Synthesis of 2-Methyl-3-oxa-A-norestra-1,5(10)-dien-17β-ol and 2-Methyl-3-oxa-4,19-bisnorpregna-1,5(10)-dien-20-one1)

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The titled compounds were synthesized from the corresponding 10-propargyl-des-A-9(10)-en-5-one derivatives through the 3,5-seco-4-nor-dioxo steroids. The preparation of des-A-19-norpregn-9(10)-ene-5,20-dione involving the condensation of phenyl methyl sulfone or dimethyl sulfone with methyl 1β-methoxycarbonyl-5,5-ethylenedioxy-7α-methyl-3αz, 7αβ-hexahydroindan-4α-y1 propionate is also described.

In the preceding paper of this series,1) A-furanosteroids with or without a methyl substituent at the β position in the furan ring were synthesized through 10β-phenylsulfonyl-17β-hydroxy-des-A-ester-9(11)-en-5-one (1) derived from 7α-methy1-1,5-dioxo-3αz,7αβ-hexahydroindan-4α-yl propionate. The present paper deals with synthesis of both an estrane and a pregnane system of A-furanosteroids having a methyl group at the α position in the furan ring.

Since it is well known that a γ-diketone upon treatment with acid gives a furan, a starting material suitable for synthesizing α-methylfuranosteroids was considered to be a 3,5-seco-4-nor-2,5-dioxo steroid and such a compound can be prepared for example from the product of alkylation of 5-pyrrolidyl-17β-hydroxy-des-A-ester-5-(10),9(11)-diene(5) with 1,2-dichloro-2-propene as described by Nominé, et al.3) who have used this compound for the preparation of 17β-hydroxy-A-norester-3-en-2-one. Recently, Pandit, et al.4) have reported the reaction of a conjugated enamine with α-haloketone leading to the direct formation of a

![Chart 1](attachment:chart1.png)

1) This work is Part XXXIV of "Thiosteroids"; Part XXXIII: T. Komeno, S. Ishihara, and H. Itani, Tetrahedron, 28 4719 (1972).
2) Location: Fukushina-ku, Osaka, 553, Japan.
fused furano derivative. Unfortunately, an attempted alkylation of the tricyclic dienamine (5) with α-bromoacetone was unsuccessful and its hydrolysis product, 17β-hydroxy-des-A-estr-9(10)-en-5-one, was completely regenerated. However, preparation of the desirable 17β-acetoxy-3,5-seco-4-norestr-9(10)-ene-2,5-dione (4a) could be achieved by a scheme involving propargylation of either the dienamine (5) or the phenylsulfonyl compound (1), the latter process giving the better yield of 4a. Thus, treatment of the dienamine (5) with propargyl bromide in dimethylformamide (DMF) followed by acetylation gave a propargyl enone (3) in rather lower yield (27%) and the improved yield (50%) of 3 was obtained when the alkylation of 5 was carried out in dimethyl sulfoxide. The compound (3) in turn was converted in high yield to the above enedione (4a) by hydration with mercuric sulfate in methanol containing a trace of sulfuric acid.\(^5\) The structure of 4a thus obtained was suggested by the ultraviolet (UV) spectrum and by the indication in the proton magnetic resonance (PMR) spectrum of the presence of two sharp singlets for acetyl moieties and an AB-type quartet due to methylene protons in an acetonyle group. A modified hydration of 3 with mercuriated cation exchange resin\(^6\) caused hydrolysis of the product partly accompanied by cyclization affording a γ-diketone (4b) and a vinyl furan (6b) in yields of 44.6% and 23.8% respectively. Acetylation of 4b gave an acetate identical with 4a obtained from 5. On the other hand, alkylation of the phenylsulfonyl compound (1) with propargyl bromide in the presence of α-methylsulfinyl carbanion\(^1\) and subsequent acetylation of the product obtained afforded in 76% yield a propargyl compound (2), in which the α equatorial configuration of the introduced propargyl group was assumed from its PMR spectrum. The C\(_{11}\)-proton resonance at 5.89 ppm is not significantly deshielded compared to that observed at 6.49 ppm in the dienol acetate of 1 in which the sulfonyl group is apparently in proximity to the vinyl proton as discussed in the preceding paper.\(^1\) Desulfurization reaction of compound (2) with zinc dust in acetic acid gave rise the concomitant hydration of the propargyl moiety in the molecule and there was obtained a mixture which consisted of 38% of the expected propargyl enone (3), 41% of its hydrated product (4a) and 2.7% of a vinyl furan derivative (6a), these compounds being separated by preparative thin-layer chromatography (TLC). The former two compounds were identified with the samples prepared through the dienamine (5) respectively, by mixed melting points, comparison of infrared (IR) spectra and TLC. Thus, when the phenylsulfonyl propargyl compound (2) was desulfurized with zinc dust in acetic acid and the product was hydrated without further purification, there was obtained a 79% yield of the acetonyle compound (4a) together with a 5.7% yield of the vinyl furan (6a). Compound (6a), whose structure can be readily assumed from the UV (\(\lambda_{\text{max}}\) 241.5 nm) and PMR spectrum (a broadened singlet due to aromatic methyl protons at 2.22 ppm), was also obtained in 53.7% yield by heating 4a in benzene in the presence of p-toluene sulfonic acid. However, the reaction was accompanied by concomitant rearrangement and aromatization of the B-ring to give a vinyl furan (7) different from 6b and a benzofuran derivative (8) in yields of 11% and 6% respectively, neither of which could be crystallized. The former exhibits quite similar UV and PMR spectral properties to those of 6b, except that the 13-methyl signal was observed at a field 0.27 ppm lower than that of 6b; hence the 8α-isomeric structure was tentatively assumed for 7. Compound (8), whose UV spectrum shows an absorption maximum at 255 nm and an absorption band containing fine structures at about 280 nm, was assigned as the benzofuran derivative in accord with the PMR spectral evidence of signals due to two vicinal and one isolated vinyl protons. The acetonyl compound (4a) on hydrogenation over palladium on charcoal led to a saturated γ-diketone (9), which in turn was heated in boiling benzene in the presence of p-toluene sulfonic acid yielding the desired compound, 2-methyl-3-oxa-A-norestra-1,5-(10) dien-17β-ol acetate (10b). Though preparation of a 2-methylthienosteroid was attempted

