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SHORT PAPER

3-(3-ALKYLAMINO-2-HYDROXYPROPOXY)-DERIVATIVES OF ESTRATRIENE. SYNTHESIS AND PRELIMINARY PHARMACOLOGICAL STUDY.

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SUMMARY

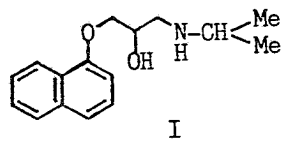
17β-hydroxy and 17-hydroxyimino derivatives of 3-(3-alkylamino-2-hydroxypropoxy)-estrone were synthesized.The title compounds were examined for β-blocking activity.

Key words: estratriene, β-adrenoreceptor blocking activity.

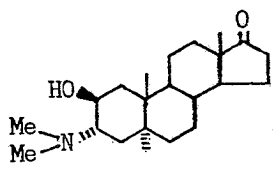
INTRODUCTION

Compounds combining an aromatic or heteroaromatic system with a 3-alkylamino-2-hydroxypropoxy moiety (the alkyl being an i-propyl or a tert-butyl group) are potent sympatholytic agents. Propranolol (I) is the most important representative of these compounds which exert their action by blocking β-adrenoreceptors and are widely used in the treatment of cardiac arrhythmias, angina pectoris etc. It has also been reported[1,2,3] that steroid derivatives bearing an aminalcohol system (II,III) have been studied for similar activity.

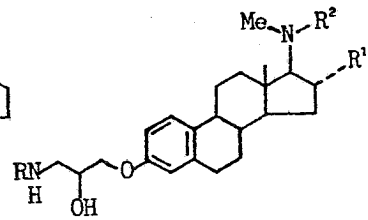
Considering the above data we synthesized derivatives of estrone coupling the propanolamine group with the aromatic ring of the steroid molecule. Our aim was the study of the biological behaviour of these compounds (*3a,3b,4a,4b,5a and 5b* , FIG. 1) which have a bulkier and more extended system in the place of the napthalene group of propranolol. We also modified the 17 ketone group of estrone to 17β alcohol and 17 oxime in order to examine if these modifications influence



I



II



III

R: i-Pr,t-Bu
R^1: H,OH
R^2: H,Me

their biological activity.

The pathways followed for the synthesis of the target compounds are depicted in FIG. 1. Estrone (*1*) was condensed with epichlorhydrine[3] in alkaline medium to yield the epoxypropyl ether *2* . The epoxide ring was opened with isopropylamine or *tert* -butylamine leading to the corresponding amino compounds *3a* and *3b* . Reduction of the latter with $NaBH_4$ in methanol gave the alcohols *4a* and *4b* .The oximes were obtained by reaction of *3a* and *3b* with $NH_2OH.HCl$ in the presence of CH_3COONa. The title compounds were purified by means of their hydrochloric salts.

EXPERIMENTAL

Melting points were determined on a Buchi capillary apparatus and are not corrected. IR spectra were recorded in Nujol on a Perkin-Elmer 177 spectrophotometer. NMR spectra were taken on a Varian EM 360A spectrometer in $CDCl_3$ containing TMS as internal standard. Elemental analyses were performed in the microanalytical laboratories of Centre National de la Recherche Scientifique (France) and of the Nuclear Research Centre "Demokritos" (Greece). The analytical results obtained were within ±0.4% of the theoretical values. Hydrochloric salts were prepared with addition of ethereal solution of HCl in solutions of the bases in absolute ethanol

