TRANSFORMED STEROIDS

COMMUNICATION 80*. NUCLEOPHILIC ADDITION TO ISOMERIC STEROIDAL ARYLAZOOLEFINS

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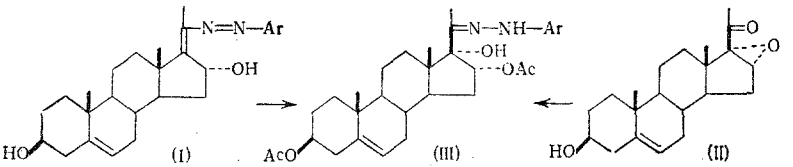
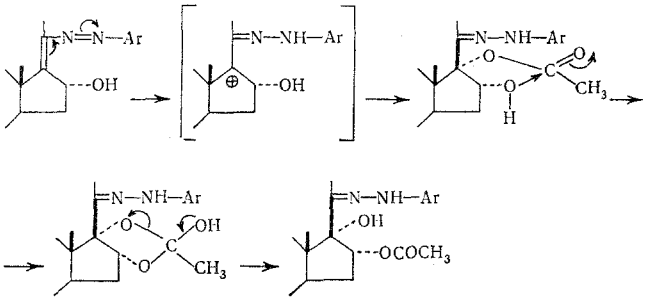
UDC 542.91:547.92

Steroidal arylazoallyl alcohols in the presence of strong acids are isomerized to the arylhydrazones of enols, which then cyclize to steroidal pyrazoles [2, 3]. At the same time, the treatment of 20-phenylazopregna-5,17(20)-diene-3β,16α-diol with AcOH under the conditions for the cis-opening of ketooxide hydrazones [4] did not lead to the cis-diol derivatives. This confirmed the assumption that the cis-opening of ketooxide hydrazones does not proceed via the azoolefin structure. A nucleophilic reagent could be added to the azoolefin only on the example of the p-nitrophenyl derivative by treating 20-p-nitrophenylazopregna-5,17(20)-diene-3β,16α-diol (I) [2] with AcONa in AcOH. The pregn-5-ene-3β,16α,17α-triol-20-one 3,16-diacetate 20-p-nitrophenylhydrazone (III) formed after acetylation proved to be identical with that obtained by the cis-opening of 16α,17α-epoxypregn-5-en-3β-ol-20-one (II).



Ar = $C_6H_4NO_2$

As a result, the electron-acceptor effect of the p-nitro group in the phenyl ring facilitates the 1,4-addition of the elements of AcOH, with the initial insertion of acetate ion at C-17 from the α-region of the steroid molecule and subsequent acyl migration to C-16.



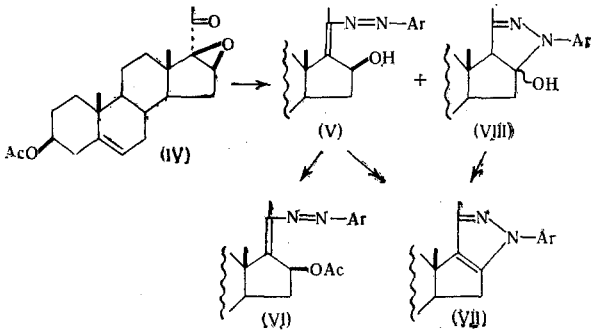
In order to make a comparative study of the reactivity of the isomeric ketooxides of steroids it seemed of interest to follow the behavior of 16β,17β-epoxy-17α-pregnane compounds under the described conditions.

It proved that the reaction of β-oxide 3-acetate (IV) with p-nitrophenylhydrazine in ethanol in the presence of AcOH is not as well defined as for the 16α,17α-oxide, and leads to a mixture of two principal compounds. The mixture was separated by thin-layer chromatography on Al_2O_3: separation of the mixture on SiO_2 causes the transformation of one of the components. By analogy with the reaction product of the 16α,-17α-oxide, the compound that was obtained as bright orange crystals was assigned the structure of 20-p-nitrophenylazopregna-5,17(20)-diene-3β,16β-diol 3-acetate (V), which was confirmed by a number of transformations. 16β-Hydroxyazosteroid (V) is acetylated under the usual conditions to give 20-p-nitrophenyl-

*See [1] for Communication 79.

