NEW COMPOUNDS

Steroidal Lactamquinoxalines, Lactamindoles, and Lactamthiazoles

Charalambos Camoutsis and Panayotis Catsoulacos*

Laboratory of Pharmaceutical Chemistry, University of Patras, Patras, Greece

C. I. Stassinopoulou

Department of Chemistry and Biology, Nuclear Research Center "Democritos", Athens, Greece

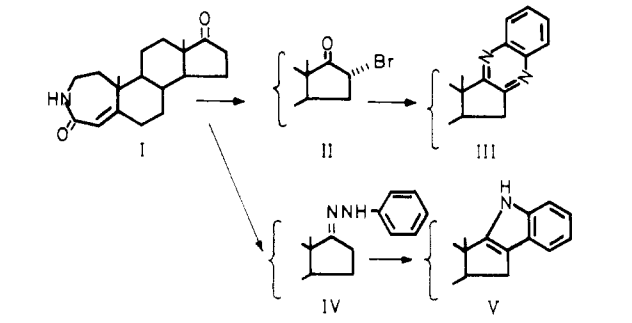
A synthetic method for the preparation of steroidal lactamquinoxalines, lactamindoles, and lactamthiazoles is described.

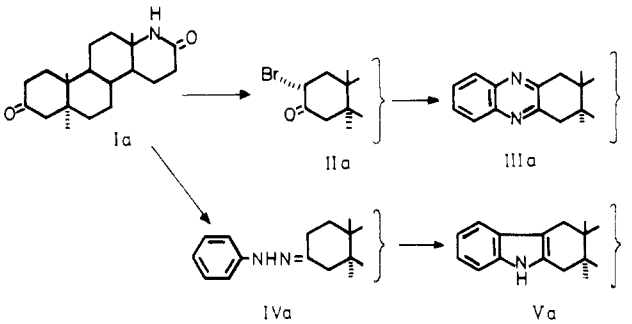
Steroidal lactams have been reported to possess unusual anticancer activity (*1*, *2*). On the other hand, steroidal quinoxaline, indole, and thiazole derivatives present biological action (*3*).

It was of interest to combine these three heterocyclic nuclei to the steroid lactam and to study their biological activity.

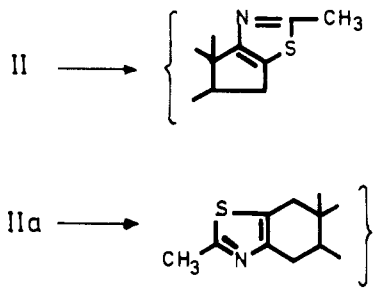
Extension of Fisher indole cyclization to ketolactam steroids with phenylhydrazine yielded the corresponding indole derivatives of A and D ring, respectively (*4*-*6*).

By condensation of 16α-bromo-3-aza-*A*-homo-4α-androsten-4,17-dione (II) and 2α-bromo-13α-amino-13,17-seco-5α-androstan-17-oic-13,17-lactam-3-one (IIa) (*7*) and the *o*-phenylenediamine by refluxing xylene according to a similar procedure (*8*), quinoxalines (III) and (IIIa) were obtained.





The condensation of 16α-bromo-3-aza-*A*-homo-4α-androsten-4,17-dione (II) and 2α-bromo-13α-amino-13,17-seco-5α-androstan-17-oic-13,17-lactam (IIa) with thioacetamide by refluxing xylene gave 2′-methylthiazolo-[5′,4′:16,17]-3-aza-*A*-homo-4α-androsten-4,17-dione (VI) and 2′-methylthiazolo[5′,4′:2,3]-13α-amino-13,17-seco-5α-androstan-17-oic-13,17-lactam (VIa), respectively.



The structures of the compounds were verified by elemental IR, UV, and NMR spectral analyses.

Experimental Section

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. The IR spectra were recorded with a Perkin-Elmer 298 in solid-phase potassium bromide. Ultraviolet spectra measured in methanol solutions on a Perkin-Elmer 551S instrument. Elemental analyses were performed by the Analytical Laboratory of Nuclear Research Center "Democritos". All of the compounds gave elemental analyses (C, H, N) within ±0.45% of the calculated values.

3-Aza-A-homo-4 α-androsten-4,17-dione [16,17-β]-quinoxaline (III). 16α-Bromo-3-aza-*A*-homo-4α-androsten-4,17-dione, mp 229–230 °C, was obtained by the reaction of I (*9*) with cupric bromide.

To a solution of 380 mg of II in 20 mL of anhydrous xylene was added 216 mg of *o*-phenylenediamine. The mixture was heated under reflux for 96 h. The solvent was evaporated under reduced pressure and the residue was dissolved in chloroform–water. The chloroform layer was washed with water and dried over magnesium sulfate. The residue was chromatographed on a column of silica gel prepared with chloroform. Elution with chloroform–methanol (95:5) gave 250 mg of III afer recrystallization from chloroform–methanol: mp >300 °C; IR, ν_{max}, 3260 (NH), 1650, 1630 (NHCO), 1600 (C=C), 780 cm^{-1} (aromatic ring); UV λ_{max} 243(ϵ=35.000), 203(ϵ=35390); NMR δ 7.88 (aromatic protons, m) 5.59 (C=CH), 1.23 (18-CH_3), 1.10 (19-CH_3).

13α-Amino-13,17-seco-5α-androstan-17-oic-13,17-lactam[2,3-β]quinoxaline (IIIa). Under the same reaction conditions as quanoxaline (III), quinoxaline IIIa in 46% yield was obtained, using as starting material bromoketone (IIa) (*7*). Recrystallization from chloroform–methanol gave IIIa, mp 269–270 °C; IR ν_{max} 765 cm^{-1} (aromatic ring); UV λ_{max} 236-

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(ε=26230); 203(ε=30590); NMR δ 7.82 (aromatic protons, m) 0.69 (18-CH_3), 1.11 (19-CH_3).

