TRANSFORMED STEROIDS.

# 172. REACTION OF 16-METHYL-20-KETOSTEROIDS WITH IODOBENZENE DIACETATE

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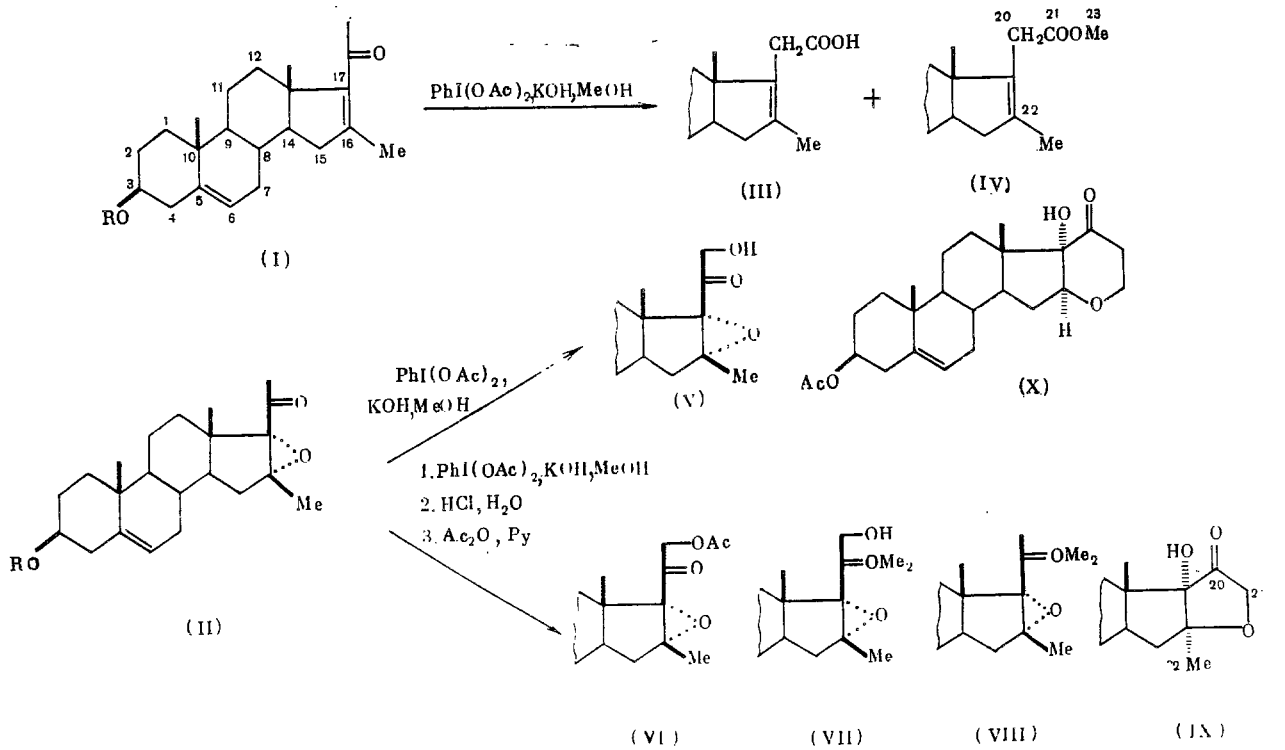
In a search for methods of functionalization of 20-ketosteroids at the $C^{16}$, $C^{17}$, $C^{21}$ atoms by iodobenzene diacetate in a methanolic alkali solution [1, 2], we studied this reaction using 16-methyl-20-ketosteroids (I), (II), which are precursors in the synthesis of biologically active preparations of the dexamethasone type.

