TRANSFORMED STEROIDS

COMMUNICATION 62.* SYNTHESIS OF STEROIDS, CONDENSED WITH THE PYRAZOLE RING IN THE 4,5,6-POSITIONS

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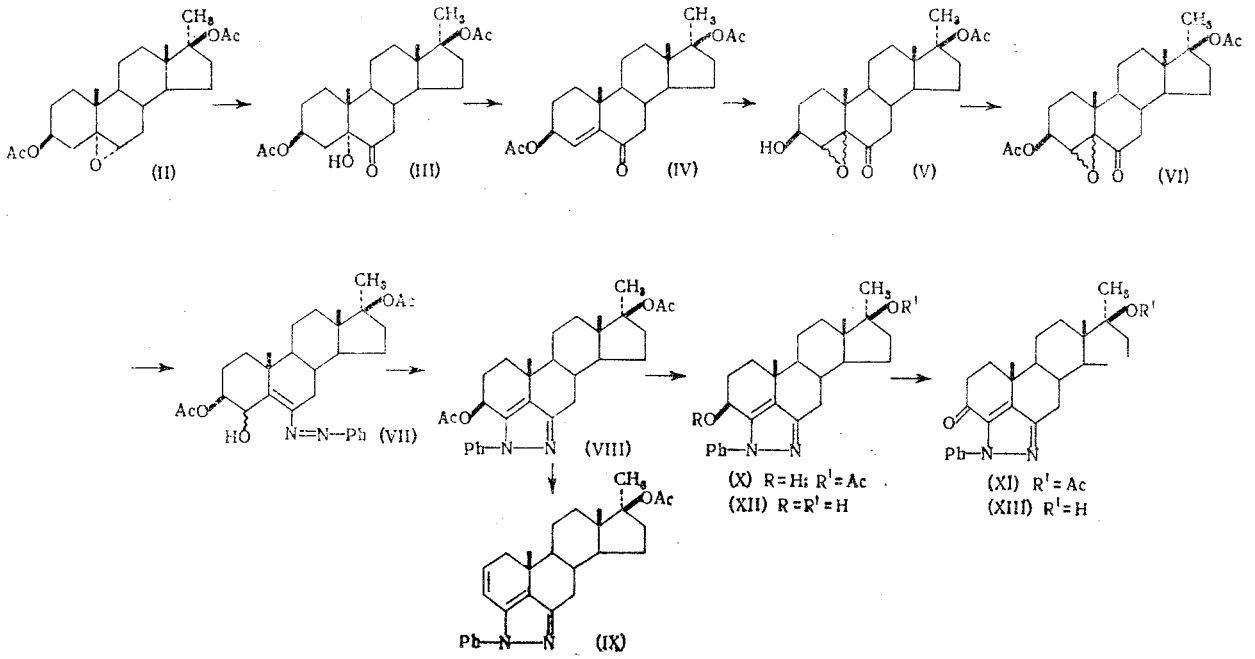
The steroidal [3,2-c]pyrazoles of the androstane and pregnane series possess an exceedingly interesting physiological activity. In the androstane series the insertion of the pyrazole grouping makes it possible to effect a separation of the androgenic and anabolic activity [2, 3]. Of the known antiinflammatory agents the corticosteroid derivatives, containing [3,2-c]pyrazole rings with 2'-aryl substituents, surpass cortisol in this activity by a matter of hundreds and even thousands of times [3-5]. In view of this we undertook the synthesis of steroids that bear the arylpyrazole grouping in the 4,5,6-positions. Here the Δ^4-3-keto grouping in ring A, which is absent in steroido[2,3-c]pyrazoles, could be retained. To synthesize the steroido-[4,5,6-c]arylpyrazoles we used the method previously proposed by us [6]. As the model steroids we selected 17α-methyltestosterone and progesterone. The epoxidation of the Δ^5-bond of the 3,17-diacetate of 17α-methylandrostan-5-en-3β,17β-diol (I) [7] with m-chloroperbenzoic acid [8] led to the corresponding 5α,6α-epoxide (II) [9, 10], which was oxidized in known manner [11] to the 3,17-diacetate of 17α-methylandrostane-3β,5α,17β-triol-6-one (III). The dehydration of the latter employing $SOCl_2$ in pyridine gave the



*See [1] for Communication 61.

