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Short Communication

A FACILE ROUTE FOR THE SYNTHESIS OF BISQUARTENARY AZASTEROIDS

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ABSTRACT

Objective: The synthesis and pharmacological profile of steroidal mono- and bisquaternary ammonium derivatives as neuromascular blocking agents have been extensively reported. Keeping in view the key structural features of pancuronium bromide and chandonium iodide, bis quarternary azasteroids have been designed and synthesised in the present study.

Methods: The designed molecules were synthesis via a sequence of reaction. For the synthesis, the oxidation of 17α-Aza-D-homo-5-androsten-3β-ol has been carried out by two different reactions (Moffat oxidation and Oppenaur oxidation).

Results: The synthesised molecules were characterized by spectroscopic techniques such as I.R and NMR. The proton resonances of the final compound has been discussed.

Conclusion: The present study proposes a feasible route for the synthesis of bisquartenary azasteroids. The desired molecules have been designed keeping in view the key pharmacophoric features essential for neuromascular blocking agents.

Keywords: Azasteroids, Neuromascular blocking agents, Oxidation

INTRODUCTION

The steroid system, selected by the evolutionary process to perform some of the most fundamental biological functions, has not only inspired biochemists and endocrinologists, but also become the basis of many important discoveries in organic chemistry [1]. Steroids can regulate a variety of biological processes and thus have the potential to be developed as drugs for the treatment of a large number of diseases including cardiovascular [2], autoimmune diseases [3], brain tumours, breast cancer, prostate cancer, osteoarthritis etc. [4].

Modified steroids have attracted a great deal of attention during the last few years. Their preparation is a stimulating challenge to the organic chemist, often demanding the development of new and generally useful reactions [5–7]. The replacement of one or more carbon atoms of a steroid molecule by a heteroatom affects the chemical properties of asteroid and often results in useful alterations to its biological activity. The potential of heterosteroids in general, and azasteroids in particular, as novel drugs and the challenge of their synthesis prompted numerous research groups to undertake studies in this field. Particularly, the biological activity of azasteroids has been the subject of some reviews. These steroids are one of the best known classes of xenobiotics and several have been described as inhibitors of 5α-reductase [8].

Regan and Hayes, in their exemplary work, have synthesized several aza-D-homosteroids from several 17-ketosteroid oximes [9]. But azasteroids attracted more attention when chandonium diiodide was established as a potent neuromuscular blocker [10]. Azasteroids have been found to possess numerous biological activities like gamma aminobutyric acid (GABA) receptor antagonistic [11-13], antifungal [14], antineoplastic, mutagenic [15-16] and anti-inflammatory activity [17].

The search for new neuromuscular blocking agents has been motivated by the long-time course of action and pronounced side effects of the compounds available in clinical practice [18]. Since the discovery of non depolarizing neuromuscular blocking activity of pancuronium bromide [19-20], tremendous numbers of steroidal [21-28] and nonsteroidal [17, 23, 29] neuromuscular blocking agents have been synthesized and their muscle relaxation properties examined. Shortly after the development of pancuronium, azasteroidal compounds, in which the quaternary nitrogen atom is placed in the ring D of the steroidal skeleton, were synthesized and studied [21]. One of the compounds in this series, chandonium iodide, is a powerful nondepolarizing neuromuscular blocking agent with short duration and rapid onset being only slightly less active than pancuronium [30]. The general assumption between these structures and skeletal muscle relaxation is that the compounds must have two tertiary nitrogens at appropriate distances (1.0–1.2 nm) of which one or both the nitrogens should be quaternized. As the interonium distance between two quaternary heads falls below 1.0 nm, the skeletal muscle relaxation property diminishes and the ganglion blocking activity becomes prominent [31]. Pipecuronium bromide is an example that does not follow this structure activity parameter [32]. In the present study, our basic design concept was to incorporate structural features of pancuronium and chandonium [21] known to be essential for their non depolarizing neuromuscular blocking activity.

MATERIALS AND METHODS

Melting points reported are uncorrected. ^{1}H NMR spectra were recorded on AC-300F, 300 MHz, VarianEM-390, 90 MHz and EM-360, 60 MHz NMR instruments using tetramethylsilane (TMS) as the internal standard (chemical shifts in δ, ppm). IR and UV spectra were recorded on Perkin-Elmer 882 and Lambda 15 spectrophotometer models, respectively. The purity of the compounds was established by thin layerchromatography (TLC) and by elemental analysis (C, H, N). Mass spectra were recorded on a V6-11-250 J 70S. Anhydrous sodium sulphate was used as a drying agent. UV spectra were recorded in methanol. IR spectra were obtained with potassium bromide pellets (νmax in cm^{-1}).

