Heterocyclic Steroids. II. Synthesis of Some Spiro Derivatives of 7,8-Diaza-11-Oxasteroids

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A simple, one step conversion of aldol adducts **1** derived from cyclic 1,2,3-tricarbonyl compound with 1,3-cycloalkanediones into title compounds **2** is described.

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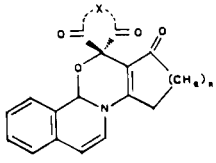
Heterosteroids have been an ongoing concern of many investigators in view of their potential biological activities [1]. Hundreds of nucleo-heterosteroids have been synthesized and among them nucleo-aza [2,3] and nucleo-oxa [4,5] heterosteroids have been more extensively studied. An examination of the existing literature however, indicates that, with few exceptions (see for instance [6,7]), the introduction of nitrogen atom(s) within the cyclopentaneperhydrophenanthrene nucleus led to the loss of the hormonal activity whereas the introduction of oxygen(s) atoms led sometimes to hormonally active compounds having usually a decreased endocrine activity. Nevertheless, research in the field is still very active because several different pharmacological activities have been found in oxa and aza-steroid derivatives [1].

Recent articles on the synthesis and promising pharmacological properties of nucleo-heterosteroids containing both nitrogen and oxygen atoms [8-10] prompted us to report a simple route to 8-aza-11-oxasteroids **1** containing a new oxazasteroid ring systems [11].



1

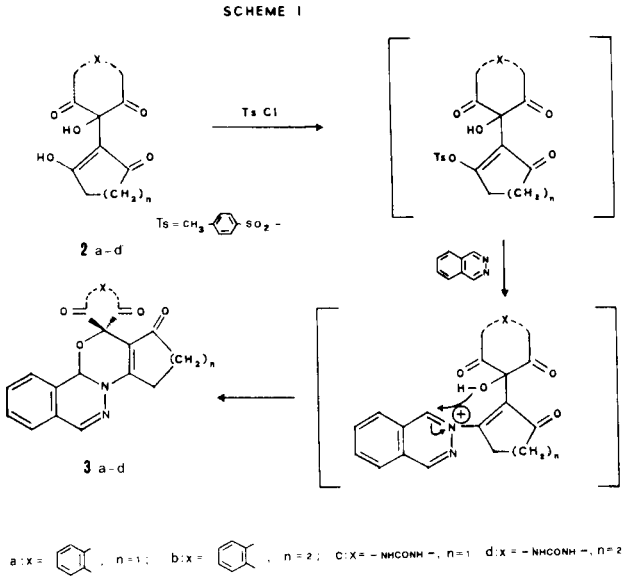
Figure 1

Such a synthesis was accomplished by applying a convenient method we described for the preparation of pyridooxazine derivatives [12].

Now we wish to report a further application of this reaction leading to 12-spiro derivatives **3a-d** of two new oxazasteroid skeletons: 7,8-diaza-11-oxa-17-oxogona and D-homogona-1,3,5(10),6,13-pentaene. Compounds **3a-d** were prepared by reacting aldol adducts **2** [11] with tosyl chloride and phthalazine according to Scheme 1.

Phthalazine has been successfully applied as an A-B ring segment synthon whereas in the same experimental conditions our attempts with other heteroatomic bases like quinoxaline, quinazoline and 1,6-naphthyridine failed.

SCHEME I



The main advantage of our route to oxazasteroids is that, by using easily obtainable starting materials, heterosteroid ring systems **1** and **3** are produced in one-step in good yields through a sequence of three consecutive reactions outlined in Scheme I.

In contrast the construction of a heterosteroid ring skeleton very often requires a multistep sequence with a very low overall yield. However, more recently new and simpler approaches to the synthesis of heterosteroids have been developed especially in the field of 8-azasteroids. By using 1,2-dihydroisoquinoline derivatives as the precursor of the A-B ring system, 8-azasteroids in which the B ring is fully saturated have been prepared in high yields [13]. Our efforts to similarly use 1,2-dihydroisoquinoline instead of isoquinoline in the preparation of 8-aza-11-oxasteroids **1** have not, however, been successful.

In view of the potential biological activities of **3** we also began preliminary pharmacological screening on some of them but unfortunately the results obtained so far are not very satisfying.

