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Note

Synthesis of Some Carbamates of Steroidal Lactams and Lactones as Possible Alkylating Agents

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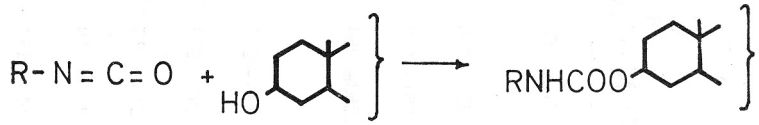
16-Oxo-17a-aza-5α-androstan-3-yl *N*-alkyl/phenylcarbamates (I—V), 16-oxo-17a-oxa-5α-androstan-3-yl *N*-ethylcarbamate (VI), 16-oxo-17a-aza-5-androsten-3-yl *N*-alkyl/phenylcarbamates (VII—IX) and 4-oxo-3-aza-A-homo-4a-androsten-17β-yl *N*-phenylcarbamate (X) were prepared by the action of substituted isocyanate on the corresponding steroidal lactams or lactone.

The fact that some carbamate derivatives of *N,N*-bis (2-chloroetyl) *p*-phenylenediamine and of *p*-(bis-2-chloroethylamino) phenol[1-3] have shown carcinostatic activity and that certain non-mustard amides of terephthalic acid possesses antitumor activity[4-6], suggested the synthesis of steroidal carbamates incorporating the lactam or lactone ring, which could have an alkylating effect[7-9].

Carbamates were prepared by treatment of steroidal lactam[10-14] or lactone[15] with substituted isocyanate in pyridine or benzene.



Some of the compounds were tested against T_8 Guerin tumor in Wistar rats, B_{16} melanoma in C57 BL mice, and Theagenion-Bahner (Th-B) angiosarcoma in C3H/b mice and they did not show significant antitumor activity.

EXPERIMENTAL

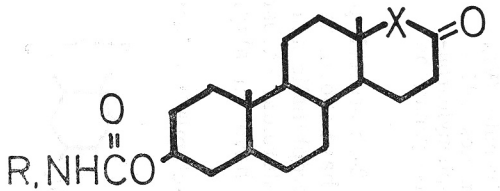
Melting points were determined on a Büchi melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. Elemental analyses were performed by the »DEMOKRITOS« Analytical Laboratory of the Chemistry Department.

General Synthetic Procedure

A. Reaction of lactams or lactone with alkylisocyanates. — To a flask containing lg of lactam[10-14] or lactone[15] in 5—10 ml of anhydrous pyridine, an excess of corresponding alkyl isocyanate (5 ml) was added and the reaction mixture was heated on a steam bath for one hour. Then the solvent and the excess of the isocyanate were evaporated under reduced pressure and ice-water was added to yield the corresponding carbamates (I—IV, VI—VIII). The compounds prepared are reported in Table I.

TABLE I

Carbamates of steroidal lactams and lactones



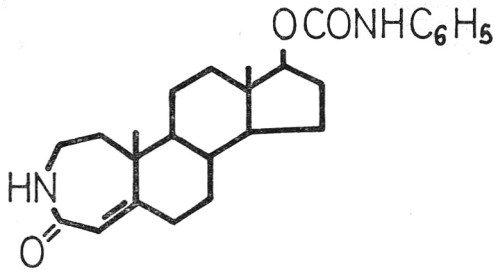
Compound	R	X	M.p. °C	Solv. Recr.	Formula	Yield %	Anal. Calc'd	Anal. Found	
							C	H	N
I	CH_3CH_2, 5α	NH	269—270	$CH_3COOC_2H_5$	$C_{22}H_{36}N_2O_3$	75	70.17 69.94	9.64 9.81	7.44 7.32
II	$CH_3CH_2CH_2$, 5α	NH	251—253	,,	$C_{23}H_{38}N_2O_3$	71	70.74 70.60	9.81 9.69	7.17 7.38
III	CH_3—CH(CH_3), 5α	NH	253—254	,,	$C_{23}H_{38}N_2O_3$	70	70.74 70.83	9.81 10.00	7.17 7.10
IV	$CH_3CH_2CH_2CH_2$, 5α	NH	230—231	,,	$C_{24}H_{40}N_2O_3$	50	71.26 71.49	9.97 9.98	6.92 7.14
V	C_6H_5, 5α	NH	273—275	,,	$C_{26}H_{36}N_2O_3$	60	73.58 73.90	8.49 8.70	6.60 6.90
VI	CH_3CH_2, 5α	O	215—217	,,	$C_{22}H_{35}NO_4$	55	69.98 69.76	9.35 9.11	3.72 4.00
VII	$CH_3CH_2CH_2$, Δ^5*	NH	217—219	,,	$C_{23}H_{36}N_2O_3$	71	71.10 70.96	9.34 9.57	7.21 7.12
VIII	$CH_3CH_2CH_2CH_2$, Δ^5	NH	143—144	,,	$C_{24}H_{38}N_2O_3$	47	71.61 71.58	9.51 9.44	6.96 7.05
IX	C_6H_5, Δ^5	NH	260—262	$CHCl_3$—$CH_3COOC_2H_5$	$C_{26}H_{34}N_2O_3$	70	73.93 73.29	8.05 7.80	6.63 7.06

* Δ^5 means the corresponding 5-androsten

B. *Reaction of lactams with phenylisocyanate.* — 2 mmoles of lactam were dissolved in 30 ml of anhydrous benzene and 4 mmoles of phenylisocyanate were added. The mixture was heated under reflux for 24 hours. Then the solvent was evaporated under reduced pressure and the residue was recrystallized from an appropriate solvent.

The compounds prepared are reported in Table I.

4-Oxo-3-aza-A-homo-4a-androsten-17β-yl-N-phenylcarbamate (X)



This compound was obtained in 65% yield, m.p. 190—192 °C from $CH_3COOC_2H_5$.

Anal. $C_{26}H_{34}N_2O_3$ (422) calc'd.: C 73.93; H 8.05; N 6.63%
found: C 73.81; H 8.40; N 6.50%

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SAŽETAK

Sinteza nekih karbamata iz steroidnih laktama i laktona kao mogućih alkilirajućih agensa

E. Souli i P. Catsoulacos

Reakcijom steroidnih laktama i laktona sa supstituiranim izocijanatima sintetiziran je niz steroidnih karbamata. Ispitana je antitumorska aktivnost dobivenih spojeva.

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