20-Oxo-5, 16-pregnadien-3β-yl acetate (2)

(*25R*)-5-Spirosten-3β-ol (Diosgenin) (**1**) (5 gm, 12.0 mmol) and methylamine hydrochloride (5 gm, 73 mmol) were refluxed in acetic anhydride (20 ml) and pyridine (20 ml) for 8 hr. The reaction mixture was then cooled and poured into ice cold water (500 ml). The residue was filtered at vacuum pump, washed repeatedly to remove pyridine, dried and dissolved in dichloromethane (DCM) (50 ml) and glacial acetic acid (25 ml). The solution was cooled to -5°C, stirred and to this was added drop wise cold solution of chromium trioxide (1.6 gm) in acetic acid (90%, 35 ml). The reaction mixture was stirred for further 1 hr at -5°C. Excess of chromium trioxide was destroyed by adding sodium metabisulphite solution (10%, 35 ml) at 0°C. After separating the organic layer, the aqueous layer was extracted with DCM (5 x 100 ml) with separating funnel. The combined organic layer was washed with water, aqueous sodium bicarbonate (5%) and water. The extract was dried, filtered and the

solvent removed under reduced pressure. The oily residue so obtained was refluxed with glacial acetic acid (50 ml) for 2 hr, cooled and poured into water (500 ml). It was extracted with DCM (3 x 100 ml), washed with water, aqueous sodium bicarbonate (5%) and water. The extract was dried, filtered and the solvent removed under reduced pressure to give a residue which was crystallized from methanol to yield 20-Oxo-5, 16-pregnadien-3β-yl acetate (16-Dehydropregnenolone acetate) (**2**) (2.25 gm, 45%) m.pt. 170-172°C. IR (KBr): 2850, 1740, 1660 and 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.9 (s, 3H, 18-CH_3), 1.03 (s, 3H, 19-CH_3), 2.03 (s, 3H, 21-CH_3), 2.3 (s, 3H, CH_3COO), 4.61 (m, 1H, 3α-H), 5.4 (m, 1H, 6-vinylic), 6.75 ppm (t, 1H, 16-vinylic).

20-Oximino-5, 16-pregnadien-3β-yl acetate (3)

A solution of 20-Oxo-5, 16-pregnadien-3β-yl acetate (**2**) (5 gm, 14.0 mmol) and hydroxylamine hydrochloride (2.5 gm, 35.5 mmol) in pyridine (25 ml) was heated on steam bath for 1 hr. The reaction mixture was poured into ice cold water (500 ml) with stirring. The precipitated material was filtered at pump, washed repeatedly to remove pyridine, dried to afford the crude product which was recrystallized by refluxing with acetone-n-hexane to yield 20-oximino-5,16-pregnadien-3β-yl acetate (**3**) (4.6 gm, 92%) m.pt. 211-213°C. IR (KBr): 3480, 2850, 1730 and 1260 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (s, 3H, 18-CH_3), 1.05 (s, 3H, 19-CH_3), 2.01 (s, 3H, 21-CH_3), 2.3 (s, 3H, CH_3COO), 4.6(m, 1H, 3α-H), 5.4 (m, 1H, 6-vinylic) and 6.07 ppm (m, 1H, 16-vinylic).

17-Oxo-5-androsten-3β-yl acetate (4)

20-Oximino-5,16-pregnadien-3β-yl acetate (**3**) (1 gm, 2.7 mmol) was dissolved in pyridine (10 ml) and the cold solution of phosphorus oxychloride (4 ml) in dry pyridine (12 ml) was added drop wise to the above stirred solution below 0°C with contineous stirring. The reaction mixture was occasionally shaken for 3 hr at 0°C. It was poured into a mixture of crushed ice (50 gm) and conc. HCl (30 ml). The suspension was allowed to stand for 30 min at room temperature and then diluted with water (50 ml). The precipitated material was then filtered and crystallized from upper layer of acetone-petroleum ether to afford 17-oxo-5-androsten-3β-yl acetate (**4**) IR (KBr): 2850, 1735 and 1240 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90 (s, 3H, 18-CH_3), 1.03 (s, 3H, 19-CH_3), 2.3 (s, 3H, CH_3COO), 4.6 (m, 1H, 3α-H) and 5.4 ppm (m, 1H, 6-vinylic).