From the literature data on the use of the $PhI(OAc)_2$ —MeOH—KOH oxidation system for the functionalization of α,β-unsaturated enones [2-5] we might have expected that both $C^{21}$-hydroxylation and addition products at the $\Delta^{16}$-bonds (hydroxylation, methoxylation, epoxidation products) would be obtained from ketone (I). Contrary to these expectations, the reaction with (I) led to the formation of acid (III) and its methyl ester (IV) [in the presence of a large excess of alkali and 1.1-1.2 M excess of the reagent (Scheme 1)]. This course of the reaction is, apparently, the result of a competing path, by which the reductive elimination of iodoxybenzene from the postulated intermediates (A) or (B) [3, 4] proceeds not in the expected direction (path a, Scheme 2), but by the Favorskii rearrangement, presuming [6, 7] the formation of cyclopropanone (C) and its subsequent opening. It should be noted that the predominating direction in the opening of the cyclopropanone ring is the cleavage of the $C^{17}-C^{20}$ bond, and not the cleavage of the $C^{20}-C^{21}$ bond, observed in similar cases, with the formation of methyletianic acids [6, 7]. This course of the Favorskii's rearrangement, once already noted in the reaction of 16α-methyl-17α-bromo- 20-ketosteroids with the MeONa—MeOH




R = H (Ia), (IIa), (IIIa), (IVa), (V); R = Ac (Ib), (IIb), (IIIb), (IVb), (VI)—(IX).

Scheme 1

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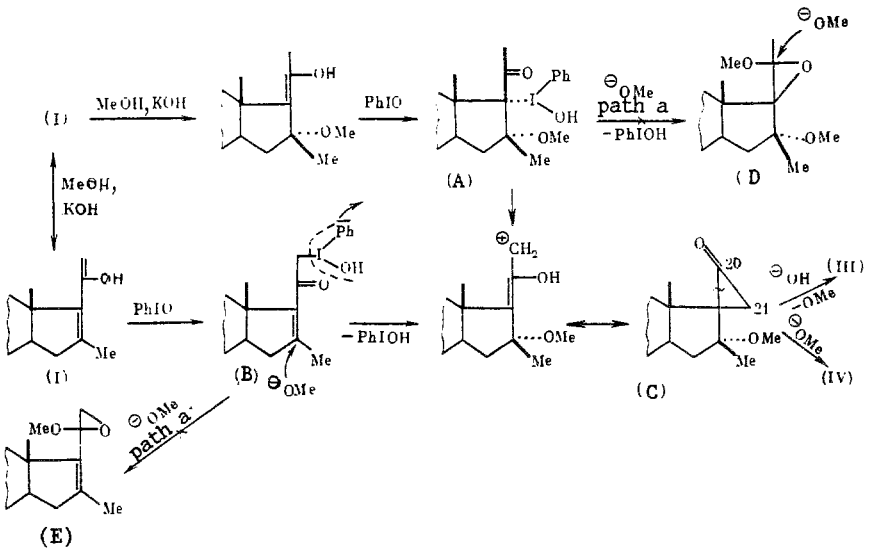

Scheme 2

system [8], is probably due to the steric influence of the 16-methyl substituent present. This, we believe, is the specific factor, which changes the general direction of the reaction of (I) with the $PhI(OAc)_2$–KOH–MeOH system. As a matter of fact, the expediency of hydroxylation of polyvalent iodine compounds presumes a synchronous attack at $C^{20}$ by an external nucleophile (a methoxide ion) at the stage of elimination of iodoxybenzene with the formation of epoxides (D) or (E) (path a, Scheme 2). Since in (I) this attack is hindered by the presence of the 16-methyl group, the reaction is concluded by intramolecular stabilization of intermediates (A), (D) with the formation of cyclopropanone (C).

The reaction of iodobenzene diacetate with epoxide (II) under standard conditions for $C^{21}$-hydroxylation of 20-ketosteroids does not proceed so unequivocally, as in the case of an analogous desmethyl oxide [1], leading to a multicomponent mixture of the end products. The characteristic feature of this transformation is a direct and preferential formation of ketol (V), and not its expected 20,20-dimethylacetal, which is only one of the minor components. The formation of ketol (V) is possibly explained by a competitive attack on the 20,21-epoxy intermediate of type (E) (Scheme 2) at the $C^{20}$ atom by a hydroxide and not a methoxide anion, the attack by the latter being sterically hindered by the presence of a 16β-methyl group in (II).

