STEROIDS

# XXVII. Synthesis of steroido [17, 16-d] pyrazoles

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As we have reported [1], steroido [17, 16-d] isoxazoles can be used as the starting materials [2, 3] for the synthesis of steroido [17, 16-d] pyrazoles [4, 5]. The hydrogenation of steroido [17, 16-d]-3'-methylisoxazoles (Ia, b) in the presence of an Adams platinum catalyst or 2% $Pd/CaCO_3$ in alcoholic solution leads to the rupture of the isoxazole ring at the nitrogen-oxygen bond with the formation of the 20-ketoimines of 3β, 16-dihydroxypregna-5, 16-dien-20-one (IIa) and its 3-acetate (IIb). Previously [1], compounds (IIa, b–Va, b) were assigned the structure of compounds hydrogenated in the 5, 6 positions.

The hydrogenation of steroido [17, 16-d]-3'-methylisoxazoles of the allo series (Ic, d) under the same conditions leads to the formation of the 20-ketoimines of 3β, 16-dihydroxypregn-16-en-20-one (IIc) and its 3-acetate (IId). The hydrogenation of the steroidoisoxazoles (I) over Raney nickel does not rupture the isoxazole ring. The alkaline hydrolysis of the steroido[17, 16-d] isoxazoles (I) is not accompanied by the rupture of the bonds of the isoxazole ring, either, and in the case of the acetates (Ib, d) only the ester group in position 3 is saponified, with the formation of compounds (Ia, c). The imino group in the ketoimines (II) is stable to the action of water and alkaline agents. When aqueous alcoholic solutions of the ketoimines (II) are boiled, these compounds remain unchanged, and when (IIb, d) are boiled with alkaline agents only the ester groups in position 3 are saponified, with the formation of compounds (IIa, c).

The acetylation of the ketoimines (II) by heating with acetic anhydride gives the O, N-diacetates of the 20-ketoimines of 3β-hydroxypregn-5-en-16-one and of the corresponding 5α-pregnane derivative (III), the alkaline saponification of which leads to the formation of the ketoimines (IIa, c). Certain conclusions on the predominance of one tautomeric form or another for compounds (II, III) can be drawn on the basis of the IR spectra, taken in paraffin oil and in solutions, the UV spectra, the qualitative reaction for an enolic group with alcoholic solutions of ferric chloride, and the reactions with 2, 4-dinitrophenylhydrazine (Table 1). According to these results, in the solid state the ketoimines (II) exist predominantly in the iminoenol form (I), while in solution in a polar solvent (for example, alcohol) the equilibrium is displaced in the direction of the ketoenamine structure 3 [6]. In the case of the O, N-diacetates (III), the ketoimine form 2 predominates in the solid state, while in alcoholic solutions an equilibrium between all three tautomeric forms is probably established (cf. the formula on page 336).

