Novel 2'-Substituted Amino-3-methoxy-16α-bromo-17-oxoestra-3,5(10)-dieno[1,2-*b*]thiazoles

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A novel series of steroidal[1,2-*b*]thiazoles was synthesized by cyclization of several thiourea derivatives with bromine according to Hugerschoff synthesis. The H-nmr spectral analyses elucidating the structure of the products and the orientation of ring closure are reported.

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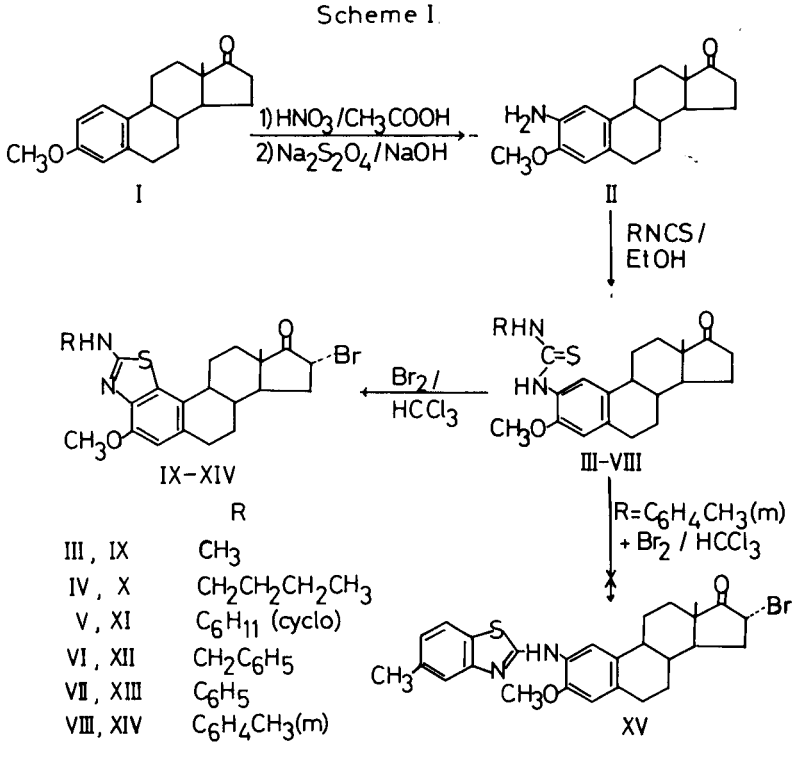
The fusion of a heterocyclic ring to the various positions of steroids has been the subject of many studies which led, in the past decades, to the development of many steroidal agents possessing diverse pharmacological activities [3-6]. Correlative with these studies, we have recently synthesized a variety of steroidal heterocycles, including estrone-2,3- and 3,4-oxazole [7] and oxazoline [8] derivatives, estrone-2 and 3-thiazolines [9] and estradiol-17α-triazolines [10], and the products were evaluated for different biological properties.

Keeping with this line of interest, in accordance with an extensive program studying the effect of structure modification on the biological activities of hormones [11-13], we here report on the synthesis and spectral analysis of novel series of steroidal[1,2-*b*]thiazoles IX-XIV, Scheme I.

2-Amino-3-methoxy-17-oxoestra-1,3,5(10)-triene (II), prepared by nitration of estrone-3-methyl ether (I) and reduction of the nitro products as reported [7,14], was reacted with the equivalent amount of alkyl, aryl and aralkylisothiocyanate in boiling ethanol to give the steroidal thioureas III-VIII in high yields. These on treatment with bromine in chloroform [15-18], according the the Hugerschoff synthesis, produced the required thiazole derivatives IX-XIV having a bromine function introduced in the 16α-position of the steroidal nucleus (Table I).

The ^{1}H-nmr spectrum of 2'-*m*-toluidino-3-methoxy-16α-bromo-17-oxoestra-3,5(10)-dieno[1,2-*b*]thiazole (XIV) indicated that the cyclization of the thiourea VIII was oriented, as in the case of other thioureas II-VII, towards the fusion of the thiazole ring to the 1,2-positions of estrone rather than to the *m*-tolyl ring to form compound XV. In this respect, the singlet around 7.3 ppm for the steroidal-C_1-proton [7] was absent, and only that for the C_4-proton was shown at 6.7 ppm. The additional signals due to the various protons of the products were identified in the expected chemical shifts (Table II). The thiazole-*N*-proton in

Scheme I



	R
III, IX	CH_3
IV, X	$CH_2CH_2CH_2CH_3$
V, XI	C_6H_{11} (cyclo)
VI, XII	$CH_2C_6H_5$
VII, XIII	C_6H_5
VIII, XIV	$C_6H_4CH_3$(m)