17-Oximino-5-androsten-3β-yl acetate (5)

17-Oxo-5-androsten-3β-yl acetate (**4**) (5 gm, 15.1 mmol) was dissolved in 95% ethanol (72 ml) and refluxed. To this was added aqueous solution of hydroxylamine hydrochloride (2.4 gm, 34.0 mmol) and sodium acetate trihydrate (6.2 gm) in water (30 ml) and the reaction mixture was refluxed further for 4 hr. The solvent was partially removed by distillation and the reaction mixture was poured into ice cold water (250 ml). The precipitated material was filtered, washed with water, dried and crystallized from methanol to afford 17-oximino-5-androsten-3β-yl acetate (**5**) IR (KBr): 3400, 2960, 1740 and 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H, 18-CH_3), 1.04 (s, 3H, 19-CH_3), 2.3 (s, 3H, CH_3COO), 4.6 (m, 1H, 3α-H), 5.4 (m, 1H, 6-vinylic) and 8.43 (s, 1H, NOH).

17-Oxo-17α-aza-D-homo-5-androsten-3β-yl acetate (6)

A solution of thionyl chloride (2.5 ml) in dioxane (5 ml) was added to the stirring solution of 17-oximino-5-androsten-3β-yl acetate (**5**) (5 gm, 14.4 mmol) in benzene (90 ml) cooled to 15°C and the reaction mixture was kept at 20°C for 15 min. It was then cooled in an ice bath and water (30 ml) was added. The solution was made alkaline with ammonia. The upper benzene layer was separated in separating funnel and the aqueous layer was extracted with chloroform (4 x 100 ml). The combined organic portion was washed with water (4 x 30 ml). The solvent was removed under vacuum to get brownish residue, which was crystallized from methanol to afford 17-oxo-17α-aza-D-homo-5-androsten-3β-yl acetate[39,40] (**6**). IR (KBr): 3220, 2860, 1740, 1680 and 1240 cm^1. ^1H NMR ($CDCl_3$): δ 1.01 (s, 3H, 18-CH_3), 1.18 (s, 3H, 19-CH_3), 2.3 (s, 3H, CH_3COO), 4.6 (m, 1H, 3α-H), 5.4 (m, 1H, 6-vinylic) and 6.2 ppm (s, 1H, NH).

17α-Aza-D-homo-5-androsten-3β-ol (7)

Sodium metal (6.0g) was added slowly to a refluxing solution of 17-oxo-17α-aza-D-homo-5-androsten-3β-yl-acetate (6) (1.5g) in 1-pentanol (120ml). The reaction mixture was refluxed till the sodium metal had completely reacted. The hot solution of reaction mixture was steam distilled. The solid residue was collected by filtration, washed with water, dried and crystallized from methanol to afford (**7**). IR (KBr): 3481, 2937, 1440, 1058 and 919 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.0 (s, 3H, 18-CH_3), 1.06 (s, 3H, 19- CH_3), 3.50 (m, 1H, 3α-CH) and 5.36 ppm (m, 1H, 6-CH).

17α-Aza-D-homo-5-androsten-3-one (Moffat oxidation) (8)

0.85g of 17α-aza-D-homo-5-androsten-3β-ol (7) was dissolved in mixture of benzene (3ml), dimethylsulfoxide (3ml), pyridine (0.16ml) and triflouroacetic acid (0.1ml), then dicyclohexylcarbodimide (0.24g) was added and mixture was kept overnight at room temperature. Diethyl ether (50ml) was added and then oxalic acid(0.54g) in 5ml methanol. After 30 min water (50ml) was added. The obtained DCU (dicyclohexyl urea) was removed by filtration. Product was extracted from filtrate with ether, washed with sodium bicarbonate and water. Ethereal solution was dried over anhydrous sodium bicarbonate and evaporated under reduced pressure and crystallized from ethanol to give 17α-aza-D-homo-5-androsten-3-one (**8**). IR (KBr): 3320, 2840, 1635, 1225 cm^{-1}. ^1H NMR: 0.9 (m, 3H, 18-CH_3), 1.3 (m, 3H, 19- C3`H_3), 1.4 (m, 2H, 7-CH_2), 1.7 (s, H, NH), 4.0 (t, 1H, 6-vinylic), 3.5 (m, 2H, 4- CH_2).