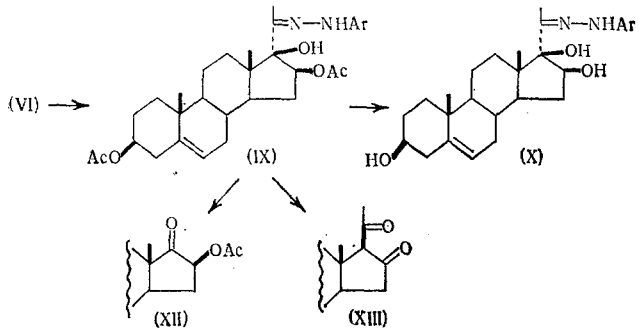
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6, pp. 1353-1357, June, 1976. Original article submitted June 16, 1975.

azopregna-5,17(20)-diene-3β,16β-diol 3,16-diacetate (VI), while in the presence of strong acids, similar to the 16α-epimeric azoolefin, it is easily converted to the previously obtained [2] p-nitrophenylmethylpyrazole 3-acetate (VII). The second, bright yellow compound proved to be the product of the further transformations of (V), and it was assigned the structure of 1'-p-nitrophenyl-3'-methyl-5'-hydroxyandrost-5-en-3β-ol[16, 17-c]pyrazoline 3-acetate (VIII). The cyclic, and not the hydrazone structure of the latter was confirmed by its stability under the conditions of forming the azoolefin, and also by the easy conversion to pyrazole (VII).



As a result, the arylazoolefin obtained from the 16β,17β-epoxide is much more inclined to cyclize than the azoolefin from the 16α,17α-epoxide.

The treatment of (V) with AcONa in AcOH does not lead to the addition of the elements of AcOH, and instead causes intramolecular cyclization with the formation of hydroxypyrazoline (VIII). The cyclization could be avoided by running the same transformation with the 16β-hydroxyazoolefin 16-acetate (VI). Only one compound was obtained here, which, on the basis of the physicochemical analysis data and the chemical transformations, was assigned the structure of 17α-pregn-5-ene-3β,16β,17β-triol-20-one 3, 16-diacetate 20-p-nitrophenylhydrazone (IX).



Compound (IX) does not coincide with the authentic pregn-5-ene-3β,16α,17α-triol-20-one (III) and pregn-5-ene-3β,16β,17α-triol-20-one (XI) 3,16-diacetates 20-p-nitrophenylhydrazones. The IR spectrum of (IX) resembles the IR spectra of hydrazones (XI) and (III). The mild hydrolysis of (IX) leads to the diol hydrazone (X), whose IR spectrum lacks a CO group, which indicates the absence of an acetate group in the tertiary 17-position. At the same time, the molecular weight of diol hydrazone (X), determined by mass spectrometry, M^+ = 483 m/e, corresponds to the calculated value. A comparative examination of the NMR spectra of compounds (IX), (III), and (XI) confirms the structure assigned to hydrazone (IX), and also indicates the presence of a 17α-side chain in this structure. Thus, the signal of the 21-CH_3 group in the NMR spectrum of (IX) is found downfield (2.03 ppm) when compared with the corresponding signals in the spectra of the authentic hydrazones of cis-diacetate (III) (1.90 ppm) and trans-diacetate (XI) (1.84 ppm). Such a signal from the protons of the 21-CH_3 group is characteristic for compounds of the isopregnane series [5]. Finally, the treatment of the 3,16-diacetate p-nitrophenylhydrazone (IX) with $Pb(AcO)_4$ leads, as was shown in [6], to the elimination of the side chain and the formation of androst-5-ene-3β,16β-diol-17-one 3,16-diacetate (XII), which is identical with an authentic specimen [7]. The last transformation proves the 16β-configuration of the acetate group in hydrazone (IX), and consequently also its structure.

The treatment of diacetate hydrazone (IX) with acetylacetone in AcOH, i.e., under the conditions of removing the hydrazone protection, does not lead to the desired ketone diacetate, but only to the 16,20-diketone 3-acetate (XIII), which coincides with an authentic specimen [8].

As a result, the obtained experimental data show that the spatial structure of arylazoallyl alcohol (V),

or of the intermediate compound formed by its protonation, is incapable of adding a nucleophilic reagent from the α-region. Approach to C-17 from the β-region of the molecule is sterically hindered, and such attack can be realized only intramolecularly. These data corroborate the previously expressed [9] considerations regarding the mechanism of the involvement of the hydrazone fragment in reactions of the adjacent center.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra were taken on a UR-10 instrument in KBr. For the TLC we used KSK silica gel deposited on microplates, and for the development we used a solution of vanillin in H_2SO_4 and I_2 vapors. The NMR spectra were taken on a Varian spectrometer at an operating frequency of 60 MHz.