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by reaction of the acetonyl compound (4a) with phosphorous pentasulfide in boiling benzene, formation of the expected thienosteroid was not observed and instead the 2-methylfurano-steroid (10b) was obtained in high yield. The structure of 10b and its hydrolysis product (10a) were supported by their UV, PMR and mass spectral data described in Experimental.

Since 5,5-ethylenedioxy-10β-methylsulfonyl-des-A-estr-9(11)-en-17-one (11) resists hydrolysis of the ketal moiety under the acidic conditions usually employed\(^1\) and also contains a keto function convertible to a pregnane derivative, the transformation of 11 into a pregnane system through its cyanohydrin was first attempted, though this scheme was unfavorable for the following reasons. Whereas treatment of 11 with potassium cyanide in methanol and acetic acid\(^7\) gave a cyanohydrin (12) in 58% yield, on transcyanohydration of 11 with acetone cyanohydrin\(^8\) an isomeric cyanohydrin (13) was deposed as crystals from the reaction mixture in high yield. Because it is known that there is a preference for α-attack of the C\(_{17}\)-carbonyl group by the CN ion\(^9,10\) the cyanohydrin (12) was assigned as 17α-cyano-17β-ol and hence (13) as 17β-cyano-17α-ol. These assignments were also supported by the molecular rotation difference shown in Table I and by the IR spectral data. The IR spectrum of 13 shows a more intense absorption band due to a CN group than that in the spectrum of 12, this being in keeping with Nagata's observation that an equatorial cyano compound shows a higher CN band intensity than an axial epimer despite slight fluctuation of the absorption maximum in both epimers.\(^11\) It was reasonably considered that the reaction of 11 with acetone cyanohydrin might proceed accompanied by an equilibrium and that precipitation of the less soluble cyanohydrin (13) with the CN group in the β configuration causes shifting the equilibrium in its favor. A similar predominant formation of 17β-cyano-17α-ol has been observed in the reaction of 3,3-ethylenedioxyestra-5(10),9(11)-dien-17-one with potassium cyanide.\(^12\) Dehydration of the cyanohydrin (13) with phosphoryl chloride in pyridine\(^13\) gave a dieneketal (14) in 90% yield, which in turn was hydrolized in high yield to a dienone (15) by treatment with perchloric acid in boiling acetone. Reduction of 15 with zinc dust in acetic acid afforded in moderate yield a desulfurized dienone (16), in which the keto function was protected by conversion to a ketal (17) with ethylene glycol. Grignard reaction of 17 with methyl magnesium bromide gave a complex mixture, from which the desired des-A-19-norpregna-9(10),16-diene-5,20-dione (18) could not be obtained. Column chromatography of the product over silica gel afforded a 20% yield of compound (19) as the only crystalline substance, the PMR spectrum of which shows three singlets assignable as methyl protons at 0.83, 1.09, and 2.25 ppm together with a multiplet due to an O-CH₂-CH₂-O group.

