SYNTHESIS OF ISOXAZOLINE AND AMINOISOXAZOLINE DERIVATIVES OF STEROIDS. A STUDY OF THE REACTIONS OF FORMAMIDE AND UREA WITH DERIVATIVES OF THE 17α-HYDROXYPREGNANE SERIES

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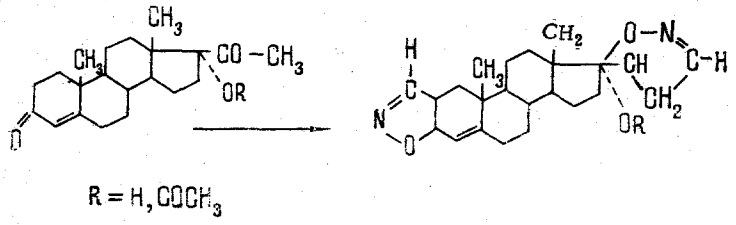
In the last two decades, the search for biologically active steroids has developed in the direction of seeking heterocyclic steroid derivatives. In view of the fact that isoxazoline and its derivatives form the basis of a series of biologically active compounds, and steroid isoxazoles have found practical use as anabolic drugs [1], it appeared of interest to develop a method for synthesizing such derivatives among steroids of the pregnane series.

Steroid isoxazolines can be synthesized by the reaction of hydroxylamine and steroid hydroxy ketones [2], by the action of hydroxamoyl halides on α,β-saturated steroid ketones [3], or by the reaction of formamide with steroid ketones [4]. Among pregnane derivatives, steroid isoxazoline compounds in which an isoxazoline ring is condensed with a steroid molecule have been obtained by the reaction of pregn-16-en-zo-one with ethyl cyanoformate oxide [5, 6].

We have investigated the possibility of obtaining isoxazoline and aminoisoxazoline derivatives by the reaction of formamide and of urea with 17α-hydroxyprogesterone, its Δ^6-dehydrogenated derivative, and their 17α-acyl derivatives under conditions analogous to those described previously [4].

We have shown that in the presence of hydrochloric acid this reaction with formamide takes place with the formation of a diisoxazoline derivative in which one isoxazoline ring is condensed with ring A or the steroid skeleton, and the other is attached as a residue at C_{17} (Scheme 1). The reaction at derivatives dehydrogenated at C_6 takes place similarly (Table 1).



R = H, $COCH_3$

Scheme 1

Thus, both the C_{21} methyl group and a methylene group in ring A and the corresponding carbonyl groups take part in the condensation reaction, derivatives of the androstane series being formed from pregnane compounds.

The reaction with 17α-hydroxyprogesterone and its Δ^6-dehydrogenated derivative and their 17α-O-acylated derivatives with urea took place differently. If the reaction was performed in an aprotic solvent (β-methylnaphthalene) in the absence of acid catalysts, even under very severe conditions (200-210°C) only one molecule of urea reacted, with the formation of 5'-aminopregnano[3,2-d]-isoxazolines, i.e., under these conditions the acyl group at C_{17} did not take part in the reaction (Scheme 2).

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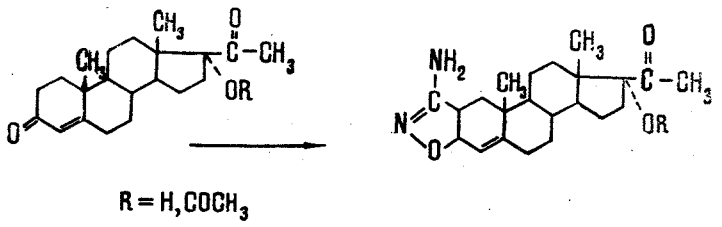

Scheme 2

The reaction with its Δ^6-dehydrogenated derivative took place similarly (Table 2).

The structures of the steroid isoxazolines and 5'-aminopregnanoisoxazolines synthesized were shown on the basis of their elementary analyses and IR spectra in which absorption bands characteristic for the given groupings as described in the literature [7] were observed (Tables 1 and 2).