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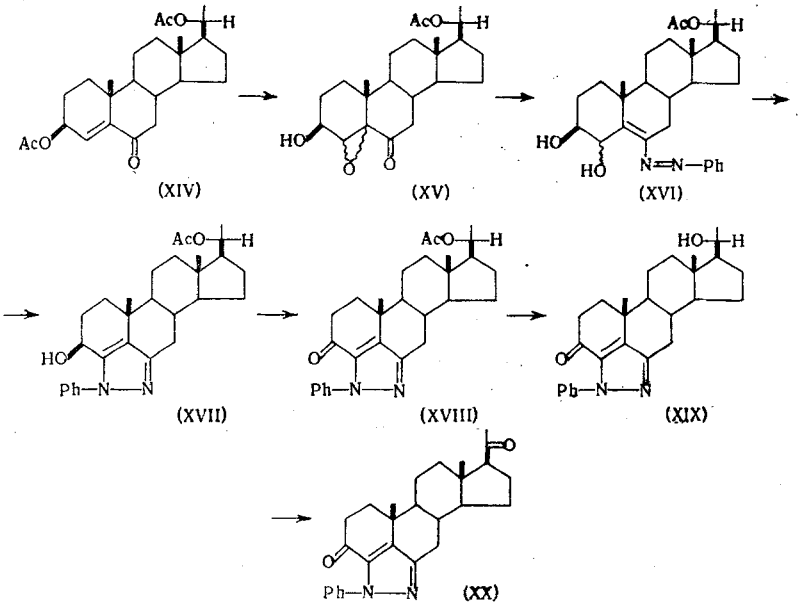
3,17-diacetate of the Δ^4-6-ketone (IV), which by epoxidation with H_2O_2 under alkaline conditions gave the 17-acetate of 4ξ,5ξ-epoxy-17α-methylandrostane-3β,17β-diol-6-one (V). The conventional acetylation of epoxide (IV) gave its 3,17-diacetate (VI). The structure of epoxides (V) and (VI) was proved by their physicochemical characteristics.

We selected phenylhydrazine as the hydrazine component for the synthesis of the steroidopyrazoles. The same as in the case of the 16α,17α-epoxy-20-ketosteroids [6], the reaction of phenylhydrazine with 4,5-epoxy-6-ketone (VI) in EtOH in the presence of a little AcOH led to the formation of the bright orange 3,17-diacetate of 6-phenylazo-17α-methylandrost-5-ene-3β,4ξ,17β-triol (VII), which could not be isolated in the crystalline state.

A study of the conditions for the cyclization of azoolefin (VII) disclosed that the reaction for the formation of the pyrazole proceeds most smoothly in the presence of HCl. When azohydroxysteroid (VII) in dioxane is heated with HCl it is cyclized in good yield to the 3,17-diacetate of the phenylpyrazole (VIII). Not only cyclization, but also cleavage of the 3-acetoxy group occurs when H_2SO_4 or sulfonic acids are used, which leads to the 17-acetate of 17α-methylandrosta-2,4-dien-17β-ol-[4,5,6-c]-1'-phenylpyrazole (IX). The absence of an acetoxy group in the 3-position follows from the fact that compound (IX) remains unchanged either when saponified under mild conditions or during subsequent oxidation.

