Tetrahedron Letters No. 19, pp. 1677-1680, 1970. Pergamon Press. Printed in Great Britain.

(20βH, 22αO,25R)-5α-SPIROSTAN-3β-AMINO-6α-OL AND ITS ISOMERS

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(Received in UK 16 March 1970; accepted for publication 26 March 1970)

The systematic chemical and pharmacological study of the alkaloids of Solanum paniculatum, carried out in our Laboratories, made it possible to isolate a new group of spirostan alkaloids including glucosides and aglycones (1).

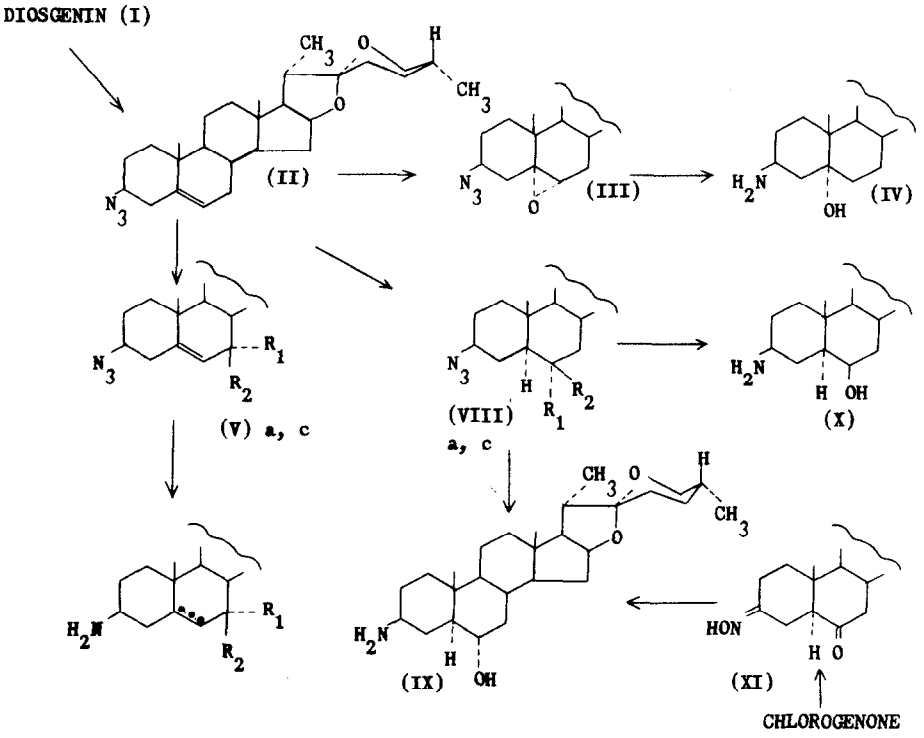
Both acid and enzymatic hydrolysis of the glucoside SG5 ($C_{33}H_{57}NO_9$, m.p. 162-171°C, $[\alpha]_D$= - 20° (pyridine)), lead to the same aglycone SPA III (IX) ($C_{27}H_{45}NO_3$), for which the results of various investigations (2) suggested that the most likely structure was (20βH,22αO,25R)--5α-spirostan-3β-amino-6α-ol.

In the mass spectrum of compound (IX) we find the fragment m/e 98, which prevents complete definition of the structure of the compound: the same fragment is to be expected whenever an amino group in position 3 of a steroid, lacking a double bond in position 5, is associated with an hydroxyl function in position 5, 6, or 7 (3), to the exclusion of position 4 (4,5).

In order to obtain further confirmation of the proposed structure, we decided to prepare all the possible isomers from the diosgenin (I), whose configuration of the spirostan rings E and F corresponds to that advocated for the natural product.

Utilizing methods described elsewhere (6), we converted diosgenin (I) to 3β-azido-(20βH, 22αO,25R)-spirost-5-ene (II),with m.p. 156-157°C, $[\alpha]_D$= - 104° (7). This compound, which insures the 3β- configuration of the potential 3-amino group (8), was utilized as the starting material for the synthesis of 5, 6, and 7-ol-3-amino-spirostans.

