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STEROIDS, PART VI[1]: SYNTHESIS OF B-HOMO-A, 19-BISNORANDROSTA-5(10)-ENE-3,17-DIONE.

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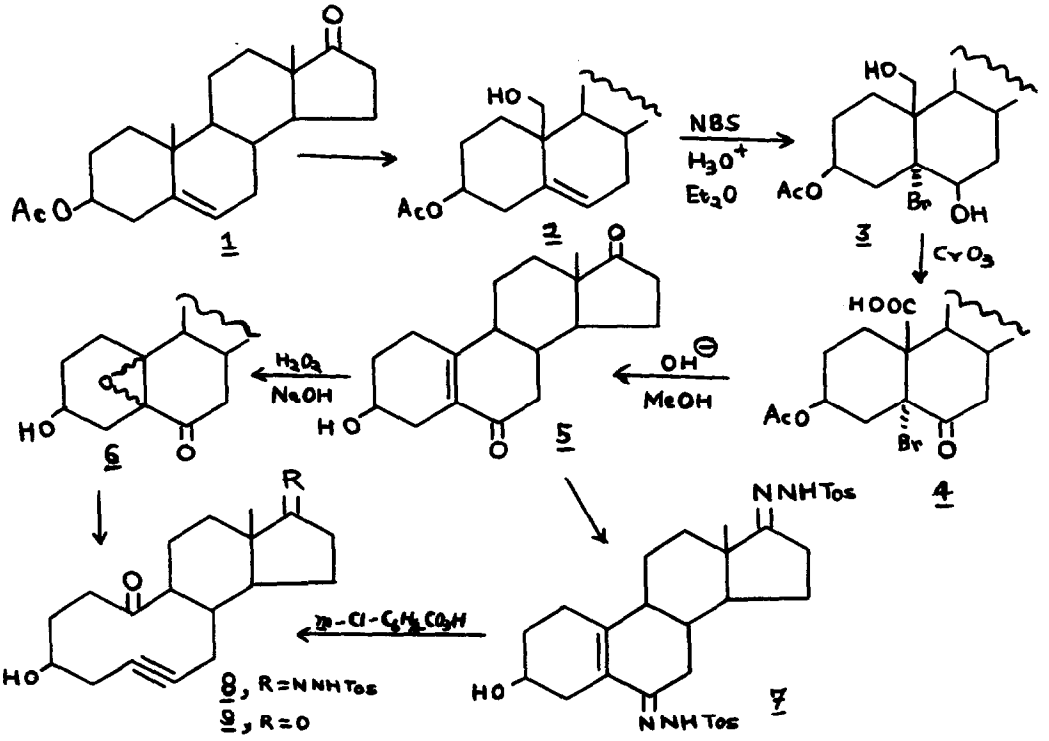
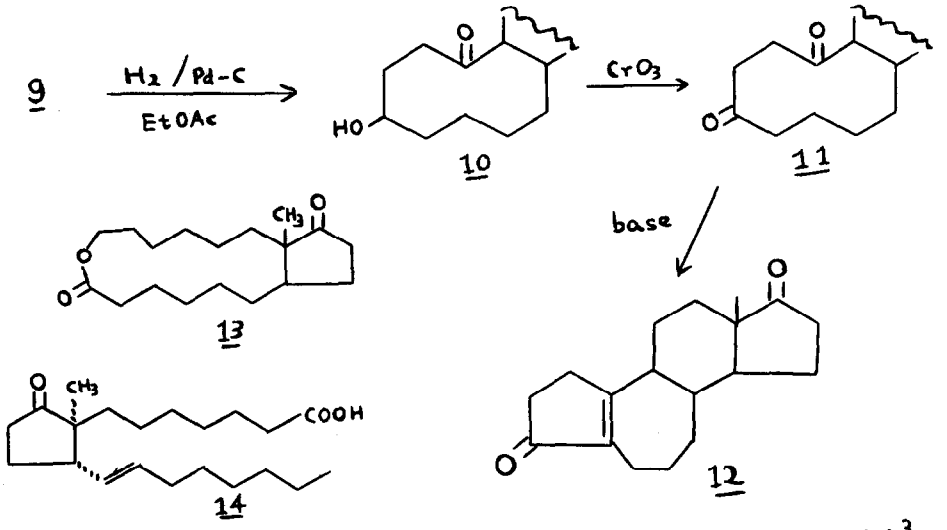
Amongst the modified steroids, B-homo-A,19-bisnorsteroids have been reported in the patent literature to possess enhanced androgenic and anabolic activities[2]. However, the synthetic details of these compounds are not reported. As a part of the general synthesis of such compounds, we wish to report the synthesis of the title compound (12), starting from the easily available, 3β-acetoxy-5-androsten-17-one (1), involving fragmentation of the key intermediate (5), as illustrated below:-