17α-Aza-D-homo-4-androsten-3-one (9)

17α-aza-D-homo-5-androsten-3β-ol (7) (1 gm, 3.3 mmol) was dissolved in a mixture of cyclohexanone (10 ml), dry toluene (90 ml) and dry dioxane (45 ml). Traces of moisture were removed by azeotropic distillation of toluene (10 ml). The distillation was continued at a slow rate while adding a solution of aluminium isopropoxide (1 gm) in dry toluene (15 ml) drop wise. The reaction mixture was refluxed for 4 hr, and was allowed to stand at room temperature for 12 hr. The slurry was filtered and the residue was washed with dry toluene. The combined filtrate and the washings were steam distilled until the complete removal of organic solvents was effected. The residual aqueous suspension was allowed to stand at r.t. and then it was extracted with chloroform (4 x 30 ml). The combined chloroform extract was washed with water, dried and the solvent removed to obtain a pale yellow solid which was crystallized from acetone to afford 17α-Aza-D-homo-4-androsten-3-one (9) (0.65 gm, 65%) m.pt. 259-261°C. Anal. UV_{max} (MeOH): 239.0 nm. IR (KBr): 2940, 2917.3, 2848.9, 1669.4 and 1232 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (s, 3H, 18-CH_3), 1.35 (s, 3H, 19-CH_3), 5.69 (s, 1H, 4-vinylic) and 7.44 ppm (s, 1H, NH).

17α-Allyl-17α-aza-D-homo-5-androsten-3-one (10)

A mixture of 17α-aza-D-homo-5-androsten-3-one (1g), allyl bromide (1g) and dry ethyl methyl ketone (50ml) was refluxed for 15 min. Anhydrous potassium carbonate (1g) was then added to the reaction mixture and the reaction mixture was refluxed for 4 hr with continuous stirring. The slurry obtained was filtered and solvent removed under reduced pressure. The residue was crystallized from n-hexane to afford 17-a-Allyl-17α-aza-D-homo-4-androsten-3one (**10**) (0.85g, 74%). IR (KBr): 3320, 2820, 1630, 1220 cm^{-1}. ^1H NMR: δ 5.19 (t, 1H, 6-vinylic), 4.08 (d, 2H, 22-CH_2), 3.5 (m, 1H, 21-CH), 2.17 (m, 2H, 20-CH_2), 1.8 (m, 2H, 4-CH_2), 1.3 (m, 3H, 19-CH_3), 0.95 (m, 3H, 18-CH_3).

17α-Allyl-17α-aza-D-homo-4-androsten-3-one (11)

A mixture of 17α-aza-D-homo-4-androsten-3-one (1.0g), allyl bromide (1.0 ml) and dry ethyl methyl ketone (50 ml) was refluxed for 15 min. Anhydrous potassium carbonate (1.0g) was then added to the reaction mixture and the reaction mixture was refluxed for 4 hr with continuous stirring. The slurry obtained was filtered and solvent removed under reduced pressure. The residue obtained was crystallized from n-hexane to afford (0.85g, 74.63%), mp 130-135°C. IR (KBr): 2934, 2841.6, 1661, 1250.8 and 1108 cm^{-1}. ^1H NMR ($CDCL_3$): δ 2.75 (dd, 1H, >N-CH(H)-CH=CH_2), 3.54 (dd, 1H, >N-

C(H)H-CH=CH_2), 5.15 (dd, 2H, >N-CH_2-CH=CH_2), 5.72 ppm (m, 1H, >N-CH_2-CH=CH_2).

17α-Allyl-3-Piperidino-17α-aza-D-homo-3, 5-androstadiene (12)

Freshly distilled piperidine (9 ml) was added to the boiling solution of 17α-Aza-D-homo-4-androsten-3-one (**11**) (1.5 gm, 5 mmol) in methanol (20 ml). It was then refluxed for 15 min. and then the solution was concentrated to induce crystallization. The yellow needle shaped crystals which crystallized out on cooling, were filtered, washed with methanol and dried in a vacuum desiccator to give 17α-Allyl-3-Piperidino-17α-aza-D-homo-3, 5-androstadiene (**12**) (1.4 gm, 93.33%) m.pt. 280-283°C. IR (KBr): 3433.8, 2938.5, 1663.5, 1603.3, 1390, 1226.3 and 831.2 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (s, 3H, 18-CH_3), 1.2 (s, 3H, 19-CH_3), 3.0-3.2 (m, 5H, N-methylenes of piperidino function), 4.20 (s, 1H, 4-vinylic) and 5.75 ppm (s, 1H, 6-vinylic).

17α-Allyl-3-piperidino-17α-aza-D-homo-5-androstene dimethiodide (13)

17-a-Allyl-17α-aza-D-homo-5-androsten-3one (**10**) (1g) was dissolved separately in DCM (20ml) and then piperidinoe was added to refluxing solution and refluxed for 20 min. Then added methyl iodide and refluxed for 2hrs.Solvent was evaporate the under reduced pressure. Added acetone to the residue and cooled it, filtered the product and washed with acetone and recrystalized from ethanol to give iminium product 17α-Allyl-3-piperidino-17α-aza-D-homo-5-androstene dimethiodide (**13**) via intermediate. IR (KBr): 2938.5, 1647, 1603, 1390 and 1226.3 cm^{-1}. ^1H NMR (Figure 1).