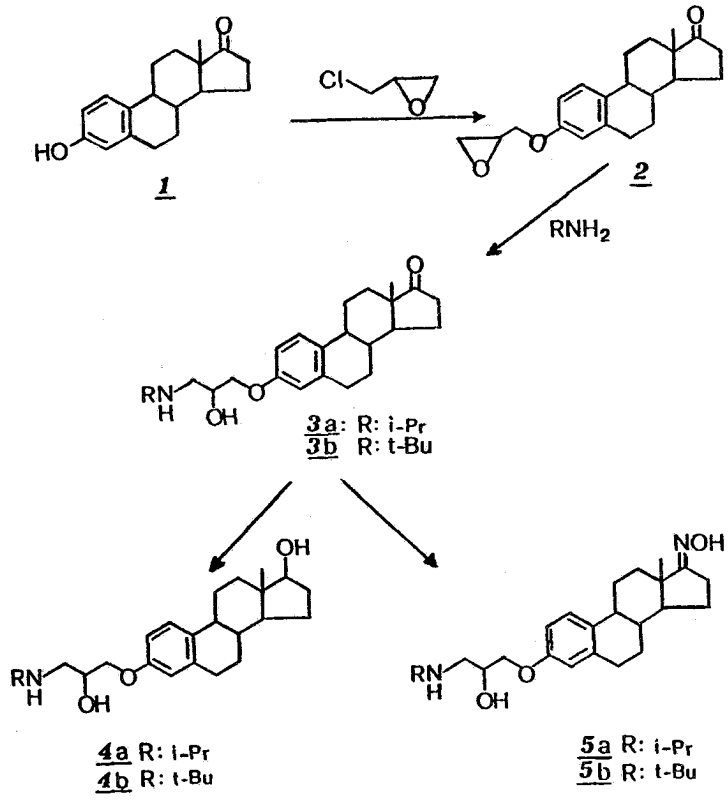


FIG. 1

and were recrystallized from absolute ethanol-anhydrous ether.

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-one , 3b .

1.65 gr (5 mmol) 3-epoxypropoxy-estra-1,3,5(10)-trien--17-one[3] was dissolved in 50 ml methanol and 3.6 gr (50 mmol) tert-butylamine were added. The mixture was refluxed for 20 h, the solvent and excess tert-butylamine were distilled off and the solid residue (1.7 gr, 85%), m.p. 125-30 °C was recrystallized twice from methanol-water and once from ethyl ether-methanol to reach a melting point of 152-53 °C. HCl salt: M.p. 211-13 °C (dec.). Elemental analysis: $C_{25}H_{39}ClNO_3$: 436 (C,H,N).

3-(3-Isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-one[3], *3a* .

Its preparation was similar to the above. HCl salt: M.p. 318-21 °C (~300 °C[3]). Elemental analysis: $C_{24}H_{36}ClNO_3$: 422·(C,H,N).

3-(3-Isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17β-ol , 4a .

In a solution of 0.96 gr (2.5 mmol) 3a in 50 ml methanol were added 0.28 gr (7.5 mmol) $NaBH_4$ and the mixture was stirred at room temperature for 1 h. Following addition of water the resulting mixture was extracted with $CHCl_3$, the chloroform layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure to give 0.77 gr (80%) of the crude base. HCl salt: M.p. 326-27 °C. Elemental analysis: $C_{24}H_{38}ClNO_3$: 424 (C,H,N).

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17β-ol , 4b .

It was prepared in a similar way from 1.2 gr (3 mmol) *4a* yielding 1.0 gr (83%) of the base, m.p. 188-90 °C. HCl salt: M.p. 254-56 °C (dec). Elemental analysis: $C_{25}H_{40}ClN_2O_3$: 438 (C,H,N).

3-(3-isopropylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-oxime , 5a .

In 20 ml ethanol were dissolved 1.93 gr (5 mmol) 3a and a solution of 1.4 gr (20 mmol) $NH_2OH.HCl$ and 3.3 gr (40 mmol) sodium acetate in 20 ml ethanol was added. The mixture was refluxed for 2h, cooled, diluted with water and extracted twice with $CHCl_3$. The chloroform layer was dried over anhydrous Na_2SO_4 and the solid residue (1.6 gr,80%),m.p. 147-50 °C was recrystallized from MeOH/n-C_5H_{12} to reach a melting point of 166-68 °C. HCl salt: M.p. 272-73 °C (dec.). Elemental analysis: $C_{24}H_{37}ClN_2O_3$:437 (C,H,N).