The steroid (1) was initially converted to 19-hydroxy derivative (2)[3] (mp.170°C; yield: 35%). This was treated with N-bromosuccinimide in aqueous ether, giving the bromohydrin (3), which was carefully oxidized by Jone's reagent at low temperatures (0-10°C), affording the 5α-bromo-6-keto-19-oic acid (4). This was refluxed with alkali in methanol, yielding the α,β-unsaturated ketone (5). (mp. 157°C; yield: 33-35% from 2; I.R. ν max.($CHCl_3$): 3400 cm^{-1} (3-OH), 1725 cm^{-1} (17-ketone), 1665 cm^{-1} (6-ketone); NMR: ($CdCl_3$): δ 0.8 (18-CH_3), δ 3.5 (3α-H), 19-CH_3 and vinyl protons absent.)

The conjugated ketone (5) was epoxidized using alkaline hydrogen peroxide, in very low yields (13%), however, the epoxyketone (6), thus obtained, was successfully transformed to the acetylenic compound (8), by treatment with two equivalents of tosylhydrazine[4]. In order to prepare the compound (8) in better yields, a change in sequel[5], involving the prior formation of tosylhydrazone and its subsequent epoxidation was found to be more convenient. Thus, the α,β-unsaturated ketone (5), was converted to its ditosylhydrazone (7), by refluxing in methanol with two equivalents of tosylhydrazine. The resulting ditosylhydrazone (7) was mixed with monoperphthalic acid in chloroform at 0-5°C for 48 hours, affording the 5,10-seco steroid (8). (m.p. 133-4°; yield 40-42% from 5. I.R.: ν max.(KBr): 3460, 3260, 1748, 1670, 1343, 1173 cm^{-1}). To avoid complications during hydrogenation of the triple bond, the 17-tosylhydrazone group was removed at this stage, by boiling with pyruvic acid in acetic acid, for 5 minutes, giving

the 17-keto compound (9) (mp.104°C). This compound absorbed two moles of hydrogen over Pd/C (10%), affording the saturated compound (10) (mp.96°C; yield: 68-70% from 8; I.R.νmax.($CHCl_3$): 1725 cm^{-1} (3,17-diketone), 3350 cm^{-1} (3-OH); NMR ($CdCl_3$): δ 0.8 (18-CH_3), δ 3.48 (3α-H), NO vinyl protons). The saturated compound (10) was oxidized by Jone's reagent, for a short time, giving the triketo compound (11), which underwent intramolecular aldol condensation, in the presence of potassium t-butoxide in methanol, affording the title compound (12). (mp.107°C[6]; yield: 30-33% from 10; IR νmax.($CHCl_3$): 1730 cm^{-1} (17-ketone), 1670 cm^{-1} (3-ketone).

The ten membered ring compound (10), is of multiple importance, for the synthesis of diverse products of biological interest, like macrolide (13) and prostaglandin type of compound (14), after the clevage of C_8-C_9 and C_2-C_3 bonds, with requisite structural elaborations. Experiments in this direction, are now under progress, in our laboratory.

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Note: All the compounds provided satisfactory elemental analyses.