Table I. Molecular Rotation Difference between Cyanohydrins and the Parent Ketones

<table>
<thead>
<tr>
<th>Parent ketone</th>
<th>M(_\circ)</th>
<th>α-CN, β-OH</th>
<th>β-CN, α-OH</th>
<th>(\Delta_1)</th>
<th>(\Delta_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3β-Acetoxy-5α-androstan-17-one(^a)</td>
<td>+285</td>
<td>-82</td>
<td>+105</td>
<td>-367</td>
<td>-180</td>
</tr>
<tr>
<td>3β-Acetoxyandrost-5-en-17-one(^b)</td>
<td>+14</td>
<td>-470</td>
<td>-198</td>
<td>-484</td>
<td>-212</td>
</tr>
</tbody>
</table>

\(\Delta_2\) \(\Delta_1\)

\(^a\) Ref. 9

\(^b\) Ref. 7, 8, 9, 10, 11

13) A. Butenandt and J. Schmidt-Thomé, Chem. Ber., 71, 1487 (1938); 72, 182 (1939).
coupled with an absorption band due to a hydroxyl group in the IR spectrum indicate that 19 arises from the formation of an acetyl side chain concurrently accompanied by cleavage of the ether linkage in the ketal moiety by the reagent.\(^{14}\)

Successful condensation of dimethyl sulfone or phenyl methyl sulfone with methyl 1,1,5,5-bisethylenedioxy-7a-methyl-3az,7aβ-hexahydroindan-4az-yl propionate as described previously\(^{14}\) led us to investigate a scheme including the reaction of the reagents with methyl 1β-methoxy carbonyl-5-oxo-7a-methyl-3az,7aβ-hexahydroindan-4az-yl propionate, the free acid (21) of which is readily obtainable by the microbiological oxidation of 3-oxoandrost-4-ene-17β-carboxylic acid (20) with Arthrobacter simplex.\(^{15}\) When the dimethyl ester of 21 in which the keto function was protected by conversion to the ketal (22) by the usual ketalization was subjected to condensation with dimethyl sulfone, followed successively by treatment with acid then with alkali, there was obtained in 74% yield an expected bismethylsulfonyl compound (23) as an amorphous material, which was characterized by its spectral properties. Slow distillation of a solution of 23 in ethylene glycol in the presence of p-toluene sulfonic acid gave a high yield of a monoketal (24) as crystals. Unfortunately, desulfurization of 24 with sodium in liquid ammonia, followed by acid treatment and reoxidation with Jones reagent afforded only about 60% yield of a neutral fraction, from which 11.8% yield of the desired des-A-19-norpregn-9(10)-ene-5,20-dione (27) was obtained in addition to 33.8% yield of a compound containing a methylsulfonyl group. The latter compound was identified as 21-methylsulfonyl-des-A-19-norpregn-9(10)-ene-5,20-dione (28) by the UV spectrum