3-(3-tert-Butylamino-2-hydroxypropoxy)-estra-1,3,5(10)-trien--17-oxime ,5b .

It was prepared employing the same method. 1,5 gr (3,75 mmol *3b* gave 1.25 gr (80%) *5b* , m.p. 188-90 °C. HCl salt: M.p. 254-56 °C (dec.). Elemental analysis: $C_{25}H_{39}ClN_2O_3$: 451 (C,H,N).

SPECTRA

IR (cm^{-1})

3a , 3b : 3360-3260 ν(OH,NH), 1600-1560 ν(C=C), 1725 ν(C=O).
4a , 4b : 3400-3260 ν(OH,NH), 1600-1560 ν(C=C).
5a , 5b : 3480-3160 ν(OH,NH), 1600-1560 ν(C=C), 1660 ν(C=N).

NMR (d,ppm)- Bases.

3a : 0.9(s,3H,18-CH_3), 1.05 (d,6H,CH_3,i-Pr), 2.2 (t,2H,16--CH_2), 2.9-3.3(m,2H,CH_2NH), 4.0(d,2H,CH_2O), 4.5 (m,1H,CHOH), 6.6-7.2 (m,3H.aromatic).
3b : 0.9(s,H,18-CH_3), 1.45(s,9H,CH_3,t-Bu), 2.2(t,2H,16-CH_2), 3.0 (d,2H,CH_2NH), 4.0 (d,2H,CH_2O), 4.5 (m,1H,CHOH), 6.6-7.2 (m,3H, aromatic).
4a : 0.85 (s,3H,18-CH_3), 1.15 (d,6H,CH_3,i-Pr),1.6 (m,2H, 16-CH_2), 2.8-3.3 (m,3H,CH_2NCH), 3.8 (t,1H,17-CH), 4.15 (d,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).
4b : 0.9 (s,3H,18-CH_3), 1.45 (s,9H,t-Bu), 1.6 (m,2H,16-CH_2), 3.1 (d,2H,CH_2NH), 3.8 (t,1H,17-CH), 4.0 (d,2H,OCH_2), 4.5 (m,1H, CHOH), 6.6-7.2 (m,3H,aromatic).
5a : 0.9 (s,3H,18-CH_3),1.05 (d,6H,CH_3,i-Pr), 2.0 (t,2H, 16-CH_2), 2.85-3.3 (m,3H,CH_2NCH), 3.95 (m,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).
5b : 0.9 (s,3H,18-CH_3), 1.45(s,9H,t-Bu), 2.0 (t,2H,16-CH_2), 3.2 (d, 3H,CH_2NH), 3.95 (m,2H,OCH_2), 4.6 (m,1H,CHOH), 6.6-7.2 (m,3H,aromatic).

PHARMACOLOGY

β_1-Blocking activity was determined on isolated right and left atria of male guinea pig (~500 gr) using isoprenaline hydrochloride as agonist[4,5]. β_2-blocking activity was determined on isolated trachea strip of male guinea pig (400-600 gr), using methacholine chloride as spasmogen and salbutamol as agonist[6-8]. None of the tested compounds *3a,3b,4a,4b,5a* and *5b* showed significant β-blocking activity.

ΠΕΡΙΛΗΨΗ

3-(3-Αλκυλαμινο-2-υδροξυπροποξυ)-παράγωγα του οιστρατριενίου. Σύνθεση και προκαταρκτική φαρμακολογική μελέτη.

Παρασκευάστηκαν τα 17β-υδροξυ και 17-υδροξυιμινο παράγωγα της 3-(3-αλκυλαμινο-2-υδροξυπροποξυ)-οιστρόνης και μελετήθηκε η ανταγωνιστική δράση τους στους β-αδρενεργικούς υποδοχείς.

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