Compound **3d** possesses only a borderline reflex depression and a very weak diuretic effect whereas a weak

Table 1

Physical Analytical and Spectroscopic Data of 7,8-Diaza-11-oxasteroids **3a-d**

Compound	Mp, °C (Crystallization solvent)	Formula	Analysis, % Calcd./Found C	H	N	IR (potassium bromide discs) ν max, cm^{-1}	^{1}H-NMR DMSO-d_6, δ (ppm), J (Hz)
3a	272-276 dec (Chloroform-hexane)	$C_{22}H_{14}N_2O_4 \cdot H_2O$	68.03 68.00	4.15 3.76	7.21 7.01	1750, 1710, 1630, 1595, 1565	240 (m, 2H, CH_2-C=C, part masked), 3.05 (m, 2H, CH_2-CO), 7.08 (s, 1H, H-9), 7.53 (m, 4H arom A-ring), 7.86 (s, 1H, H-6), 8.10 (m, 4H, arom indane)
3b	295-297 dec (Aqueous DMSO)	$C_{23}H_{16}N_2O_4$	71.87 71.70	4.20 4.09	7.29 7.23	1750, 1710, 1630, 1585, 1560	1.8-2.2 (m, 4H, CH_2-CH_2-C=C), 2.7-3.2 (m, 2H, CH_2-CO), 6.70 (s, 1H, H-9), 7.50 (m, 4H, arom A-ring), 7.80 (s, 1H, H-6), 8.0 (m, 4H, arom indane)
3c	>360 dec (Aqueous DMSO)	$C_{17}H_{12}N_4O_5$	57.96 58.30	3.43 3.28	15.90 15.61	3220, 3060, 1760, 1720, 1700, 1660, 1635, 1580, 1550	2.2-2.6 (m, 2H, CH_2-C=C, part masked), 2.8-3.1 (m, 2H, CH_2-CO), 7.08 (s, 1H, H-9), 7.55 (m, 4H, arom), 7.85 (s, 1H, H-6), 11.70 (s, 2H, NH)
3d	305-310 dec (Dioxane-hexane)	$C_{18}H_{14}N_4O_5$	59.01 59.37	3.85 3.56	15.29 15.07	3280, 3100, 1770, 1730, 1710, 1640, 1590, 1550	1.8-2.3 (m, 4H, CH_2-CH_2-C=C), 2.7-3.2 (m, 2H, CH_2-CO), 6.70 (s, 1H, H-9), 7.55 (m, 4H, arom), 7.82 (s, 1H, H-6), 11.80 (s, 2H NH)

[a] Only the most significant and intense absorption bands are reported.

locomotion activity stimulation associated with a mild action at the DOPA level has been found in compound **3b**. No endocrine activity has been detected.

The very poor solubility of the compounds tested might cause a very low bio-availability and thus biological activities could be lowered or at least partially masked.

Furthermore, the presence of very bulky spiro-substituents might prevent the binding to steroid receptors and thus the lack of any endocrine activity.

On the basis of these considerations our efforts now are directed to the synthesis of more hydrophilic compounds possibly without spiro substituents.

EXPERIMENTAL

Melting points were determined by the capillary method on an electrically heated melting point apparatus (Mark II, Electrothermal) and are uncorrected. Elemental analysis were made by the technical staff of our department using a Hewlett-Packard 185 C, H, N autoanalyzer. The ir spectra were recorded as potassium bromide pellets on a Perkin-Elmer model 283 spectrophotometer. The pmr spectra were taken on a Varian EM 390, 90 MHz instrument using tetramethylsilane as internal standard. Exchange with deuterium oxide was used to identify NH protons.

Preparation of 12-Spiro-7,8-diaza-11-oxo-17-oxogona-1,3,5(10),6,13-pentaene Derivatives **3a-d**.

General Procedure.

Tosyl chloride (0.42 g, 2.2 mmoles) was added to a stirred solution of **2** (2 mmoles) and phthalazine (0.52 g, 4 mmoles) in 2-3 ml of dry dioxane. After 8-10 hours stirring the reaction mixture was poured on ice and the precipitate was collected, washed with water and recrystallised to give **3a** and **3c** in 89% and 79% yield respectively. Compounds **3b** and **3d** were obtained in 88% and 80% yield respectively by the following slight modification of the experimental conditions of the general procedure. The reaction mixture was heated with stirring for 3-4 hours at 55-60° and worked-up as described above.

Physical, analytical and spectroscopic data of compounds **3** are listed in Table 1.

Acknowledgement.

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