Scheme II

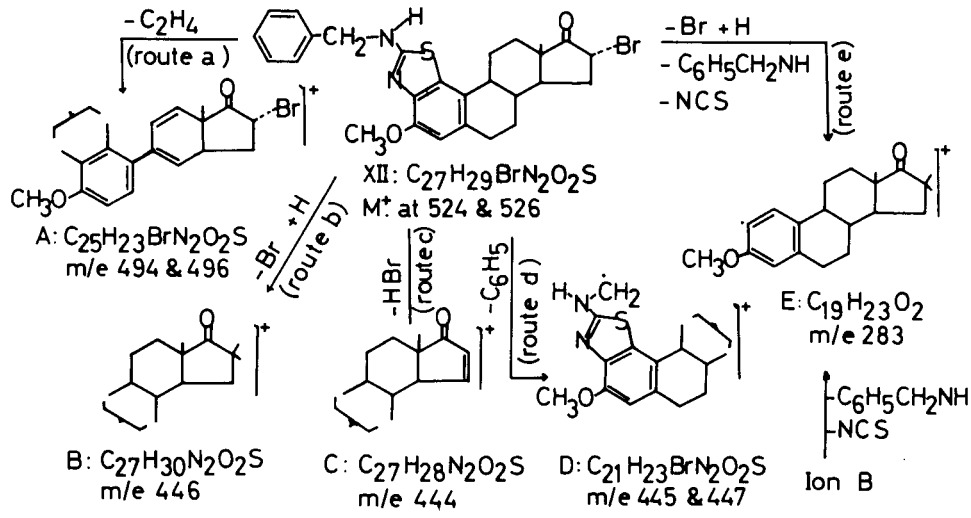


Table I

2'-Substituted Amino-3-methoxy-16α-bromo-17-oxoestra-3,5(10)-dieno[1,2-*b*]thiazoles IX-XIV

Compound No.	Yield (%)	Mp (°C)	Formula (MW)	Analysis % Calcd./(Found) C	H	N
IX	75	253-254 (S at 240) [a]	$C_{21}H_{25}BrN_2O_2S$ (449)	56.12 (59.95	5.56 5.93	6.23 6.45)
X	66	215-217 (D at 208)	$C_{24}H_{31}BrN_2O_2S$ (491)	58.65 (58.80	6.31 6.52	5.70 5.53)
XI	85	246-248 (D at 205)	$C_{26}H_{33}BrN_2O_2S$ (517)	60.34 (60.51	6.38 6.54	5.41 5.63)
XII	94	166-168 (D at 138)	$C_{27}H_{29}BrN_2O_2S$ (525)	61.71 (61.79	5.71 5.45	5.33 4.93)
XIII	60	176-178 (D at 155)	$C_{26}H_{27}BrN_2O_2S$ (511)	61.05 (60.90	5.28 5.40	5.48 5.60)
XIV	58	203-204 (S at 190)	$C_{27}H_{29}BrN_2O_2S$ (525)	61.71 (61.93	5.71 5.92	5.33 5.60)

[a] Abbreviations: S = softened and D = darkened.

Table II

^{1}H NMR Data for the 2'-Substituted Amino-3-methoxy-16α-bromo-17-oxoestra-3,5(10)-dieno[1,2-*b*]thiazoles IX-XIV

Compound	δ (Deuteriochloroform) C_{18}-CH_3	3-OCH_3	16β-H	C_4-H	2'-NH	Others
IX	0.98 (s)	3.98 (s)	4.68 (t) [a]	6.65 (s)	6.30 (s)	3.19 (s, 3H, N-CH_3)
X	1.12 (s)	3.98 (s)	4.64 (m)	6.63 (s)	5.63 (s)	0.75 (t, 3H, J = 6 Hz, Bu-CH_3), 3.41 (t, 2H, J = 6 Hz, N-CH_2)
XI	1.12 (s)	3.95 (s)	4.70 (m)	6.60 (s)	5.88 (s)	
XII	0.95 (s)	3.95 (s)	4.68 (m)	6.63 (s)	6.50 (s)	4.68 (s, 2H, CH_2), 7.4 (s, 5H, Ar-H)
XIII	0.98 (s)	3.90 (s)	4.63 (t)	6.68 (s)	7.44 (s)	7.44 (m, 5H, Ar-H)
XIV	0.98 (s)	3.90 (s)	4.60 (m)	6.70 (s)	7.40 (s)	2.48 (s, 3H, Ar-CH_3), 7.32 (m, 4H, Ar-H)

[a] J = 4 Hz.

compounds III-VI was found to be resonating at a relatively higher field (between 5.3 and 6.7 ppm) than in compounds VII and VIII when it was mixed with the aromatic protons (Table II). The mass spectrum of 2'-benzylamino-3-methoxy-16α-bromo-17-oxoestra-3,4(10)-dieno[1,2-*b*]thiazole (XII) showed the molecular ion peak at m/e 254 and