TABLE 1. Di-isoxazoline Derivatives of the Androstane Series

Compound	Yield, %	mp, °C	Emperical formula	IR spectrum, cm⁻¹			
				OH	C=N	C=O	isoxazoline ring
I.. 17α-Hydroxy-17β-isoxazolyl-androst-4-eno [3,2-d]isoxazo-line	42,0	218—220	$C_{28}H_{32}N_2O_3$	3300	1560	—	1650, 1510, 1450, 1130
II. 17α-Hydroxy-17β-isoxazol-ylandrosta-4, 6-dieno[3,2-d]isoxazoline	34,5	140—144	$C_{23}H_{30}N_2O_3$	3310	1540	—	1650, 1510, 1115
III. 17α-Acetoxy-17β-isoxazol-ylandrost-4-eno[3,2-d] isoxazoline	40,0	160—164	$C_{25}H_{34}N_2O_4$	—	1540	1720	1650, 1450, 1510, 1115
IV. 17α-Acetoxy-17β-isox-azolylan-drosta-4,6-dieno[3,2-d] isoxazoline	26,0	155—158	$C_{25}H_{32}N_2O_4$	—	1580	1730	1660, 1510, 1450, 1120

TABLE 2. Aminoisoxazoline Derivatives of the Pregnane Series

Compound	Yield, %	mp, °C	Emperical formula	IR spectra, cm⁻¹				
				NH_2	OH	C=O	C=N	isoxazole ring
V. 5'-Amino-17α-hydroxy--20-oxo-pregn-4-eno[3,2-d] isoxazoline	30	356—360	$C_{22}H_{32}N_2O_3$	3300, 3220	3410	1730	1560	1640, 1520, 1450, 1430, 1180
VI. 17-Acet-oxy-5'-amino-17α-hy-droxy-20-oxopregna--4,6-di-eno[3,2-d] isoxazoline	54	153—155	$C_{24}H_{32}N_2O_4$	3250	3410	1730	1590	1660, 1540, 1450, 1180, 1155

EXPERIMENTAL

The analyses of the compounds obtained corresponded to the calculated figures.

17α-Hydroxy-17β-isoxazolylandrost-4-eno[3,2-d]isoxazoline (I). A mixture of 0.5 g of 17α-hydroxyprogesterone, 3 ml of formamide, and 1 ml of 70% of perchloric acid was heated at 200-210°C for 5 h. The residue was dissolved in 20 ml of chloroform, 10 ml of 25% ammonia solution was added, and the volatile substances were distilled off with steam. The product that separated out was filtered off and was heated in methanol. The insoluble residue was separated off. The filtrate yielded 0.25 g of 17α-hydroxy-17β-isoxazolylandrost-4-eno[3,2-d]-isoxazoline (I) with mp 218-220°C (42% of theoretical).

The following compounds were obtained similarly: 17α-hydroxy-17β-isoxazolylandrosta-4,6-dieno[3,2-d]isoxazoline (II), 17α-acetoxy-17β-isoxazolyl-androst-4-eno[3,2-d]isoxazoline (III), and 17α-acetoxy-17β-isoxazolylandrosta-4,6-dieno[3,2-d]isoxazoline (IV) (see Table 1).

5'-Amino-17α-hydroxy-20-oxopregn-4-eno[3,2-d]isoxazoline (V). A mixture of 0.5 g of 17α-hydroxyprogesterone, 3 g of urea, and 10 g of β-methylnaphthalene was heated at 200-210°C for 5 h. After cooling, the β-methylnaphthalene was distilled off from the reaction mixture with steam. The isolated product was purified by crystallization from methanol. This gave 0.2 g of 5'-amino-17α-hydroxy-20-oxopregn-4-eno-[3,2-d]isoxazoline (V) with mp 356-360°C (30% of theoretical).

17α-Acetoxy-5'-amino-20-oxo-4,6-dieno[3,2-d]isoxazoline (VI) was obtained similarly (Table 2).

SUMMARY

1. A method of synthesizing di-isoxazoline derivatives of the androstane series in which one of the isoxazoline rings is condensed with ring A of the steroid skeleton and the second is attached in the form of a residue at C_{17} by the reaction of 17α-hydroxyprogesterone derivatives with formamide has been developed.

2. It has been shown that the reaction of 17α-hydroxyprogesterone derivatives with urea forms only 5'-aminopregnano[3,2-d]isoxazolines. Under the given conditions of synthesis, the 17β-acyl group does not react with urea.

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