Ketol (V) was isolated by direct crystallization of the reaction mixture, while its 20,20-dimethylacetal was characterized through its 3-acetate (VII), obtained by chromatography of the reaction mixture after its acetylation. The maximal yield of (V) in the reaction of (IIb) with the $PhI(OAc)_2$–KOH–MeOH system was obtained by treating of the reaction mixture separated from the reagent with acetone in the presence of p-$MeC_6H_4SO_3H$ (p-TSA). This treatment leads to the elimination of the 20-acetal group from the minor components and to the obtainment of a more homogeneous mixture, from which (V) is isolated by crystallization and subsequent chromatography of the mother liquor (60-65%). Attempts were made to isolate (V) through its 3,21-diacetate (VI) by crystallization of the acetylated reaction mixture, but this method gives a product (mp 130-145°C after a single crystallization from MeOH) contaminated with 20,20-dimethylacetal (VIII), which cannot be separated by the subsequent chromatography. Therefore to obtain (VI) by this method, the acetylation stage should be preceded by the above-indicated acid treatment of the reaction mixture. Neutralization by mineral acids recommended in [3, 4] for these reactions, is not desired in this case because of the ready opening of the expoxide ring under acid conditions. Thus, even a brief treatment of the reaction mixture with a dilute HCl leads to furanone (IX).

The structure of compounds (V), (VI) was verified by their identity with the previously obtained samples, and that of the remaining compounds, by physicochemical methods of analysis. In the PMR spectra of acids (IIIa, b) and their methyl esters (IVa, b) there are two proton signals of nonequivalent methylene protons at $C^{20}$ (the AB spectrum), displaying a geminal interaction with a constant J = 15 Hz. The position of these signals (δ ~ 2.9 and ~3.1 ppm) differs very substantially from that described in [8] for the 17α-H-analog (a doublet with

TABLE 1. Data of $^{13}C$ NMR Spectra for Compounds (IVa) and (IX)

| Number of atom | (IVa) | (IX) | Number of atom | (IVa) | (IX) |
|---|---|---|---|---|---|
| | δ, ppm (J, Hz) | | | δ, ppm (J, Hz) | |
| 1 | 37,21 | 37,05 | 13 | 47,66 | 47,83 |
| 2 | 31,62 | 27,80 | 14 | 55,65(120) | 52,17(120) |
| 3 | 71.76(142) | 73,85(149) | 15 | 37,05 | 42,52 |
| 4 | 42,36 | 38,15 | 16 | 135,93 | 93,83 |
| 5 | 141,18 | 139,82 | 17 | 138,40 | 88,58 |
| 6 | 121,52 | 122,12(154) | 18 | 15,50 | 13,99 |
| 7 | 31,68 | 31,82 | 19 | 19,38 | 19,42 |
| 8 | 30,39 | 31,46 | 20 | 30,84 | 218,69 |
| 9 | 50,83(122) | 49,56 (124) | 21 | 172,76 | 71.18 d.d (146 and 151) |
| 10 | 36,82 | 36,73 | 22 | 51,76(146) | 20,65 |
| 11 | 20,75 | 19,91 | 23 | 14,75 | – |
| 12 | 34,72 | 30,70 | 3-$\underline{C}OCH_3$ | – | 170,53 |
| | | | 3-$CO\underline{C}H_3$ | – | 21,49 |

δ 2.28 ppm), this being due to the decreasing effect by the $\Delta^{16}$-bond. Its presence in the compounds under consideration was proven by the presence of molecular peaks in the mass spectra of compounds (IIIa, b), (IVa) (m/z 344, 386, and 358, respectively) and by the $^{13}C$ NMR spectrum data for (IVa) (Table 1).

In the IR spectrum of (IX) there is a characteristic absorption for the carbonyl group with ν 1748 $cm^{-1}$. The opening of the epoxy ring is indicated, firstly, by the fact of the appearance in the IR spectrum of an absorption band of a tertiary hydroxyl group with ν 3450 $cm^{-1}$ which is not acetylated under mild conditions, and secondly, by a change in the chemical shift of the 16-methyl group protons in the PMR spectrum of (IX), compared with the spectrum of epoxide (Ia) (1.28 and 1.44 ppm, respectively). The mass spectrum of (IX) has no molecular peak, but the observed fragmentation with the successive elimination of water and the methyl group corresponds to the ascribed structure. The cis-coupling of rings D and E is assumed based on the general patterns governing the epoxy ring opening. The $^{13}C$ NMR spectral data for (IX) given in Table 1, and their comparison with the data for the closest analog, steroid (X) [9], confirm the furanone structure.