and by indication in the PMR spectrum of the presence of a methylsulfonyl group and of the lack of a methyl signal due to an acetyl moiety. The poor recovery of the neutral fraction in this reaction may suggest the occurrence of C–S bond fission of the methylsulfonyl moiety at C21 and loss of the β-ketosulfinic acid, or its reduced acid, either of which may be formed and dissolved into alkali during the post-treatment of the reaction. Moreover, reduction of the carbonyl group at C20 in 24 with sodium borohydride, followed by desulfurization with sodium or lithium in liquid ammonia, aicd treatment, and Jones oxidation afforded only the methylsulfonyl compound (28) in high yield. Therefore, it was considered that replacement of the methylsulfonyl group with a phenylsulfonyl counterpart may be suitable for preparation of 27. This was demonstrated with the following successful result. Condensation of 22 with phenyl methyl sulfone, followed by treatment with acid and alkali, gave a bisphenylsulfonyl compound (25) as an oily substance, ketalization of which by the slow distillation method afforded a monoketal 26 as crystals in 69.9% overall yield based on the dicarboxylic acid 21. In another run, employing the same sequence of the reactions except that the prolonged ketalization was performed, we obtained 11.1% yield of a bisketal (30) and 3.9% yield of a compound (29) containing an unreacted methyl carboxylate group besides 59.4% yield of the monoketal. Compound (29) was assigned as methyl 5,5-ethylenedioxy-10β-phenylsulfonyl-des-A-estr-9(11)-ene-17β-carboxylate from the PMR spectrum (in C6D6) showing a singlet due to methoxy methyl protons at 3.38 ppm and a broadened singlet owing to the 10α-proton at 3.84 ppm. Desulfurization of 26 with sodium in liquid ammonia, followed by acid treatment and reoxidation with Jones reagent gave the expected des-A-19-norpregn-9(10)-ene-5,20-dione (27) in 70% yield. The physical constants of the compound (27) so obtained are in good agreement with those described by Bucourt, et al.16)

As described above, alkylation of the dienamine (31), readily prepared from 27 with propargyl bromide in hexamethylphosphoramide, gave a propargyl compound (32) in 53.1% yield, which in turn was hydrated quantitatively to an acetonyl compound (33) with mercuric sulfate. Hydrogenation of 33 over palladium on charcoal afforded 88.7% yield of 3,5-seco-4,19-bisnorpregnane-2,5,20-trione (34a) in addition to two minor products (34b and 35) in yields of 5.1% and 1.3%, respectively. Of these minor compounds, 35 was assigned as 5β-hydroxy-3,5-seco-4,19-bisnorpregnane-2,20-dione from the IR (νOH 3459 cm⁻¹) and PMR spectra. In the latter spectrum two acetyl methyl signals at 2.09 and 2.12 ppm besides one tertiary methyl signal at 0.63 ppm and a double triplet pattern at 3.26 ppm (J=4.5 and 14.5 Hz) assignable as an axial proton geminal to a hydroxyl group were observed. Furthermore, this assignment was proved by the fact that Jones oxidation of 35 gave 34a. Finally, heating both 34a and 34b in boiling benzene in the presence of p-toluenesulfonic acid afforded the desired 2-methyl-3-oxa-4,19-bisnorpregna-1,5(10)-dien-20-one (36) in high yield, the structure of which was confirmed by the spectral data including the mass spectrum. Hence, 34b was assigned as an epimer of 34a.

Experimental[17]