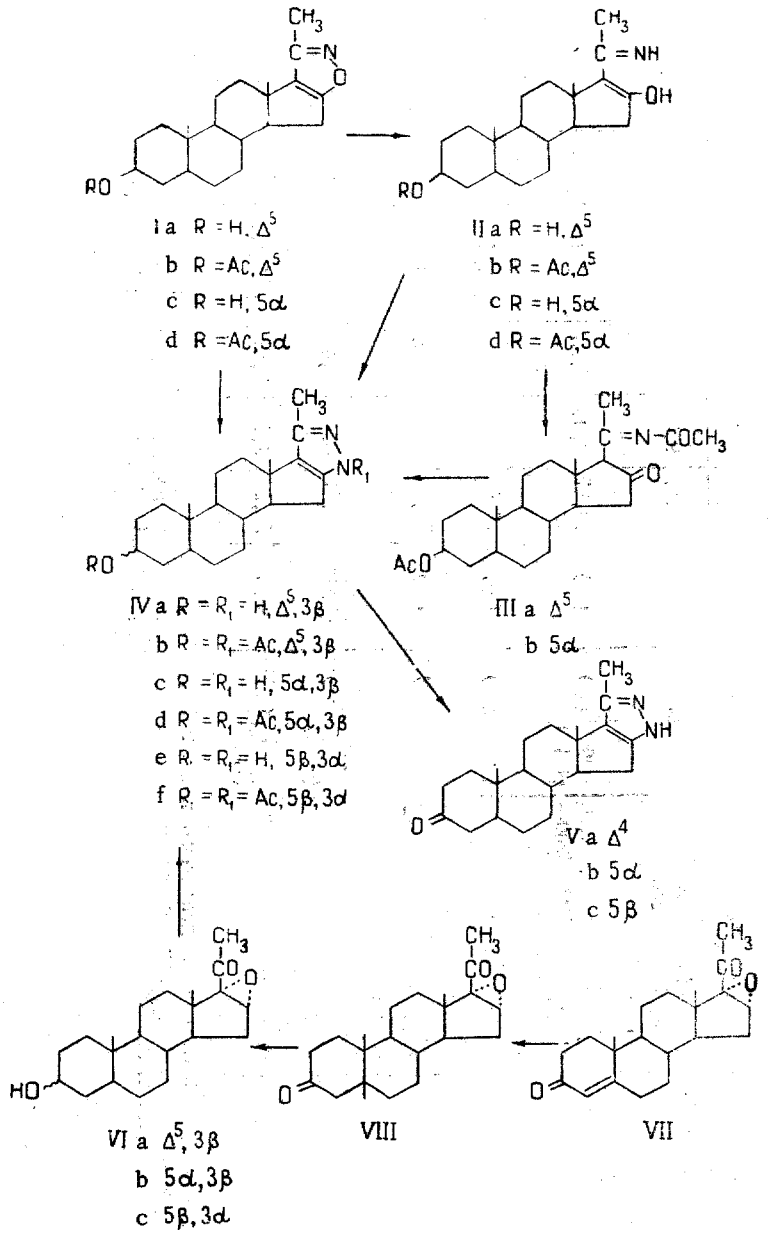
Since substances (II, III) are potential 1, 3-dicarbonyl compounds, on reaction with hydrazine hydrate they form steroido [17, 16-d]-3'-methylpyrazoles (IVa, c). The severe alkaline hydrolysis of 3β-acetoxyandrost-5-eno[17, 16-d]-3'-methylisoxazole (Ib) in the presence of hydrazine hydrate also gives the pyrazole (IVa) (Table 2) [7].

For comparison, we synthesized the steroido [17, 16-d]pyrazoles (IV), which have been described in general form in the patent literature, by Dodson's method [5], by the reaction of compounds of the type of hydroxyoxidopregnenone with hydrazine hydrate in boiling alkaline ethylene glycol. As starting material for this synthesis we used 3β-hydroxy-16α, 17α-oxidopregn-5-en-20-one (VIa), 3β-hydroxy-16α-oxido-5α-pregnan-20-one (VIb) [8] and 3α-hydroxy-16α, 17α-oxido-5β-pregnan-20-one (VIc). The latter was obtained from the oxidoprogesterone (VII) as follows. The oxidoprogesterone (VII) was reduced in an alkaline medium over Pd/C [9] to form 16α, 17α-oxido-5β-pregnane-3, 20-dione (VIII). The selective reduction of the keto group in position 3 to compound (VIII) could not be performed with sodium borohydride. In addition to 3α-hydroxy-16α, 17α-oxido-5β-pregnan-20-one (VIc), 3α, 20-dihydroxy-16α, 17α-oxido-5β-pregnane was always formed by the reduction of both carbonyl groups as has been shown by Suverov and Yaroslavtseva [10]. The steroido-[17, 16-d]-3'-methylpyrazoles synthesized by Dodson's method [5] were identical with those that we obtained in respect of their analyses, IR and UV spectra, and physical constants. The acetylation of compounds (IVa, c, e) led to the formation of their O, N-diacetyl derivatives (IVb, d, f). The oxidation of the hydroxy group in position 3 by Oppenauer's method for compound (IVa) and by Killiani's method for compounds (IVc, e) led to the formation of androst-4-en-3-ono-[17, 16-d]-3'-methylpyrazole (Va) and 5α- and 5β-androstan-3-ono[17, 16-d]-3'-methylpyrazoles (Vb, c).

## Experimental

The IR spectra were taken in paraffin oil (unless specifically stated otherwise) on a UR-10 instrument, and the UV spectra on an SF-4 spectrophotometer in alcohol.

3β-Hydroxyandrost-5-eno[17, 16-d]-3'-methylisoxazole (Ia). A. 0.5 g of (Ib) in 7 ml of dry benzene was added to a solution of sodium alkoxide obtained from 0.06 g of metallic sodium and 3 ml of absolute methanol. The solution was




stirred for 1 hr at room temperature and then 20 ml of water and 10 ml of benzene were added; the benzene extract was washed with water and evaporated to dryness. Weight 0.45 g, mp 176°–178° C (from a mixture of benzene and hexane or from aqueous methanol), $[\alpha]_D^{20}$ −45° (c 1.0; chloroform). IR spectrum: 3360, 3440 $cm^{-1}$ (−OH), 1610 $cm^{-1}$ (C=N, arom.).