17α-Allyl-3β-piperidino-17α-aza-D-homo-5-androstene (14)

Sodium borohydride (1.0 g, 27 mmol) was added to a stirred suspension of 17α-allyl-3-Piperidino-17α-aza-D-homo-3,5-androstadiene(12) (1.0 g, 4.2 mmol) in methanol (50 ml) in small quantities during 4 hr at r.t. The reaction mixture was stirred for further 2 hrs, poured into ice cold water (500 ml) and the aqueous suspension was extracted with chloroform (4 x 100 ml). The combined chloroform extract was washed with water, dried and solvent removed under reduced pressure to give a solid residue, which was crystallized from methanol to afford 17α-allyl-3β-Piperidino-17α-aza-D-homo-5-androstene (0.7 g, 69.0%), m.pt. 130-135°C. IR (KBr): 2960.1, 2851.2, 1658.1, 1225.1 and 859.1 cm^{-1}. ^1H NMR ($CDCl_3$): In the ^1H NMR spectrum of 30 resonance signal, signal at δ 4.67 (s, 1H, 4-vinylic H) was missing.

17α-Allyl-3β-piperidino-17α-aza-D-homo-5-androstene dimethiodide (15)

Methyl iodide (0.4 ml) was added to a refluxing solution of 17α-allyl-3β-Piperidino-17α-aza-D-homo-5-androstene(10) (0.20 gm, 0.52 mmol) in absolute ethanol (10 ml) and the solution was refluxed for 1 hr. The solvent was removed under reduced pressure and the residue obtained was refluxed with dry solvent ether (50 ml) subsequently with dry acetone (25 ml). The residue obtained was crystallized from ethanol-acetone to afford (**15**) (0.19 gm, 95%), m.pt. 225-228°C. IR: strong CH stretching (CH_3) at 2924 cm^{-1} and medium peak at 1230 cm^{-1} for C-N stretching and a sharp strong peak at 1646 cm^{-1} for C=C stretching. IR (KBr): 2924, 1646, 1603, 1390, 1230, 831.2 cm^{-1}. ^1H NMR (Figure 1).

RESULTS AND DISCUSSION

Synthesis

For the preparation of these compounds, diosgenin (1) was used as starting material. (25 *R*)-5-Spirosten-3β-ol (diosgenin) (1) was subjected to Marker degradation, refluxed with acetic anhydride in pyridine in the presence of methylamine hydrochloride and the product was oxidized with chromium trioxide in acetic acid to obtain 20-Oxo-5,16-pregnadien-3β-yl acetate (16-dehydropregnenolone acetate) (2). 20-Oxo-5, 16-pregnadien-3β-yl acetate (2) was treated with hydroxylamine hydrochloride in pyridine to get the oxime, 20-oximino-5, 16-pregnadien-3β-yl acetate (3). Beckmann rearrangement of the oxime (3), thus prepared, using phosphorus oxychloride-pyridine system yielded 3a followed by acid hydrolysis gave 17-oxo-5-androsten-3β-yl acetate (4) which was converted to its oxime (5) using hydroxylamine hydrochloride and sodium acetate trihydrate in ethanol. Beckmann rearrangement of the oxime (5) was done using thionyl chloride as the catalyst, to obtain the lactam (6). The lactam (6) so obtained was reduced with sodium-pentanol to give secondary amine (7) which on moffat oxidation yielded the product (8) and on Oppenauear oxidation yielded the α,β-unsaturated ketone (9). The product 9 exhibited UV maximum at 239.0 nm indicating the prescence of enone system. The ^1H NMR spectrum of 9 exhibited the proton resonance signal at δ 5.70 (1H, 4-CH) for 3α-proton. The products 8 and 9 were treated with allyl bromide in ethyl methyl ketone in the presence of anhydrous potassium carbonate to obtain the tertiary amines 10 and 11. In infrared spectrum, band at 1673 cm^{-1} was present due to C=O stretching. The NMR spectrum exhibited the proton resonance signal at δ 4.20 (d, 1H, 4-CH) and 5.67 (m, 1H, 6-CH). The compounds 10 and 11 was refluxed with freshly distilled piperidine to get the respective enamine 12. The reduction of 12 with sodium borohydride in the presence of methanol gave the tertiary amines 14**.** Compound 12 showed a band at 1220 cm^{-1} due to C-N stretching in the IR Spectrum. The compounds 14 was quaternized by using methyl iodide in the presence of ethanol to give the final compound 15. The Compound 12 was quaternized with methyl iodide giving the final compound 13 which displayed C=N 1670.03, C=C 1484.85 cm^{-1} bands in IR spectrum (Scheme 1).