10α-Propargyl-10β-phenylsulfonyl-17β-acetoxy-des-A-estr-9(11)-en-5-one (2) — To a stirred solution of s-methylsulfinyl carbamion generated from 270 mg of NaH with petroleum ether and 1.2 ml of DMSO in 5 ml of monoglyme, were added 1 (2.023 g) and 16 ml of monoglyme under nitrogen. The resulting mixture was warmed at 50° for 30 min then cooled to room temperature. To the mixture was added 0.6 ml of propargyl bromide. The stirred reaction mixture was allowed to stand for 22 hr at room temperature and then at 50° for 7 hr. The product extracted with CH₂Cl₂ was acetylated with 5 ml of Ac₂O in 10 ml of pyridine at room temperature overnight. After usual work-up, chromatography on 220 g of silica gel gave 1.922 g of 2, which was recrystallized from acetone–hexane to afford 1.890 g (76.4%) of the pure sample, mp 180–182°. [α]D +104.0 ± 1.3° (c = 1.082). IR υmax cm⁻¹: 3272 (≡CH), 1718, 1259 (C=O, Ac), 1635 (β), 1556, 758, 716, 686 (C₆H₅), 1323, 1312, 1143 (SO₃). CD (in [dioxane]: [θ]225 = -2588, [θ]243 = -7490, [θ]231 = -11010, [θ]302,4 = -11730, [θ]251 = +18720, [θ]323 = +18720, [θ]310 = +14210. PMR (δ): 1.00 (s, 3, Me), 1.81 (t, J = 2.5 Hz, 1, ≡CH), 2.06 (s, 3, OAc), 2.55–3.22 (m, 2, CH₃), 4.78 (t, 1, 17α-H), 5.89 (m, 1, 11-H), 7.60 (m, 5, C₆H₅-H); (in C₆D₆) 1.04 (s, 3, Me), 1.62 (t, J = 2.5 Hz, 1, ≡CH), 1.72 (s, 3, OAc), 2.78 & 3.19 (AB-type q, JAB = 15.5 Hz, 2, CH₂), 4.76 (t, 1, 17α-H), 5.93 (m, 1, 11-H). Anal. Calcd. for C₂₅H₂₈O₃: C, 75.97; H, 8.05. Found: C, 76.09; H, 8.19. In another run, a solution of 5 (6.489 g) in 32 ml of DMF was treated with 2.3 ml of propargyl bromide at room temperature for 65 hr then 15 ml of water was added. The mixture was warmed on a steam bath for 3 hr and then extracted with CH₂Cl₂ gave a material which was acetylated with 12 ml of Ac₂O in 20 ml of pyridine. The product (ca. 5.8 g) was chromatographed on 150 g of Al₂O₃. The fraction eluted with petroleum ether–benzene (9:1–1:1) was recrystallized from ether–isopropyl ether giving 1.929 g (27.0%) of 3, mp 128–129.5°. [x]D = -64.0 ± 1.0° (c = 1.093). IR υmax cm⁻¹: 3311 (≡CH), 2111 (C=O), 1738, 1248 (OAc), 1658, 1610 (C=C-C=O). UV λmax nm (e): 247.5 (13700). CD (in MeOH) : [α]337 = -1137, [α]323 = +1271, [α]321 = -13790, [α]219 = +16320. PMR (δ): 0.98 (s, 3, Me), 1.88 (t, J = 2.5 Hz, 1, ≡CH), 2.05 (s, 3, OAc), 3.28 (br, s, W/2 = 5.5 Hz, 2, CH₂), 4.68 (t, 1, 17α-H). Anal. Calcd. for C₁₅H₁₄O₃: C, 75.97; H, 8.05. Found: C, 75.97; H, 8.19. In another run, a solution of 5 (1.000 g) in 50 ml of DMSO was treated with propargyl bromide and worked up in the same way as described above. Chromatography of the acetylated product and recrystallization afforded 547 mg (49.7%) of 3.

Desulfurization of 2 — A mixture of 2 (135 mg) and zinc dust (1.0 g) in 10 ml of AcOH was stirred under reflux for 2.5 hr. The reacetylated product was separated by preparative TLC (cyclohexane:AcOEt = 2:1). In order of their decreasing mobility, the fractions afforded 2.5 mg (2.7%) of 6a and 35 mg (38.0%) of 4a, mp 119–120°, which were identified with authentic samples by mixed mps and comparison of IR spectra, respectively.