20-p-Nitrophenylazopregna-5,17(20)-diene-3β,16β-diol 3-acetate (V) and 1'-p-nitrophenyl-3'-methyl-5'-hydroxyandrost-5-en-3β-ol[16,17-c]pyrazoline 3-acetate (VIII). To a solution of 2 g of β-oxide 3-acetate (IV) in 60 ml of alcohol was added a solution of 2 g of p-nitrophenylhydrazine in 80 ml of alcohol and 12 ml of AcOH, and the mixture was let stand at ~20°C for 3 h. Then the mixture was diluted with water and the obtained precipitate was filtered, washed with water, and dried. The obtained mixture was separated by preparative TLC on Al_2O_3 in the system: 4:1 ether–hexane, and then in ether. We obtained: a) 500 mg of the 16β-hydroxyazoolefin 3-acetate (V), mp 119-120° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1525, 1730, 3400-3470. Found: C 68.80; H 7.91; N 7.64%. $C_{29}H_{37}N_3O_5$. Calculated: C 68.64; H 7.30: N 8.27%. b) 880 mg of the p-nitrophenylhydroxypyrazoline 3-acetate (VIII), mp 216-218°. Infrared spectrum (ν, cm^{-1}): 1490, 1510, 1595, 1720, 3480.

1'-p-Nitrophenyl-3'-methylandrost-5-en-3β-ol[16,17-c]pyrazole 3-acetate (VII). A solution of 200 mg of the hydroxypyrazoline (VIII) in 10 ml of abs. dioxane and 0.92 ml of conc. H_2SO_4 was kept at ~20° for 5 h. The reaction mass was diluted with water, and the obtained precipitate was filtered, washed with water, and dried. We obtained 180 mg of the p-nitrophenylpyrazole (VII), mp 251-252° (from aqueous acetone), which did not depress the mixed melting point with an authentic specimen [2].

A solution of 60 mg of the 16β-hydroxyazoolefin 3-acetate (V) in 3 ml of anhyd. AcOH was let stand overnight at 20°. The mixture was diluted with water, and the obtained precipitate was filtered, washed with water, and dried. The obtained yellow precipitate was dissolved in dioxane, treated with five drops of HCl, and let stand overnight at 20°. After the usual workup we obtained 32 mg of the p-nitrophenylpyrazole (VII), mp 251-252° (from aqueous acetone), which coincided with an authentic specimen.

Pregn-5-ene-3β,16α,17α-triol-20-one 3,16-diacetate 20-p-nitrophenylhydrazone (III). A solution of 200 mg of the p-nitrophenylazo-16α-hydroxyolefin (I) [2] and 200 mg of AcONa in 10 ml of AcOH was let stand at 20° for 2 h. The mixture was diluted with water, and the obtained yellow precipitate was filtered, washed with water, and dried. After acetylation with 5 ml of pyridine and 2.5 ml of Ac_2O we obtained 120 mg of the diacetate p-nitrophenylhydrazone (III), mp 233-235° (from aqueous MeOH), which coincided with the above-obtained sample.

To a solution of 500 mg of the 16α,17α-oxide (II) in 10 ml of AcOH was added a solution of 500 mg of p-nitrophenylhydrazine and the mixture was let stand overnight at ~20°. After the usual workup we isolated 350 mg of yellow crystals (from aqueous MeOH), the acetylation of which gave 270 mg of the diacetate hydrazone (III), mp 233-235° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1508, 1600, 1718, 1735, 3315, 3415-3540. NMR spectrum (δ, ppm): 0.60 (18-CH_3), 0.93 (19-CH_3), 1.90 (21-CH_3), 1.94, 1.98 (CH_3COO at 3-C and 16-C), 1.73 (OH at 17-C), 4.51 (H at 3-C), 5.28 (H at 6-C), 6.16 (H at 16-C), 7.66 (H at N), 6.86-8.11 (multiplet of aromatic protons).