3-Aza-A-homo-4α-androsten-4,17-dione[17,16-β]indole (V). To a solution of 1.204 g of I (*9*) in 35 mL of ethanol, 0.454 g of phenylhydrazine was added. The mixture was heated under reflux for 5 h. Then, water was added and the resulting precipitate was collected by filtration to give phenylhydrazone IV with 95% yield. Recrystalization from chloroform–methanol gave IV, mp 174–176 °C.

A solution of 1.2 g of phenylhydrazone IV in 25 mL of glacial acetic acid was refluxed for 24 h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate. After evaporation of the solvent the residue was crystallized from chloroform–methanol to give 40% yield of V: mp >300 °C; IR ν_{max} 3360 (NH), 1635 (NHCO), 1600 (C=C), 740 cm^{-1} (aromatic ring); UV λ_{max} 228(ε=41.800); NMR δ 10.72 (NH), 7.48 (NHCO) 7.10 (aromatic protons m), 5.54 (C=CH), 0.75 (18-CH_3), 1.12 (19-CH_3).

13α-Amino-13,17-seco-5α-androstan-17-oic-13,17-lactam[3,2-β]indole (Va). To a solution of 1.20 g of Ia (*10*) in 25 mL of glacial acetic acid was added excess of phenylhydrazine. The mixture was heated under reflux for 24 h. After work up as for V and recrystallization from methanol, indole Va was obtained in 55% yield: mp >300 °C, ν_{max} 3400 (NH), 1640 (NHCO), 735 cm^{-1} (aromatic ring); UV λ_{max} 228(ε=11560); NMR δ 10.4 (NH), 7.10 (aromatic protons, m), 0,75 (18-CH_3), 1.12 (19-CH_3).

2′-Methylthiazolo[5′,4′:16,17]-3-aza-A-homo-4α-androsten-4,17-dione (VI). Bromoketone II (380 mg) and thioacetamide (150 mg) were added in 10 mL dimethylformamide and the mixture was heated under reflux for 2 h. Then, it was poured into ice water and the precipitate collected by filtration to give crude compound VI. This precipitate was chromatographed on a silica gel column prepared with chloroform. Elution with chloroform–methanol (98:2) gave 250 mg of VI which was recrystallized from $CH_3COOC_2H_5$: mp 264–266 °C; IR ν_{max} 3250 (NH), 1650, 1630 (NHCO), 1150 cm^{-1}; NMR δ 7.50 (NHCO), 5.52 (CH=C), 2.60 (CH_3–C–S), 0.9 (18-CH_3), 1.16 (19-CH_3).

2′Methylthiazolo[5′,4′:2,3]-13α-amino-13,17-seco-5α-androstan-17-oic-13,17-lactam (VIa). Under the same reaction conditions of VI, thiazole VIa in 40% yield was obtained, using as starting material bromoketone IIa. Recrystallization from $CH_3COOC_2H_5$–$CHCl_3$ gave VI: mp 289–291 °V; ν_{max} 3190, 3040 (NH), 1650 (CO), 1170 cm^{-1}; NMR δ 7.19 (NHCO), 2.48 (CH_3–C–S), 0.70 (18-CH_3), 1.08 (19-CH_3).

Registry No. I, 20986-87-2; Ia, 71178-08-0; II, 105431-58-1; IIa, 105431-60-5; III, 105431-59-2; IIIa, 105431-61-6; IV, 105431-62-7; V, 105431-63-8; Va, 105431-64-9; VI, 105431-65-0; VIa, 105431-66-1; *o*-phenylenediamine, 95-54-5; phenylhydrazine, 100-63-0; thioacetamide, 62-55-5.

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The Stobbe Condensation. 6. Reaction of Aryl Aldehydes with Dimethyl Adipate

Nizar El-Rayyes* and Abdel-Jabbar Al-Johary

Department of Chemistry, University of Kuwait, Kuwait

Aromatic aldehydes (Ia–h) were condensed with dimethyl adipate in the presence of sodium hydride to give the corresponding half-esters (IIIa–h). Saponification of these esters produced the dibasic acids (Va–b). The structures of all products were substantiated by chemical and spectral methods.

The Stobbe condensation with succinic esters was the subject of several studies (*1–3*). Other ester components were successfully used (*4–8*). The present work deals with the extension of the Stobbe condensation of aromatic aldehydes with a new ester component. Thus benzaldehyde and some of its derivatives as well as furan-2-carboxaldehyde and 1-naphthaldehyde were condensed with dimethyl adipate by using sodium hydride as a base, to produce the half-esters IIIa–h. The latter might have the (*E*) configuration, rather than the (*Z*) configuration (IV), due to the preferential formation of the intermediate lactone A which is free from steric and polar interactions (*9*) (Scheme I).

Table I. Melting Points and Yields of Compounds III and V

compd	mp, °C	yield, %	compd	mp, °C	yield, %
IIIa	oil	70	Va	96	95
b	165	78	b	170	97
c	oil	72	c	125	94
d	170	80	d	232	96
e	oil	75	e	150	91
f	oil	68	f	96	88
g	oil	65	g	140	93
h	100	72	h	115	90

Hydrolysis of the above half-esters gave the corresponding dibasic acids (Va–h).

The structures of the compounds III and V were evident from their spectral and chemical data (*10*, *11*) (Tables I and II). The infrared spectra of III show absorption bands in the

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