Found, %: C 77.41; H 8.45; N 4.32. Calculated for $C_{21}H_{29}NO_2$, %: C 77.03; H 8.93; N 4.27.

B. A mixture of 0.2 g of (Ib) and 10 ml of a 2% solution of caustic potash in methanol was boiled for 30 min. After cooling, the solution was neutralized with acetic acid and poured into water, and the precipitate that deposited was filtered off and washed with water. Weight 0.17 g, mp 172°–176° C.

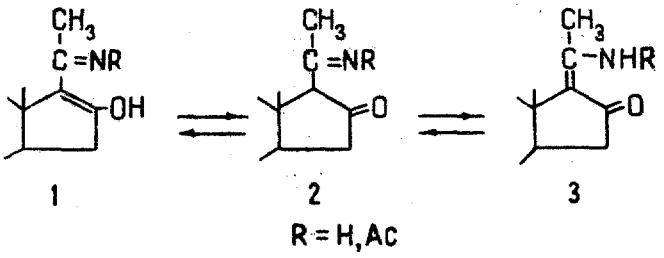


Table 1

| Substance | Mp, °C | Solvent for crystallization | $[\alpha]_D^{20}$ ($c$ 1.0; $CHCl_3$) | $\nu_{max}$ (NH, OH, CO, C=N), $cm^{-1}$ | $\lambda_{max}$ (log ε) | Reaction with $FeCl_3$ | Reaction with 2,4-dinitrophenylhydrazine | Found, % C | Found, % H | Found, % N | Formula | Calculated, % C | Calculated, % H | Calculated, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (IIa) | 266–268 (decomp.) | acetone, ethyl acetate | −89.8 | 3320–3300, 3180–3170, 1628; 3510, 3230–3180 (0.2% $CCl_4$) | — | (+) | (−) | 76.57 | 9.39 | 4.24 | $C_{21}H_{31}NO_2$ | 76.52 | 9.48 | 4.25 |
| (IIb) | 214–215.5* (decomp.) | | −81.4 | 3550, 3460, 3360, 3180, 1720, 1624; 3500, 3230–3180 (0.2% $CCl_4$) | 322 (4.12) | (+) | (−) | 73.87 | 8.94 | 3.75 | $C_{23}H_{33}NO_3$ | 74.32 | 8.95 | 3.77 |
| (IIc) | 279.5–280.5 (decomp.) | | −12.4 | 3320, 3180, 1628 | — | (+) | (−) | 75.96 | 9.93 | 4.26 | $C_{21}H_{33}NO_2$ | 76.10 | 10.0 | 4.23 |
| (IId) | 213–215.5* (decomp.) | | −66 | 3570, 3480, 3340, 3200, 1725, 1625; 3500, 3220–3180 (0.2% $CCl_4$) | 322 (4.14) | (+) | (−) | 73.82 | 9.34 | 3.75 | $C_{23}H_{35}NO_3$ | 73.94 | 9.44 | 3.75 |
| (IIIa) | 113–115.5 | aqueous ethyl alcohol | — | 1735–1708, 1660, 1600 | 306 (4.10) | (+)** | (+)*** | 72.81 | 8.70 | 3.43 | $C_{25}H_{35}NO_4$ | 72.59 | 8.53 | 3.39 |
| (IIIb) | 144–147 | | +19.5 | 1736, 1720, 1660, 1600 | 306 (4.12) | (+)** | (+) | 72.29 | 9.15 | 3.51 | $C_{25}H_{37}NO_4$ | 72.26 | 8.97 | 3.37 |

*A mixture of samples of (IIb) and (IId) gave a depression, mp 203°–205° C.

**When the solutions were mixed the reaction was negative, but it became positive after prolonged standing.

***The 2,4-dinitrophenylhydrazone had mp 139.5°–142° C (decomp.). Found, %: N 11.80. Calculated for $C_{31}H_{39}NO_7$, %: N 11.82.