## EXPERIMENTAL

The melting points were determined on a Koffler apparatus. The NMR spectra were recorded in $CDCl_3$ on Bruker WM-250 and Bruker AM-300 spectrometers, relative to TMS; the IR spectra were run in KBr tablets or in a $CHCl_3$ solution, on a UR-20 spectrophotometer and the mass spectra were measured on a Varian MAT CH-6 mass spectrometer. In the analytical TLC, Silufol plates were used, with detection by a $CeSO_4$ solution in dilute $H_2SO_4$. In preparative TLC, Silpearl brand silica gel was used.

Reaction of 16-Methylpregna-5,16-dien-3β-ol-20-one Acetate (Ib) with the $PhI(OAc)_2$-MeOH–KOH System. A 0.3-g portion of (Ib) and 0.33 g of $PhI(OAc)_2$ were added at 20°C to a solution of 0.4 g of KOH in 3 ml of MeOH, and then 1 ml of $CHCl_3$ was added to the solution of the precipitate. The mixture was stirred at 20-25°C for 45 min, and was then evaporated in vacuo to dryness. The residue was ground first with ether (5 × 10 ml) and then with $CHCl_3$ (3 × 10 ml), and the extracts were decanted from the precipitate. The ether and chloroform extracts were dried over $MgSO_4$, the solvent was removed in vacuum, yielding 0.09 and 0.02 g of a residue, respectively [the latter is enone (Ia) recovered in a practically pure state]. To the precipitate remaining after decantation, water (3 ml) and HCl were added up to an acid reaction, the precipitate that separated was filtered, and washed with water. Yield, 0.21 g of a product, which was crystallized from MeOH to give 16-methylpregna-15,16-dien-3β-ol-21-ic acid (IIIa), mp 255-258°C (dec.), comprising, according to the data on acetylation given below, ~75% of this fraction. IR spectrum (ν, $cm^{-1}$, KBr): 1048, 1058, 1285, 1435, 1685, 3300, 3450 sh. Mass spectrum (m/z): 344 $M^+$, 329 $[M-Me]^+$, 311 $[M-Me-H_2O]^+$, 293 $[M-Me-2H_2O]^+$, 285 $[M-CH_2COOH]^+$, 269, 251.

Partition of the ether extract (0.09 g) by the TLC method (ether–petroleum ether, 2:1) gave, together with 0.01 g of (Ia), 0.03 g of the methyl ester of 16-methylpregna-5,16-dien-3β-ol-21-ic acid (IVa), mp 172-174°C (from aqueous MeOH), IR spectrum (ν, $cm^{-1}$, KBr): 1062, 1158, 1312, 1435, 1715, 1740, 3450, 3485. IR spectrum (ν, $cm^{-1}$, $CHCl_3$): 1050, 1165, 1730, 3610. PMR spectrum (δ, ppm): 0,76 s (18-$CH_3$), 1.04 s (19-$CH_3$), 1.69 s (16-$CH_3$), 2.93 d and 3.08 d (20-$CH_2$, J = 14.9 Hz), 3.52 m (3-H), 3.66 s (OMe), 5.38 m (6-H). Mass spectrum (m/z): 358 $M^+$, 343 $[M-Me]^+$, 285 $[M-CH_2COOMe]^+$.

16-Methylpregna-5,16-dien-3β-ol-21-ic Acid Acetate (IIIb) and Methyl Ester (IVb). The above-prepared acid fraction (0.21 g) was acetylated in the usual way ($Ac_2O$ in Py, 24 h, 20°C), and was then separated by TLC ($SiO_2$, petroleum ether–ether, 2:1). As well as 0.02 g of (Ib), the following were isolated: a) 0.12 g of (IIIb), mp 187-189°C (from MeOH). IR spectrum (ν, $cm^{-1}$, KBr): 1042, 1160, 1280, 1380, 1448, 1710, 1732, 3250. PMR spectrum (δ, ppm): 0.77 s (18-$CH_3$), 1.05 s (19-$CH_3$), 1.69 s (16-$CH_3$), 2.03 s (3-OAc), 2.95 d and 3.12 d (20-$CH_2$, J = 15.6 Hz), 4.61 m (3-H), 5.4 m (6-H). Mass spectrum (m/z): 386 $M^+$, 371 $[M-Me]^+$, 326 $[M-HOAc]^+$, 320 $[M-HOAc-Me]^+$, 267 $[M-HOAc-CH_2COOH]^+$.