Hydration Reaction of 3 — a) A mixture of 3 (1.929 g), 102 mg of HgSO₄ and 0.51 ml of conc. H₂SO₄ in 57 ml of 90% MeOH was stirred under reflux for 10 min and poured into ice water. The product (2.01 g) was acetylated with 12 ml of Ac₂O in 20 ml of pyridine. After usual work-up, recrystallization of the acetate from acetone–hexane gave 2.050 g of 4a, mp 119.5–120.5°. [α]D = -81.3 ± 2.1° (c = 0.588). IR υmax cm⁻¹: 1725, 1255 (OAc & C=O), 1604, 1618, (C=C-C=O). UV λmax nm (e): 245.5 (15000). CD (in MeOH) : [α]348 = 1451, [α]338 = -1274, [α]321 = +558, [α]302 = +599, [α]300 = +181. PMR (δ): 1.00 (s, 3, Me), 1.88 (t, J = 2.5 Hz, 1, ≡CH), 2.05 (s, 3, OAc), 3.28 (br, s, W/2 = 5.5 Hz, 2, CH₂), 4.68 (t, 1, 17α-H). Anal. Calcd. for C₁₅H₁₄O₄: C, 69.12; H, 4.97. Found: C, 68.61; H, 4.81. b) Mercuriated cation exchange resin was prepared from 100 mg of Amberlite IR-120, 4 mg of HgO and 0.2 ml of 6N H₂SO₄ according to Hajos, et al.[9] A mixture of this resin and 3 (300 mg) in 2.4 ml of 80% MeOH was refluxed under nitrogen for 65 hr. The product was separated by preparative TLC (cyclohexane: AcOEt = 1:1). The more mobile fraction gave 41 mg of 6b and the less mobile fraction afforded 82 mg of 4b, which was recrystallized from hexane to yield the pure sample, mp 153–154°: [α]D = -69.5 ± 2.1° (c = 0.521). IR υmax cm⁻¹: 3516 (OH), 1716 (C=O), 1666, 1618 (C=C-C=O). UV λmax nm (e): 249 (13500). CD (in MeOH) : [α]337 = -1137, [α]323 = +1271, [α]321 = -13790, [α]219 = +16320. PMR (δ): 0.98 (s, 3, Me), 1.88 (t, J = 2.5 Hz, 1, ≡CH), 2.05 (s, 3, OAc), 3.28 (br, s, W/2 = 5.5 Hz, 2, CH₂), 4.68 (t, 1, 17α-H). Anal. Calcd. for C₁₅H₁₄O₃: C, 75.97; H, 8.05. Found: C, 75.97; H, 8.19. In another run, a solution of 5 (1.000 g) in 50 ml of DMSO was treated with propargyl bromide and worked up in the same way as described above. Chromatography of the acetylated product and recrystallization afforded 547 mg (49.7%) of 3.
N. A. reaction without further purification (Yield: 2.641 g, 97.8%). Recrystallization from CH$_2$Cl$_2$.

10 min and allowed to stand for 2 hr at room temperature. The mixture, which contained deposited crystals, was poured into water. The precipitate was collected by filtration, washed with water, dried and used for the next reaction without further purification (Yield: 2.641 g, 97.8%). Recrystallization from CH$_2$Cl$_2$.

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2 hr, the mixture was cooled and poured into iced 5% HCl. The crystals which formed were collected by filtration, washed with water and dried. Recrystallization from acetone–hexane gave 2.881 g (89.6%) of 14, mp 256.5–258.5° (decomp.). \([\mathbf{x}^\mathbf{[1]}]_22 = -68.9 ± 1.6° (c = 0.688).\) IR \(\nu_{\text{max}} \text{ cm}^{-1}: 3954 \text{ (OH)}, 3075 \text{ (C} = \text{C)}, 1647, 1597 (\text{C} = \text{O}), 1236, 1125, 1068.\) PMR (\(\delta\)): 0.83 (s, 3, Me), 1.09 (s, 3, -O-C-Me), 2.25 (s, 3, COMe), 3.58 (m, 4, OCH2CH2O), 5.35 (m, 1, 11-H), 6.60 (q, \(J_{15\alpha:16} + J_{15\beta:16} = 5.0 \text{ Hz}, 1, 16-H).\) Anal. Calcd. for \(\text{C}_{19}\text{H}_{28}\text{O}_3\text{C}_3\text{H}_6\text{O}: \text{C}, 73.84; \text{H}, 9.37.\) Found: \(\text{C}, 73.87; \text{H}, 9.67.\)