526 (for M + 2). In accordance with the ions produced under electron impact, the molecule was found to be eliminating ethylene from the steroidal skeleton [19] to produce ion **A** at m/e 494 (496), (route a), Scheme II. The cleavage of bromine (route b), hydrogen bromide (route c) or a phenyl group (roude d) from compound XII gave ion B, C, and D at m/e 446, 444 and 445 (447) respectively. The subsequent removal of the substituted thiazole ring from ion **B** gave ion **E** at m/e 283. Also identified were the different ions characteristic of the fragmentation of *N*-substituted thio-heterocycles [9,20-22]. These included the benzylisothiocyanate ion, at m/e 149, benzylamino ions, at m/e 106 and 105, benzonitrile, at m/e 103, toluene, at m/e 92, and tropylium ion as the base peak at m/e 91. The spectrum of the corresponding 2'-cyclohexylaminothiazole XI was found to follow the same pattern proposed for the fragmentation of compound XII.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were measured on a Beckman 4210 ir spectrophotometer, ^{1}H-nmr on Varian EM 360L and ms on Finnigan 3200.

N-Methyl and *N*-Cyclohexyl-*N'*-(3-methoxy-17-oxoestra-1,3,5(10)-triene-2-yl)thioureas III and V. General Procedure.

They were prepared in accordance with the general procedure reported [9] for the synthesis of compounds IV and VI-VIII, by heating, under reflux for 70 minutes, a solution of the steroidal amine II (300 mg) in absolute ethanol (15 ml) with the equivalent amount of methyl or cyclohexylisothiocyaante in 5 ml of the same solvent. The ethanol was evaporated under reduced pressure and the residue was treated with petroleum ether and scratched to deposit a solid. This was filtered and the products were crystallized from benzene/light petroleum mixture to give compounds III and V, melting at 118-120° and 126-128° and in a high yield of 99 and 91% respectively; ir (nujol): 3380-3140 (NH), 1735-1710 (C=O), 1535-1520, 1340-1310, 1190-1170 and 950-905 (N-C=S amide I, II, III and IV bands respectively) and 1290-1240 and 1080-1050 cm^{-1} (C-O-C).

Compound III.

Anal. Calcd. for $C_{21}H_{28}N_2O_2S$: C, 67.72; H, 7.58; N, 17.18. Found: C, 67.90; H, 7.80; N, 17.30.

Compound V.

Anal. Calcd. for $C_{26}H_{36}N_2O_2S$: C, 70.88; H, 8.24; N, 14.53. Found: C, 71.00; H, 8.40; N, 14.70.

2'-Substituted Amino-3-methoxy-16α-bromo-17-oxoestra-3,5(10)-dieno-[1,2-*b*]thiazoles IX-XIV. General Procedure.

To a solution of the selected thiourea derivative, III-VIII, (200 mg) in chloroform (10 ml) was added, in one portion, a solution of bromine (0.1 ml) in chloroform (2 ml). The mixture was shaken at room temperature for 5 minutes and then heated under reflux for 5 minutes. During that time, hydrogen bromide evolved and the solution acquired an orange color. The mixture was cooled to room temperature, saturated with sulfur dioxide gas, rendered alkaline with a concentrated ammonium hydroxide solution to discharge the orange color and a solid separated. The chloroform layer was treated with chloroform (15 ml) and water (15 ml), shaken to dissolve the solid, separated from the aqueous layer, washed with water (2 × 20 ml), dried (sodium sulfate) and evaporated to dryness. The oily residue was purified by elution with chloroform on a column packed with silica gel (4 g) (Kieselgel 100E, Merck, 70-230 mesh, ASTM), activated by heating at 110° for 2 hours. The combined eluates were evaporated to dryness and the residue was crystallized from chloroform/light petroleum mixture to give the products IX-XIV as white solids identified as shown in Table I; ms: m/e (relative abundance %): Compound V: 529 (54), 524 (59), 525 (24), 523 (11), 522 (14), 496 (2), 495 (4), 494 (2), 493 (3), 447 (7), 446 (22), 445 (7), 444 (14), 283 (5), 149 (7), 133 (4), 119 (3), 106 (9), 105 (5), 103 (3), 92 (10), 91 (100), 82 (16), 80 (43), 79 (16). Compound VI: 518 (95), 517 (40), 516 (100), 515 (13), 446 (10), 439 (10), 438 (35), 437 (19), 436 (71), 435 (23), 434 (74), 432 (16), 420 (8), 418 (4), 405 (9), 404 (7), 357 (7), 356 (30), 355 (9), 354 (21), 353 (21), 352 (8), 341 (5), 327 (7), 326 (4), 292 (5), 283 (4), 244 (9), 242 (8), 232 (13), 231 (9), 219 (10), 217 (9), 193 (18), 119 (7), 115 (7), 105 (7), 98 (7), 95 (8), 91 (22), 85 (8), 83 (16), 82 (27), 81 (27), 80 (30), 79 (10).

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