b) 0.02 g of (IVb), mp 100-101°C (from MeOH), IR spectrum (ν, $cm^{-1}$, KBr): 1045, 1063, 1252, 1385, 1440, 1738. PMR spectrum (δ, ppm): 0.75 s (18-$CH_3$), 1.05 s (19-$CH_3$), 2.04 s (3-OAc), 2.93 d and 3.08 d (20-$CH_2$, J = 14.8 Hz), 3.66 s (OMe), 4.61 m (3-H), 5.38 m (6-H). Mass spectrum (m/z): 340 $[M-HOAc]^+$, 325 $[M-HOAc-Me]^+$, 267 $[M-HOAc-CH_2COOMe]^+$, 251.

16β-Methyl-16α,17α-epoxypregn-5-en-3β,21-diol-20-one (V). A 0.2 g portion of (IIb) and 0.19 g of $PhI(OAc)_2$ were added to a solution of 0.15 g of KOH in 3 ml of MeOH, and then 0.5 ml of $CHCl_3$ was added to the solution of the precipitate. The mixture was stired at 20-25°C for 40 min, evaporated in vacuo to dryness, the precipitate was ground with ether (3 × 20 ml), and then with $CHCl_3$ (3 × 10 ml), and the solutions were decanted. From the ether and chloroform solutions, after evaporation of the solvents, 0.22 and 0.05 g, respectively, of dry residues were obtained. The first of these was crystallized from MeOH. Yield 0.04 g of (V), mp 149-155°C. The mother liquor was combined with the chloroform extract, the solution was evaporated to dryness, and the residue was dissolved in 3 ml of acetone containing 0.017 g of p-TSA. The solution was stirred for 40 min at 20°C, was then evaporated in vacuo, 2 ml of $H_2O$ were added to the residue, and the mixture was extracted with $CHCl_3$ (50 ml). The chloroform extract was dried over $MgSO_4$, the solvent was evaporated in vacuo, and the residue (0.15 g) was recrystallized from MeOH. Yield 0.05 g of (V), mp 153-157°C. IR spectrum (ν, $cm^{-1}$, KBr): 1062, 1098, 1382, 1480, 1710, 3300, 3380, 3475. PMR spectrum (δ, ppm): 1.03 s (18-$CH_3$), 1.14 s (19-$CH_3$), 1.44 s (16-$CH_3$), 3.08 br. s (OH), 3.51 m (3-H), 4.32 br. s (21-$CH_2$), 5.32 m (6-H). Mass spectrum (m/z): 360 $M^+$, 345 $[M-Me]^+$, 342 $[M-H_2O]^+$, 329 $[M-CH_2OH]^+$, 313.

The mother liquor was purified by TLC (ether–hexane, 3:1), whereby 0.06 g of additional (V) was isolated.

Reaction of 16β-Methyl-16α,17α-epoxypregn-5-en-3β-ol-20-one Acetate (IIb) with $PhI(OAc)_2$–KOH–MeOH System, Followed by Acetalization of the Reaction Mixture. A 1-g portion of (IIb) and 1.1 g of $PhI(OAc)_2$ were added to a solution of 0.8 g of KOH in 11 ml of MeOH, and then 1.5 ml of $CHCl_3$ was added. The mixture was stirred for 40 min at 20°C, and evaporated in vacuo, and the residue was diluted with water. The mixture was extracted with $CHCl_3$, the chloroform extract was washed with water, and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was held for 18 h at 20°C with 4 ml of $Ac_2O$ and 20 ml of Py, and was evaporated several times in vacuo with MeOH and heptane. The dry residue obtained was crystallized, first from ether, and then from MeOH, yielding 0.52 g of a product, mp 130-145°C. Repeated crystallization from MeOH gave 0.24 g of (VI), mp 152-163°C, with an analytical sample melting at 167-171°C (cf. [10]). The mother liquor was purified by TLC ($SiO_2$, acetone–hexane, 1:6). As well as 0.03 g of (IIb), the following were isolated: a) 0.13 g of 20,20-dimethoxy-16β-methyl-16α,17α-epoxypregn-5-ene-3β,21-diol 3-acetate (VII), mp 155-158°C (from MeOH). IR spectrum (ν, $cm^{-1}$, KBr): 1040, 1058, 1240, 1372, 1732, 3500. PMR spectrum (δ, ppm): 1.02 s (19-$CH_3$), 1.19 s and 1.23 s (18-$CH_3$, 16-$CH_3$), 2.03 s (3-OAc), 3.2 s and 3.3 s (20-$OCH_3$), 3.72 d and 4.07 d (the AB spectrum), 21-$CH_2$, J = 10.7 Hz), 4.6 m (3-H), 5.37 m (6-H). Mass spectrum (m/z): 448 $M^+$, 417 $[M-OMe]^+$, 388 $[M-HOAc]^+$, 356 $[M-HOAc-MeOH]^+$, 344 $[M-C(OMe)_2CH_2OH]^+$, 327 $[M-C(OMe)_2CH_2OH-OH]^+$, 284 $[M-HOAc-C(OMe)_2CH_2OH]^+$, 269 $[M-HOAc-C(OMe)_2CH_2OH-Me]^+$.