The phenylpyrazole 3,17-diacetate (VIII) was saponified with a methanol solution of K_2CO_3 to the 17-monoacetate (X). Complete saponification occurs only on long refluxing in the presence of strong alkalis and leads to dihydroxyphenylpyrazole (XII). The oxidation of the latter by the Oppenauer method gave 17α-methylandrost-4-en-17β-ol-3-one-[4,5,6-c]-1'-phenylpyrazole (XIII), while the oxidation of monoacetate (X) by the Jones method gave the 3-ketopyrazole 17-acetate (XI).

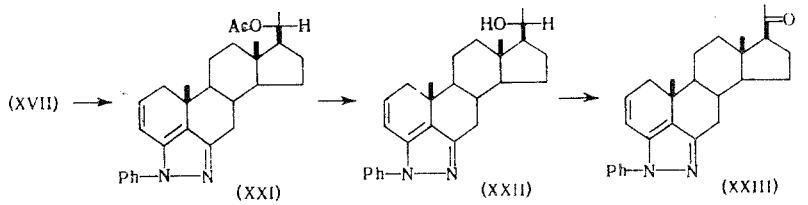
A similar series of transformations was run with the 3,20-diacetate of pregn-5-ene-3β,20β-diol, which was obtained by the reduction of the pregnenolone acetate with $NaBH_4$ in THF and subsequent acetylation of the reduction product. The alkaline epoxidation of pregn-4-ene-3β,20β-diol-6-one 3,20-diacetate (XIV) leads to epoxyketone (XV). It should be mentioned that for all practical purposes the 20-acetate group is not saponified under the epoxidation conditions. The 6-phenylazopregn-5-ene-3β,4ξ,20β-triol 20-acetate (XVI) that is obtained from epoxyketone (XV) under the usual conditions has a bright orange color, that disappears easily when heated with a dioxane solution of HCl, i.e. under the cyclization conditions. As a result, pregn-4-ene-3β,20β-diol-[4,5,6-c]-1'-phenylpyrazole 20-acetate (XVII) was obtained in good yield. The latter was oxidized by Jones reagent to the corresponding pregn-4-en-3-one-[4,5,6-c]-1'-



phenylpyrazole 20-acetate (XVIII), which by drastic saponification of the 20-acetate group with alkali and subsequent oxidation was converted to the desired pregn-4-ene-3,20-dione-[4,5,6-c]-1'-phenylpyrazole (XX).

3-Hydroxyphenylpyrazole (XVII), the same as is true in the androstane series, is easily dehydrated in the presence of H_2SO_4 to give pregn-2,4-dien-20β-ol-[4,5,6-c]-1'-phenylpyrazole 20-acetate (XXI), from

which pregn-2,4-dien-20-one-[4,5,6-c]-1'-phenylpyrazole (XXIII) was obtained. The structure of the latter was confirmed by the NMR spectrum. Two broad one-proton signals appear downfield (δ 5.7-6.7 ppm), one of which (the broader signal), with a center at 5.9 ppm, must be assigned to the signal of the proton at C-2, while the second signal, with a center at 6.55 ppm, should be assigned to the proton at C-3.



As a result, the previously observed by us [6] isomerization of azoallyl alcohols to hydrazones, and their subsequent cyclization to pyrazoles, evidently has a general character.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra were taken on a UR-10 instrument in KBr. The optical rotation was measured in chloroform. The NMR spectra were taken on a Varian NMR spectrometer (60 MHz).

4ξ,5ξ-Epoxy-17α-methylandrostane-3β,17β-diol-6-one 17-Acetate (V). To a solution of 11 g of 17α-methylandrost-4-ene-3β,17β-diol-6-one 3,17-diacetate (IV) in 550 ml of CH_3OH was added 63 ml of 4 N NaOH solution, and then 130 ml of 30% H_2O_2 solution, after which the mixture was allowed to stand at 5°C for 3 h, neutralized with AcOH, the methanol was evaporated nearly to dryness, and the residue was extracted with $CHCl_3$. The extract was washed with water, then with $NaHCO_3$ solution, again with water, and evaporated. We obtained 9 g of epoxyketone (V), mp 197-199° (from THF-hexane); $[\alpha]_D^{23}$ −48° (C 0.709). Infrared spectrum (ν, cm^{-1}): 1713, 1730. Found: C 70.46; H 8.77%. $C_{22}H_{32}O_5$. Calculated: C 70.18; H 8.57%. NMR spectrum (δ, ppm): 0.82 (18-CH_3), 0.96 (19-CH_3), 1.36 (17-CH_3), 1.91 (17-Ac), doublet with a center at 3.2 (4-H), 3.95 (3-H).