20-p-Nitrophenylazopregn-5,17(20)-diene-3β-diol 3,16-diacetate (VI). A solution of 370 mg of the 16β-hydroxyazoolefin (V) in 4 ml of pyridine and 2 ml of Ac_2O was let stand overnight at 20°. After the usual workup we obtained 325 mg of the azohydroxyolefin diacetate (VI), mp 176-177° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1230-1250, 1343, 1375, 1445, 1525, 1728. Found: N 7.61%. $C_{31}H_{39}O_6N_3$. Calculated: N 7.35%.

17α-Pregn-5-ene-3β,16β,17β-triol-20-one 3,16-diacetate 20-p-nitrophenylhydrazone (IX). A solution of 200 mg of the azoolefin diacetate (VI) and 200 mg of AcONa in 10 ml of AcOH and 1 ml of Ac_2O was let stand overnight at 20°. Then the mixture was diluted with water, and the obtained yellow precipitate was filtered, washed with water, and dried. We obtained 165 mg of the diacetate hydrozone (IX), mp 159-160° (from $CHCl_3$–hexane). Infrared spectrum (ν, cm^{-1}): 1508, 1600, 1720-1735, 3335, 3400-3580. Infrared spec-

trum (δ ppm): 0.91 (18-CH_3), 0.95 (19-CH_3), 1.91 (CH_3COO at 3-C and 16-C), 2.03 (21-CH_3), 4.43 (H at 3-C), 5.20 (H at 6-C), 5.55 (H at 16-C), 7.80 (H at N), 6.81-8.1 (multiplet of aromatic protons).

17α-Pregn-5-ene-3β,16β,17β-triol-20-one 20-p-nitrophenylhydrazone (X). To a solution of 100 mg of the 3,16-diacetate hydrazone (IX) in 5 ml of MeOH was added 1 ml of 10% K_2CO_3 solution and the mixture was let stand overnight at 20°. After the usual workup we obtained 60 mg of the triol hydrazone (X), mp 167-168° (from $CHCl_3$–hexane). Infrared spectrum (ν, cm^{-1}): 1508, 1600, 3310-3515: M^+ = 483 m/e.

Androst-5-ene-3β,16β-diol-17-one 3,16-diacetate (XII). To a solution of 40 mg of the 3,16-diacetate p-nitrophenylhydrazone (IX) in 2 ml of abs. AcOH was added 80 mg of $Pb(AcO)_4$ and the mixture was let stand overnight at 20°. After the usual workup and chromatography on SiO_2 we obtained crystals of the 17-ketone diacetate (XII), mp 179-180° (from aqueous MeOH), which did not depress the mixed melting point with an authentic specimen [7].

Pregn-5-en-3β-ol-16,20-dione 3-acetate (XIII). A solution of 100 mg of the 3,16-diacetate p-nitrophenylhydrazone (IX) in 3 ml of AcOH, containing 0.2 ml of acetylacetone and 0.2 ml of water, was refluxed for 15 min. After the usual workup we obtained 40 mg of the 16,20-diketone 3-acetate (XIII), mp 147-152° (from aqueous MeOH). Infrared spectrum (ν, cm^{-1}): 1610, 1650, 1695, 1710, 1740, which coincided with an authentic specimen [8].

Pregn-5-ene-3β,16β,17α-triol-20-one 3,16-diacetate 20-p-nitrophenylhydrazone (XI). To a solution of 210 mg of pregn-5-ene-3β,16β,17α-triol-20-one 3,16-diacetate [7] in 4 ml of abs. dioxane was added a solution of 200 mg of p-nitrophenylhydrazine in 3 ml of dioxane and 2 ml of AcOH, and the mixture was let stand overnight at 20°. After the usual workup we obtained 160 mg of the trans-diacetate 20-p-nitrophenylhydrazone (XI), mp 163-165° (from aqueous MeOH). NMR spectrum (δ, ppm): 0.97 (19-CH_3), 1.07 (18-CH_3), 1.84 (21-CH_3), 1.93 (CH_3COO at 3-C and 16-C), 4.55 (H at 3-C), 5.00 (H at 16-C), 5.28 (H at 6-C), 6.83-8.1 (multiplet of aromatic protons).

CONCLUSIONS

1. 16β,17β-Epoxy-20-ketosteroids, the same as the 16α,17α-oxides, are capable of forming arylazoallyl alcohols.

2. The ability of the 20-arylazo-16-hydroxy-$\Delta^{17(20)}$-steroids to add nucleophilic reagents in the 17-position depends on the nature of the aryl substituent and the stereochemistry of the arylazoolefin.

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