Numerous modifications on the tetracycline nucleus **1** have been reported.[2] Notably modifications on the D-ring of the tetracycline nucleus yielded many derivatives with enhanced antibacterial activities.[3] However, most of these modifications were done at the C-7 and C-9 positions through electrophilic substitution. The direct electrophilic functionalization of the C-8 position is unattainable in these reactions since this position is deactivated by the electron withdrawing carbonyl group at C-11.[2]



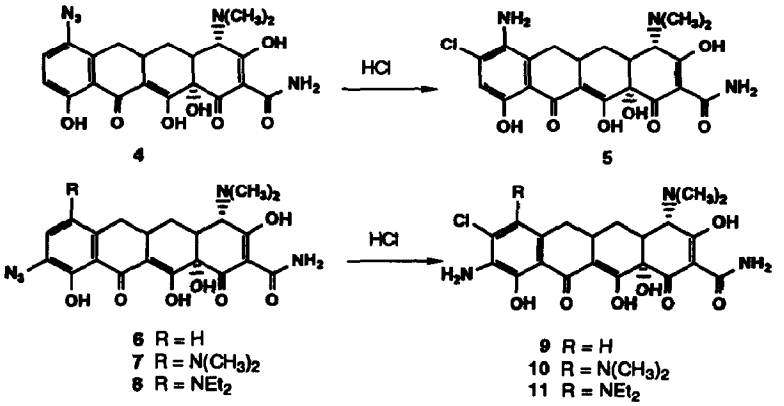
1



2 R = CH_3; R_1 = Cl; R_2 = OH; R_3 = CH_3; R_4 = OH
3 R = H; R_1 = H

Only two 8-substituted tetracyclines have been reported: 8-methoxytetracycline **2**, a fermentation product,[4] and 8-hydroxytetracycline **3**, obtained through total synthesis.[5] This communication describes the synthesis of 8-chloro tetracyclines *via* azido tetracyclines.[6] While protonolysis of aryl azides with hydrogen halides to ortho (or para) halo anilines has been studied mechanistically,[7] it has never been applied to the modification of natural products. The new 8-chloro derivatives are the first to be prepared from an intact tetracycline nucleus. We have found that the reaction of 7-azide **4** [6] [^{1}H NMR (300 MHz; DMSO-d_6) δ 6.9 (d, H-9, 1H), 7.5 (d, H-8, 1H)] in concentrated hydrochloric acid at ambient temperature gave the rearrangement product 7-amino-8-chloro-6-demethyl-6-deoxytetracycline **5** [^{1}H NMR (300 MHz; DMSO-d_6) δ 7.8 (s, H-9, 1H); HRMS (FAB) calcd. for $C_{21}H_{22}N_3O_7Cl$: 464.1225 (M+H), found : 464.1232 (M+H)]. Under similar

reaction conditions 9-azide **6** [6] was converted to 9-amino-8-chloro-6-demethyl-6-deoxytetracycline **9** [^{1}H NMR (300 MHz; DMSO-d_6) δ 7.25 (s, H-7, 1H); HRMS (FAB) calcd. for $C_{21}H_{22}N_3O_7Cl$: 464.1225 (M+H), found 464.1236 M+H)]. These rearrangements are sterically sensitive. Both products **5** and **9** were obtained in good yields (> 80%). In contrast, azido compounds **7** and **8**,[3, 6] in which there is C-7 substitution, gave lower yields (< 40%) of the desired product **10** [HRMS (FAB) calcd. for $C_{23}H_{27}N_4O_7Cl$: 507.1647 (M+H), found : 507.1639 (M+H)] and **11** [HRMS (FAB) calcd. for $C_{25}H_{31}N_4O_7Cl$: 535.1960 (M+H), found : 535.1963 (M+H)] repectively. Substitutions with nucleophiles other than halogen are under investigation.



4 **5**

6 R = H
7 R = $N(CH_3)_2$
8 R = NEt_2

9 R = H
10 R = $N(CH_3)_2$
11 R = NEt_2

The method described in this communication provides a convenient route to the rare 8-substituted tetracyclines which are important for structure-activity relationship studies.

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