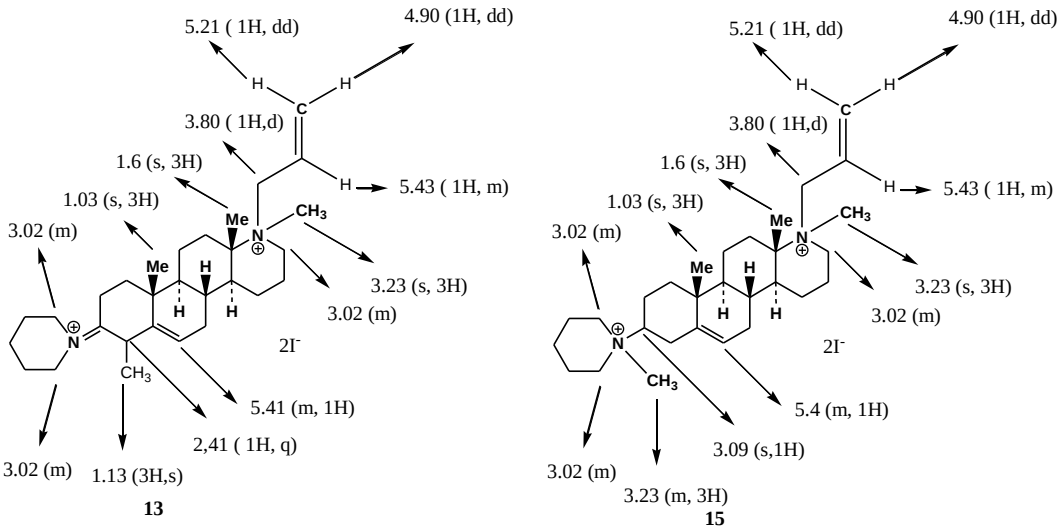
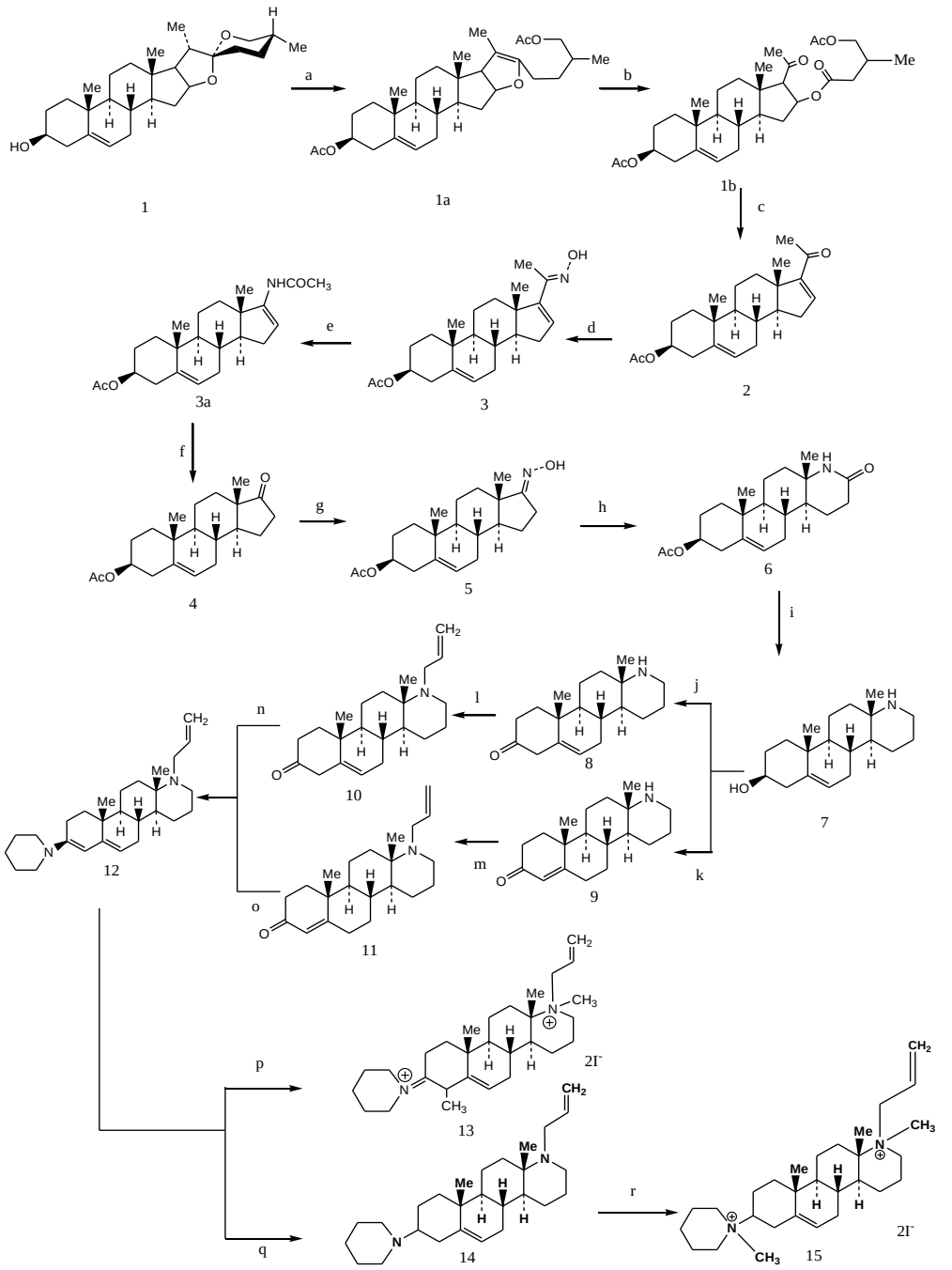