3,17-Diacetate (VI), mp 159-161° (from aqueous acetone); $[\alpha]_D^{23}$ −85° (C 0.99). Infrared spectrum (ν, cm^{-1}): 1713, 1725. Found: C 68.88; H 8.27%. $C_{24}H_{34}O_6$. Calculated: C 68.87; H 8.19%. NMR spectrum (δ, ppm): 0.82 (18-CH_3), 1.01 (19-CH_3), 1.37 (17-CH_3), 1.93 (17-Ac), 2.01 (3-Ac), doublet with a center at 3.22 (4-H), 5.01 (3-H).

17α-Methylandrost-4-ene-3β,17β-diol-[4,5,6-c]-1'-phenylpyrazole 3,17-Diacetate (VIII). To a solution of 3 g of the 3,17-diacetate of the keto oxide (VI) and 3 g of phenylhydrazine in 150 ml of EtOH was added 1 ml of AcOH and the mixture was allowed to stand for 3 h. Then the mixture was diluted with water, and the precipitate was filtered, washed with water, and dried. We obtained 3.64 g of 6-phenylazo-17α-methylandrost-5-ene-3β,4ξ,17β-triol 3,17-diacetate (VII) as an amorphous orange powder that would not crystallize. Infrared spectrum (ν, cm^{-1}): 1620, 1733, 3400, 3480. A solution of 1.5 g of phenylazo-olefin (VII) in 110 ml of dioxane, containing 35 drops of 37% HCl solution, was refluxed for 10 min, diluted with water, and the precipitate was filtered and washed with water. We obtained 1.28 g of the phenylpyrazole 3,17-diacetate (VIII), mp 215-217° (from aqueous acetone); $[\alpha]_D^{23}$ −17° (C 0.69). Infrared spectrum (ν, cm^{-1}): 1508, 1600, 1722-1735. Found: C 73.28; H 7.74; N 5.76%. $C_{30}H_{38}N_2O_4$. Calculated: C 73.47; H 7.75; N 5.71%.

17α-Methylandrost-4-en-17β-ol-3-one-[4,5,6-c]-1'-phenylpyrazole 17-Acetate (XI). To a solution of 1.05 g of the phenylpyrazole 3,17-diacetate (VIII) in 70 ml of MeOH was added 3.5 ml of 10% K_2CO_3 solution and the mixture was allowed to stand for 4 h. After the usual workup we obtained 880 mg of phenylpyrazole 17-acetate (X), mp 206-210° (from acetone—hexane). Infrared spectrum (ν, cm^{-1}): 1510, 1600, 1735, 3370-3400. A solution of 500 mg of pyrazole (X) in 50 ml of acetone was treated with 0.5 ml of 8 N CrO_3 in H_2SO_4, and after 5 min the mixture was diluted with water and the precipitate was filtered. We obtained 450 mg of 3-ketophenylpyrazole 17-acetate (XI), mp 125-130° (from aqueous acetone); $[\alpha]_D^{23}$ −220° (C 0.731). Infrared spectrum (ν, cm^{-1}): 1507, 1600, 1690, 1732.