Indeed, epoxidation of (II) with monoperphthalic acid in chloroform-ether leads to 5 ,6 - epoxide (III) with m.p. 142-143°C, $[\alpha]_D$= - 112°. This, reduced with aluminum lithium hydride in tetrahydrofuran, gave the 3β-amino-5α-hydroxyl derivative (IV) with m.p. 205-206°C, $[\alpha]_D$= - 77°.



Wohl-Ziegler bromination of (II), followed by alkaline hydrolysis of the 7-bromo intermediate in carbon tetrachloride with alumina (9), gave 3β-azido-(20βH,22α0,25R)-spirost-5-ene-7α-ol (V-a), with m.p. 174.5-175°C, $[\alpha]_D = -137°$, along with small amounts of the 7β-isomer (V-b) with m.p. 186-187°C, $[\alpha]_D = -63°$; this was more conveniently obtained by reduction with sodium borohydride in methanol of its Δ^5-7-keto derivative (V-c)with m.p. 220-222°C, $[\alpha]_D = -150°$, λ_{max}^{EtOH} 235 mμ, ε = 13,100,which was in turn prepared from V-a,b by oxidation, either with Jones's reagent (10) in acetone or with dichlorodicyanobenzoquinone (DDQ)in dioxane (11). The reduction of V-a with $LiAlH_4$ gave 3β-amino-(20βH,22α0,25R)-spirost-5-ene-7α-ol (VI-a) with m.p.

143-145°C, $[\alpha]_D$ = - 156°, whereas from V-b,c we obtained the 7β-isomer (VI-b) with m.p. 171-173°C, $[\alpha]_D$ = - 76°. And finally, catalytic hydrogenation of VI-a,b in acetic acid in the presence of 5% Pd/C gave respectively 3β-amino-(20βH,22α0,25R)-5α-spirostan-7α-ol (VII-a) with m.p. 228-232°C, $[\alpha]_D$ = - 78° and the isomer 7β-ol (VII-b) with m.p. 181-184°C, $[\alpha]_D$ = - 40°.

Hydroboration of 3β-azido-spirost-5-ene (II) with a solution of diborane in tetrahydrofuran, followed by oxidation of the alkylborane intermediate with alkaline hydrogen peroxide (12), gave 3β-azido-5α-spirostan-6α-ol (VIII-a) with m.p. 186-187°C, $[\alpha]_D$ = - 49° along with small amounts of its 6β-ol isomer with m.p. 190-192°C, $[\alpha]_D$ = - 79°.

Both isomers were oxidized to the same 3β-azido-(20βH,22α0,25R)-5α-spirostan-6-one (VIII-c) with m.p. 180-181°C, $[\alpha]_D$ = - 92°, from which reduction with sodium borohydride in methanol leads back to VIII-b.

The reduction of VIII-a with $LiAlH_4$, as well as the reduction of VIII-c with sodium and n-propanol, yielded 3β-amino-(20βH,22α0,25R)-5α-spirostan-6α-ol (IX) and this compound was found identical with the natural product.

Both the natural product and the one obtained by synthesis, as well as their N-isopropylidene derivatives, with m.p. 204-205°C, $[\alpha]_D$ = - 58°, did not show any depression in mixture.

Reduction of VIII-b,c with $LiAlH_4$ gave the 6β-isomer (X) of the natural product, with m.p. 208-210°C, $[\alpha]_D$ = - 86°.

We arrived at the same natural product, 3β-amino- (20βH,22α0,25R)-5α-spirostan-6α-ol (IX) also by sodium reduction in n-propanol of (20βH,22α0,25R)-5α-spirostan-3,6-dione-3-oxime (XI) with m.p. 223-224°C, $[\alpha]_D$ = - 96°, prepared by reacting chlorogenone (13) with a molar equivalent of hydroxylamine hydrochloride in pyridine.

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