Fig. 1: It shows proton resonances of compounds 13 and 15

*Proton resonances not shown were observed as merged signals



Scheme 1: a) acetic anhydride, pyridine, methylamine hydrochloride, reflux, 10 h; b) CrO_3, acetic acid; c) acetic acid; d) pyridine, NH_2OH, reflux, 2 h; e) $POCl_3$, pyridine, stirring , 0º C; f) Conc. HCl; g) NH_2OH, CH_3COONa, reflux 2 h; h) thionyl chloride, dioxane, stirring; i) sodium pentanol reduction; j) Moffat oxidation; k) Oppenaeur Oxidation; l) allyl bromide, ethyl methyl ketone, K_2CO_3, reflux; m) allyl bromide, ethyl methyl ketone, K_2CO_3; n) DCM, piperidine, reflux 20 min; o) DCM, piperidine, reflux 20 min; p) methyl iodide, ethanol, reflux, 1 hr; q) Sodium borohydride, Methanol; r) methyl iodide, ethanol, reflux 1 hr.

CONCLUSION

The present study proposes a feasible route for the synthesis of bisquartenary azasteroids. The desired molecules have been designed keeping in view the key pharmacophoric features essential for neuromascular blocking agents. All the reaction intermediates have been characterized by spectroscopic techniques. It was found that reaction conditions required for the key steps involved in the synthetic pathway i.e. Moffat oxidation were easy to maintain and yield of product was also satisfactory.

REFERENCES

1. Zeelen F. Medicinal chemistry of steroids. Amsterdam: Elsevier; 1990.
2. Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. Cardiovasc Res 2002; 53: 688-708.
3. Latham KA, Zamora A, Drought H, Subramanian S, Matejuk A, Offner H et al. Estradiol treatment redirects the isotype of the autoantibody response and prevents the development of autoimmune arthritis. J Immunol 2003; 171: 5820-7.
4. Sheridan PJ, Blum K, Trachtenberg M. Steroid receptors and disease. New York: Marcel Dekker; 1988.
5. Ibrahim-Ouali M, Santelli M. Recent advances in thiasteroids chemistry. Steroids 2006; 71: 1025-44.
6. Ibrahim-Ouali M. Recent advances in oxasteroids chemistry. Steroids 2007; 72: 475-508.
7. Ibrahim-Ouali M, Rocheblave L. Recent advances in azasteroids chemistry. Steroids 2008; 73: 375-407.