Table 2

| Substance | Yield (method of preparation), % | Mp, °C | Solvent for crystallization | $[\alpha]_D^{20}$, deg. | $\nu_{max}$, $cm^{-1}$ | $\lambda_{max}$ (log ε) | Found, % C | Found, % H | Found, % N | Formula | Calculated, % C | Calculated, % H | Calculated, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (IVa) | 80 (A)<br>80 (B)<br>61 (C)<br>22 (D) | 328—330 (decomp.) | Acetone, methanol, ethyl alcohol | −80 (*c* 0.5; $C_2H_5OH$) | 3610, 3260, 1608 | 225 (3,78) | 77.17 | 9.17 | 8.46 | $C_{21}H_{30}N_2O$ | 77.23 | 9.22 | 8.58 |
| (IVc) | 79.5 (A)<br>19 (D) | 292.5—295 (decomp.) | | +8 (*c* 0.5; $C_2H_5OH$) | 3610, 3250, 1610 | 225 (3,79) | 76.93 | 9.74 | 8.55 | $C_{21}H_{32}N_2O$ | 76.90 | 9.75 | 8.53 |
| (IVe) | 20 (D) | 315.5—316.5 (decomp.) | Acetone, methanol | +25 (*c* 1.0; $C_2H_5OH$) | 3610, 3260, 1605 | 225 (3,76) | 76.70 | 9.86 | 8.60 | | | | |
| (IVb) | 62 | 189—192 | Acetone, ethyl alcohol | −79 (*c* 1.0; $CHCl_3$) | 1730—1720 | 233 (3,93) | 72.87 | 8.55 | 6.88 | $C_{25}H_{34}N_2O_3$ | 73.13 | 8.35 | 6.82 |
| (IVd) | 54 | 169—170,5 | Methanol, ethyl alcohol | −20,7 (*c* 1.0; $CHCl_3$) | 1735, 1720 | 233 (3,94) | 73.22 | 8.76 | 6.88 | $C_{25}H_{36}N_2O_3$ | 72.76 | 8.80 | 6.80 |
| (IVg) | 57 | 83—85 | | — | 1738—1725 | 233 (3,94) | 72.46 | 8.83 | 6.78 | | | | |
| (Va) | 30 | 283—285 (decomp.) | | — | 3370, 3335, 1660, 1615 | 234 (4,18) | 77.59 | 8.71 | 8.54 | $C_{21}H_{28}N_2O$ | 77.71 | 8.70 | 8.63 |
| (Vb) | 76 | 268.5—270.5 (decomp.) | Water—methanol | — | 3300, 1720, 1610; 3470 (2%, $CCl_4$) | 225 (3,75) | 77.30 | 9.15 | 8.71 | $C_{21}H_{30}N_2O$ | 77.23 | 9.22 | 8.58 |
| (Vc) | 52 | 231—234 (decomp.) | | — | 3275, 3200, 1715, 1607 | 225 (3,76) | 77.00 | 8.98 | 8.36 | | | | |

3β-Hydroxy-5α-androstano[17,16-d]-3'-methylisoxazole (Ic). 2 g of (Id) was boiled with a 2% solution of caustic potash in methanol for 0.5 hr. After cooling, the solution was neutralized with acetic acid, the solvent was distilled off to dryness, water was added, and the precipitate was filtered off. Weight 1.45 g, mp 189°–192° C (from ethyl and methyl alcohols).

Found, %: C 76.10; H 9.30; N 4.41. Calculated for $C_{21}H_{31}NO_2$, %: C 76.56; H 9.48; N 4.25.

Hydrogenation of the steroido [17,16-d]-3'-methylisoxazoles (I). A. One part by weight of a steroido [17,16-d]-3'-methylisoxazole (Ia, b, d) in 150 parts by weight of ethyl (methyl) alcohol was hydrogenated over 0.1 part by weight of Adams platinum catalyst at room temperature and atmospheric pressure for 15 min. The catalyst was filtered off and washed with alcohol, the alcoholic solution was evaporated to dryness, and the residue was recrystallized. This gave (IIa, b, d) with yields of 83, 97, and 97%, respectively.

B. One part by weight of a steroidoisoxazole (Ia, b) was hydrogenated in alcohol over 0.5 parts by weight of 2% $Pd/CaCO_3$. After the procedure described for method A, (IIa, b) were obtained with yields of 50 and 68%, respectively.

20-Ketoimines of 3β,16-dihydroxypregna-5,16-dien-20-one and 3β,16-dihydroxy-5α-pregn-16-en-20-one (IIa, c). A mixture of 0.0005 mole of an acetate of a ketoimine (IIb, d) or of a O,N-diacetate of a ketoimine (III) and 20 ml of a 2% solution of caustic potash in methanol was boiled for 30 min. After cooling to room temperature, the mixture was neutralized with acetic acid, the solvent was distilled off to dryness, and the residue was transferred to a filter, washed with water, and recrystallized. The yields of (IIa, c) were 95 and 72%, respectively, calculated on the (IIb, d) and that of (IIa) was 94% calculated on the (IIa) (cf. Table 1).