b) A 0.26-g portion of a chromatographically homogeneous fraction, which was crystallized from MeOH to yield 0.1 g of (VI) mp 130-160°C. By repeating several times the chromatography of this fraction, from the upper part of the band, 20,20-dimethoxy-16β-methyl-16α,-17α-epoxypregn-5-en-3β-ol 3-acetate (VIII), mp 126°C (from MeOH) was isolated. IR spectrum (ν, $cm^{-1}$, KBr): 1032, 1062, 1240, 1368, 1442, 1735. PMR spectrum (δ, ppm): 1.02 s (18-$CH_3$, 19-$CH_3$), 1.4 s (16-$CH_3$), 1.62 br. s (21-$CH_3$), 2.02 s (3-OAc), 3.33 s and 3.42 s (20-$OCH_3$), 4.6 m (3-H), 5.38 m (6-H). Mass spectrum (m/z): 432 $M^+$.

3β-Acetoxy-16α-methyl-16β,21-epoxypregn-5-en-17α-ol-20-one (IX). A 0.4-g portion of (IIb) and 0.44 g of $PhI(OAc)_2$ were added to a solution of 0.35 g of KOH in 4 ml of MeOH. The mixture

was stirred for 50 min at 20°C, acidified with dilute HCl for 10 min, held for 5 min in an acid medium, and then neutralized by a KOH solution and evaporated in vacuo. The residue was diluted with water, the mixture was extracted with $CHCl_3$, the chloroform extract was washed with water, and dried over $MgSO_4$. The residue after the removal of chloroform was acetylated with $Ac_2O$ in Py, treated by the above-described method, and crystallized from water, and then from MeOH. Yield, 0.07 g of (VI), mp 122-145°C. The mother liquor was partitioned by TLC ($SiO_2$, acetone–hexane, 1:6), whereby, together with 0.02 g of (IIa), 0.11 g of (VI), mp 125-150°C, 0.05 g of (VII) as well as 0.09 g of (IX), mp 219-223°C (from MeOH), were isolated. IR spectrum ($\nu$, $cm^{-1}$, KBr): 1042, 1052, 1253, 1732, 1748, 3450. PMR spectrum ($\delta$, ppm): 1.2 s and 1.25 s (18-$CH_3$, 19-$CH_3$), 1.28 s (16-$CH_3$), 2.02 s (3-OAc), 4.06 d and 4.2 d (21-$CH_2$, the AB spectrum, J = 10.9 Hz), 4.6 m (3-H), 5.38 m (6-H). Mass spectrum (m/z): 342 $[M-HOAc]^+$, 327 $[M-HOAc-Me]^+$, 324 $[M-HOAc-H_2O]^+$, 309 $[M-HOAc-H_2O-Me]^+$, 299, 271.

## CONCLUSIONS

1. The reaction of 16-methylpregna-5,16-dien-3β-ol-20-one with iodobenzene diacetate in a methanolic alkali solution proceeds with a Favorskii rearrangement, with formation of 16-methylpregna-5,16-dien-3β-ol-21-ic acid and its methyl ester.

2. A new method for the synthesis of 21-hydroxy-16α,17α-epoxy-20-ketosteroids from 16β-methyl-16α,17α-epoxypregn-5-en-3β-ol-20-one has been proposed.

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