8. Aggarwal S, Thareja S, Verma A, Bhardwaj TR, Kumar M. An reductase inhibitors overview on 5. Steroids 2010; 75: 109-153.
9. Regan BM, Hayes FN. 17- and 17α-aza-D-homosteroids. J Am Chem Soc 1956; 78: 639-43.
10. Singh H, Chaudhary AK, Bhardwaj TR, Paul D. Neuromuscular blocking agents. J Sci Ind Res 1984; 43: 306-15.
11. Jiang X, Wang J, Hu J, Ge Z, Hu Y, Hu H et al. Synthesis of (5a)-17-azaandrostan-3-ols and (5a)-17-aza-D-homoandrostan-3-ols and their N-acylated derivatives. Steroids 2001; 66: 655-62.
12. Covey DF, Han M, Kumar AS, de la Cruz MAM, Meadows ES, Hu Y et al. Neurosteroid analogues. Structure–activity studies of N-acylated 17α-aza-D-homosteroid analogues of the anesthetic steroids (3a, 5a)- and (3a, 5b)-3-hydroxypregnan-20-one. J Med Chem 2000; 43: 3201-4.
13. Wang C, Wang S, Xu Y, Hu Y, Hu H. Preparation of (5a, 13a)-D-azasteroids as key precursors of a new family of potential GABAA receptor modulators. Steroids 2003; 68: 677-83.
14. Patrick G, Kinsman O. Synthesis and antifungal activity of novel aza-D-homosteroids, hydroisoquinolines, pyridines and dihydropyridines. J Med Chem 1996; 31: 615-24.
15. Andrianopoulos C, Stephanou G, Politi E, Demopoulos NA. Evaluation and characterization of micronuclei induced by the antitumour agent ASE [3b-hydroxy-13a-amino-13, 17-seco-5a-androstan-17-oic-13,17-lactam-p-bis (2-chloroethyl) amino phenyl acetate] in human lymphocyte cultures. Mutagenesis 2000; 15: 215-21.
16. Xenos C, Camoutis C. Synthesis of A- and D-homoazasteroidal isoxazoles. J Heterocycl Chem 1999; 36: 1343-4.
17. Gupta R, Pathak D, Jindal DP. Synthesis and biological activity of azasteroidal [3, 2-c]- and [17, 16-c] pyrazoles. Eur J Med Chem 1996; 31: 241-7.
18. Taylor P. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, Editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill; 1996. p. 177-197.
19. Baird WLM, Reid AM. The neuromuscular properties of new steroid compound pancuronium bromide: a pilot study in man. Br J Anaesth 1967; 39: 775-780.
20. Speight TM, Avery GS. Pancuronium bromide: a review of its pharmacological properties and clinical application. Drugs 1972; 4: 163-226.
21. Singh H, Jindal DP, Yadav MR, Kumar M. In: Ellis GP, West GB, Editors. Progress in Medicinal Chemistry. 28th ed. Amsterdam: Elsevier; 1991. p. 233-315.
22. Singh H, Chaudhary AK, Bhardwaj TR, Paul D. Neuromuscular blocking agents. J Sci Ind Res 1984; 43: 306-315.
23. Martin-Smith M. In: Ariens EJ, Editors. Drug Design. 2nd ed. New York: Academic Press; 1971. p. 453-530.
24. Buckett WR. In: Briggs MH, Christie G, Editors. Advances in Steroid Biochemistry and Pharmacology. 3rd ed. London: Academic Press; 1972. p. 39-65.
25. Verma AK, Lee CY, Habtemariam S, Harvey AL, Jindal DP. Synthesis and biological activity of 17-azasteroidal neuromuscularblocking agents. Eur J Med Chem 1994; 29: 331-338.
26. Agoston S, Salt P, Newton D, Bencini A, Boomsma P, Erdmann W. The neuromuscular blocking action of ORG NC 45, a new pancuronium derivative, in anaesthetized patients. A pilot study. Br J Anaesth 1980; 52: 53S-59S.
27. Wierda JMKH, Beaufort AM, Kleef UW, Smeuters NJ, Agoston S. Preliminary investigations of the clinical pharmacology of three short-acting non-depolarizing neuromuscular blocking agents, Org 9453, Org 9489 and Org 9487. Can J Anaesth 1994; 41: 213-220.
28. Singh H, Paul D. Steroids and related studies. XXV. Chandonium iodide (17α-methyl-3beta-pyrrolidino-17α-aza-D-homoandrost-5-ene dimethiodide) and other quaternary ammonium steroid analogues. J Chem Soc Perkin Trans 1 1974; 12: 1475-1479.
29. Stenlake JB, Waigh RD, Urwin J, Dewar GH, Coker GG. Atracurium: conception and inception. Br J Anaesth 1983; 55: 3S-10S.
30. Gandiha A, Marshall IG, Paul D, Singh H. Neuromuscular and other blocking actions of a new series of mono and bisquaternary aza steroids J Pharm Pharmacol 1974; 26: 871-877.
31. Bowman WC, Webb SN. Neuromuscular blocking and ganglion blocking activities of acetylcholine antagonists in cat. J Pharm Pharmacol 1972; 24: 762-772.
32. Boros M, Szenohradszky J, Marosi GY, Toth I. Arzneim-Forsch. Comparative clinical study of pipecuronium bromide and pancuronium bromide. Drug Res 1980; 30: 389-393.