O,N-Diacetates of the 20-ketoimines of 3β-hydroxypregn-5-en-16-one and the corresponding 5α-pregnane derivative (III). A solution of 0.0005 mole of one of the ketoimines (II) in 15 ml of acetic anhydride was left at room temperature for 20 hr. Then the solution was diluted with water, and the precipitate was filtered off, washed with water, dried, and purified by chromatography on alumina. Benzene eluted (IIIa) and (IIIb) with yields of 80 and 84%, respectively (cf. Table 1).

3β-Hydroxyandrost-5-eno- and (3β,3α)-hydroxy-(5α,5β)-androstano[17,16-d]-3'-methylpyrazoles (IVa, c, e). A. A mixture of 0.0012 mole of one of the ketoimines (IIa, c) in 40 ml of ethyl alcohol and 0.0025 mole of 80% aqueous hydrazine hydrate was boiled for 12 hr. The end of the reaction was determined by testing a sample with an alcoholic solution of ferric chloride for a negative reaction for an enolic group. After the end of the reaction, the solvent was distilled off to dryness and the residue was recrystallized.

B. A mixture of 0.0017 mole of the diacetate (III), 0.0033 mole of 80% aqueous hydrazine hydrate, and 1 g of caustic potash in 50 ml of methyl alcohol was boiled for 12 hr. The solution was neutralized with acetic acid, the solvent was distilled off, and the residue was washed in water and recrystallized.

C. A mixture of 0.009 mole of a steroido [17,16-d]-3'-methylisoxazole (I), 0.016 mole of 80% aqueous hydrazine hydrate, and 3 g of caustic potash in 70 ml of ethylene glycol was boiled for 10 hr [17]. After cooling, the solution was diluted with water, and the precipitate which deposited was filtered off, washed with water, and recrystallized.

D. A mixture of 0.03 mole of an epoxyketone (VI), 0.67 mole of 80% aqueous hydrazine hydrate, and 10 g of caustic potash in 150 ml of ethylene glycol was boiled for 10 hr [5]. After cooling, the solution was diluted with water, and the precipitate was filtered off, washed with water, and dried. (VIa) was purified by chromatography on alumina (eluant: ethyl acetate) and (IVc, e) by repeated recrystallization from acetone and methanol (cf. Table 2).

O,N-Diacetates of 3β-hydroxyandrost-5-eno- and (3β,3α)-hydroxy-(5α,5β)-androstano[17,16-d]-3'-methylpyrazoles (IVb, d, g). A solution of 0.0013 mole of one of the steroidopyrazoles (IVa, c, e) and 0.02 mole of acetic anhydride in 10 ml of dry pyridine was left at room temperature for 20 hr. The solution was poured into water, and the precipitate was filtered off, washed with water, and recrystallized (cf. Table 2).

Androst-4-en-3-ono[17,16-d]-3'-methylpyrazole (Va). A boiling solution of 0.5 g of 3β-hydroxyandrost-5-eno[17,16-d]-3'-methylpyrazole (IVa) in 250 ml of toluene and 10 ml of cyclohexanone was treated with 10 ml of aluminum isopropoxide in toluene (29.8%) and the solution was boiled for 3.5 hr. Then the solvent was distilled off with steam in the presence of 10 g of Rochelle salt. After cooling, the precipitate was filtered off, dried, and chromatographed on 40 g of alumina. Ethyl acetate eluted 0.15 g of (Va) (cf. Table 2).

5α- and 5β-Androstan-3-ono[17,16-d]-3'-methylpyrazoles (Vb, c). With boiling, 0.0015 mole of one of the steroidopyrazoles (IVc, e) was dissolved in 250 ml of acetone, and the resulting solution was added in drops at 23° C to 5 ml of Killiani's reagent [11]. The solution was left at room temperature for 3.5 hr. A few drops of water was added and the precipitate of chromium salts that deposited was separated off. The solution was neutralized with caustic potash solution and evaporated to dryness. The residue was washed with water and recrystallized (cf. Table 2).

Summary

A new method for the synthesis of steroido[17, 16-d]-3'-methylpyrazoles has been proposed on the basis of a study of the alkaline decomposition and catalytic hydrogenation of steroido[17, 16-d]-3'-methylisoxazoles.

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