17α-Methylandrost-4-ene-3β,17β-diol-[4,5,6-c]-1'-phenylpyrazole (XII). To a solution of 1.5 g of phenylpyrazole 3,17-diacetate (VIII) in 90 ml of MeOH was added 10 ml of 10% KOH solution and the mixture was refluxed until the starting (VIII) had disappeared completely (chromatographic check). After the usual workup we obtained 1.27 g of 3,17-dihydroxyphenylpyrazole (XII), mp 255-260° (from aqueous MeOH); $[\alpha]_D^{23}$ −38°C (C 0.956). Infrared spectrum (ν, cm^{-1}): 1510, 1605, 3270-3300, 3400-3430.

17α-Methylandrost-4-en-17β-ol-3-one-[4,5,6-c]-1'-phenylpyrazole (XIII). To a solution of 800 mg of 3,17-dihydroxypyrazole (XII) in 40 ml of absolute benzene was added a solution of 2 g of aluminum isopropoxide in 20 ml of absolute benzene and 3.2 ml of absolute acetone, and the mixture was refluxed for several days, running a chromatographic check on Silufol UV_{254} plates. After the starting 3-hydroxypyrazole had disappeared the excess alcoholate was decomposed with 50% AcOH solution and extracted with $CHCl_3$. Then the extract was washed in succession with $NaHCO_3$ solution, water and saturated NaCl solution, and evaporated. We obtained 510 mg of phenylpyrazole (XIII), mp 246-249° (from aqueous MeOH). Infrared spectrum (ν, cm^{-1}): 1507, 1600, 1680, 3535. Found: C 77,05; H 8.11; N 7.11%. $C_{26}H_{32}N_2O_2$. Calculated: C 77.23; H 7.92; N 7.14%.

17α-Methylandrosta-2,4-dien-17β-ol-[4,5,6-c]-1'-phenylpyrazole 17-Acetate (IX). A solution of 600 mg of phenylpyrazole 3,17-diacetate (VIII) in 25 ml of absolute dioxane, containing 3 drops of conc. H_2SO_4, was refluxed for 30 min. The mixture was diluted with water and the precipitate was filtered. We obtained 480 mg of Δ^2-phenylpyrazole (IX), mp 211-213° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1510, 1600, 1725. Found: C 77.85; H 7.75%. $C_{28}H_{34}N_2O_2$. Calculated: C 78.14; H 7.90%.

Epoxypregnan-3β,20β-diol-6-one 20-Acetate (XV). To a solution of 3.6 g of pregn-4-ene-3β,20β-diol-6-one 3,20-diacetate (XIV) in 120 ml of MeOH were added in sequence 21 ml of 4 N NaOH solution and 45 ml of 30% H_2O_2 solution, and the mixture was allowed to stand at 5° for 4 h. Then the reaction mixture was diluted with water and the obtained crystalline precipitate was filtered, washed with water, and dried. We obtained 3.05 g of keto oxide (XV), mp 204-206° (from aqueous MeOH). Infrared spectrum (ν, cm^{-1}): 1718, 1733, 3410-3560.

Pregn-4-ene-3β,20β-diol-[4,5,6-c]-1'-phenylpyrazole 20-Acetate (XVII). To a solution of 1 g of keto oxide (XV) and 1 g of phenylhydrazine in 35 ml of EtOH was added 0.3 ml of AcOH, the mixture was allowed to stand for 2 h, diluted with water, and the orange precipitate was filtered. We obtained 1.2 g of phenylazotriol (XVI), mp 163-166° (from aqueous MeOH). Infrared spectrum (ν, cm^{-1}): 1620, 1710, 3320-3400, 3510. A solution of 600 mg of azotriol (XVI) in 40 ml of dioxane, containing 10 drops of 37% HCl solution, was refluxed for 5 min, in which connection the solution became light yellow. The mixture was diluted with water and the precipitate was filtered. We obtained 460 mg of 3,20-dihydroxyphenylpyrazole 20-acetate (XVII), mp 222-223°; $[\alpha]_D^{23}$ −4.6° (C 0.863). Infrared spectrum (ν, cm^{-1}): 1510, 1600, 1735, 3300-3450.

Pregn-4-en-20β-ol-3-one-[4,5,6-c]-1'-phenylpyrazole 20-Acetate (XVIII). With stirring, a solution of 1.2 g of dihydroxypyrazole 20-acetate (XVII) in 50 ml of acetone was treated at 20° with 8N CrO_3 solution in H_2SO_4 (~1.5 ml) until a permanent orange color appeared. After 2-5 min the mixture was poured into water and the precipitate was filtered. We obtained 1.12 g of 3-ketophenylpyrazole acetate (XVIII), mp 233-235° (from aqueous acetone); $[\alpha]_D^{23}$ −180° (C 0.706). Infrared spectrum (ν, cm^{-1}): 1505, 1515, 1600, 1687, 1728.

Pregn-4-ene-3,20-dione-[4,5,6-c]-1'-phenylpyrazole (XX). A solution of 320 mg of 3-ketopyrazole 20-acetate (XVIII) in 40 ml of MeOH and 10 ml of 10% KOH solution was refluxed for 3 h, and after the usual workup we obtained 300 mg of 20-hydroxy-3-ketophenylpyrazole (XIX), mp 162-163° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1505, 1598, 1687, 3440. A solution of 200 mg of pyrazole (XIX) was treated with 0.5 ml of 8 N CrO_3 solution in H_2SO_4, and after 2 min the mixture was diluted with water and the crystalline precipitate was filtered. We obtained 160 mg of 3,20-diketopyrazole (XX), mp 196-198° (from aqueous acetone); $[\alpha]_D^{23}$ −183° (C 1.15). Infrared spectrum (ν, cm^{-1}): 1503, 1555, 1595, 1680, 1695. NMR spectrum (δ, ppm): 0.65 (18-CH_3), 1.25 (19-CH_3), 2.07 (21-CH_3), 7.0-7.5 (multiplet of aromatic protons).

Pregn-2,4-dien-20-one-[4,5,6-c]-1'-phenylpyrazole (XXIII). A solution of 450 mg of 3-hydroxyphenylpyrazole 20-acetate (XVII) in 20 ml of absolute dioxane was treated with conc. H_2SO_4 (2 drops) and refluxed for 15 min. After the usual workup we obtained 350 mg of pregn-2,4-dien-20β-ol-[4,5,6-c]-1'-phenylpyrazole 20-acetate (XXI), mp 193-195° (from aqueous acetone). Infrared spectrum (ν, cm^{-1}): 1508, 1600, 1640, 1660, 1730. To a solution of 160 mg of 2,4-dienepyrazole 20-acetate (XXI) was added 1 ml of 12% KOH solution and the mixture was refluxed for several hours until saponification was complete. After the usual workup we obtained 130 mg of 20-hydroxydienepyrazole (XXII), which was treated in acetone solution with 0.2 ml of 8 N CrO_3 solution in H_2SO_4. After the usual isolation we obtained 90 mg of phenylpyrazole (XXIII), mp 210-212° (MeOH); $[\alpha]_D^{20}$ −29° (C 0.963). Infrared spectrum (ν, cm^{-1}): 1507, 1603, 1700. NMR spectrum (δ, ppm): 0.64 (18-CH_3), 1.02 (19-CH_3), 2.06 (21-CH_3), multiplet with a center at 5.9 (H at C-2), multiplet with a center at 6.55 (H at C-3), and 7.0-7.5 (multiplet of aromatic protons).

CONCLUSIONS

1. 4,5-Epoxy-6-ketosteroids are converted under mild conditions to arylazoallyl alcohols, which in the presence of strong acids are easily cyclized to [4,5,6-c]pyrazoles.

2. A number of steroids of the androstane and pregnane series, condensed with the pyrazole ring in the 4,5,6-positions, was synthesized.

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