5,5-Ethylenedioxy-17-cyano-des-A-estra-9(11),16-diene (17) — A mixture of 14 (500 mg), 0.9 ml of 70% HClO4, and 20 ml of 75% acetone aq. was refluxed for 2 hr at room temperature then warmed at 60° for 4 hr with stirring. The cooled mixture was acidified with acq. HClO4 and extracted with CH2Cl2 yielding ca. 1.0 g of an oily substance, IR \(\nu_{\text{max}} \text{ cm}^{-1}: 1740, 1195, 1165.\) The resulting mixture was recombined with 50 mg of p-Ts0H- H2O and the mixture was refluxed for 4.5 hr and worked up. The residue (2.65 g) was dissolved in a mixture of 17 ml of 90% acetone aq. and extracted with CH2Cl2. The CH2Cl2 solution was washed with Na2CO3 aq., dried over Na2SO4 and concentrated in vacuo. The residue (2.54 g) was subjected to chromatography over 26 g of alumina (II). The fractions eluted with petroleum ether–benzene (4:1—1:1) afforded 1.149 g of a solid, which was recrystallized from acetone–hexane to give the pure sample, mp 256.5–258.5° (decomp.). \([\mathbf{x}^\mathbf{[1]}]_22 = -68.9 ± 1.6° (c = 0.688).\) IR \(\nu_{\text{max}} \text{ cm}^{-1}: 3954 \text{ (OH)}, 3075 \text{ (C} = \text{C)}, 1647, 1597 (\text{C} = \text{O}), 1236, 1125, 1068.\) PMR (\(\delta\)): 0.83 (s, 3, Me), 1.09 (s, 3, -O-C-Me), 2.25 (s, 3, COMe), 3.58 (m, 4, OCH2CH2O), 5.35 (m, 1, 11-H), 6.60 (q, \(J_{15\alpha:16} + J_{15\beta:16} = 5.0 \text{ Hz}, 1, 16-H).\) Anal. Calcd. for \(\text{C}_{19}\text{H}_{28}\text{O}_3\text{C}_3\text{H}_6\text{O}: \text{C}, 73.84; \text{H}, 9.37.\) Found: \(\text{C}, 73.87; \text{H}, 9.67.\)
with Na₂CO₃ aq., concentrated to a half its initial volume in vacuo and poured into ice water. Extraction with CH₂Cl₂ afforded 2.215 g of an oily substance, which was dissolved in 4 ml of MeOH and added to 3.3 ml of 2.5% KOH-MeOH. The mixture was stirred for 1 hr at room temperature and diluted with water. Extraction with CH₂Cl₂ gave 2.12 g (73.7% based on the acid (21)) of 23, TLC of which indicated its homogeneity. [α]D +133.4±1.8° (c=0.965). IR νmax cm⁻¹: 1714 (C=O), 1319, 1292, 1113 (SO₂). UV λmax nm (ε): 225 (2950), 3034 (1652), 1716 (1705), 1656, 1607 (C=C-C=C), 1912, 1152 (SO₂), 1265, 1065, 962. UV λmax nm (ε): 299 (17460), 300 (8770). PMR (δ): 0.86 (s, 3, H), 3.08 (s, 3, SO₂Me), 4.05 (s, 2, 21-CH₂), 5.91 (s, Wh/2=4.0 Hz, 1, 10-H). Anal. Calcd. for C₁₇H₂₄O₄S: C, 62.93; H, 7.46; S, 9.88. Found: C, 63.10; H, 7.43; S, 9.99. The less polar fraction afforded 59 mg (11.8%) of 27, which upon recrystallization from ether-petroleum ether yielded the pure sample, mp 80-81°. [α]D+53.1±1.0° (c=0.941).

**10β,21-Bisphenylsulfonyl-5,5-ethylenedioxy-des-A-19-norpregn-9(11)-en-20-one (26)** — A solution of 23 (2.12 g) and 120 mg of p-TsOH-H₂O in 120 ml of ethylene glycol was slowly distilled at 3-5 mmHg for 6 hr during which period 80 ml of distillate was removed. The remaining mixture was cooled, poured into ice water, and extracted with CH₂Cl₂. Work-up in the usual way gave 558 mg of an oily substance, which was treated with 0.28 ml of 70% HClO₄ in 3.6 ml of 70% acetone aq. for 2 hr at room temperature. After the excess of Na had been decomposed by addition of EtOH, the mixture was extracted with CH₂Cl₂. Work-up in the usual way gave 588 mg of an oily substance which was triturated with Na₂CO₃ aq. and extracted with CH₂Cl₂. After removal of the solvent, the residue was recrystallized from acetone–hexane to afford 2.084 g (65.2%) overall yield based on the acid (21) of 24, mp>250°. [α]D +86.8±1.4° (c=0.906). IR νmax cm⁻¹: 3034, 1652 (C=C), 1721 (C=O), 1294, 1132, 1125 (SO₂), 1103, 1077 (ketal). UV λmax nm (ε): 289 (54). CD (in CHCl₃): [θ]₂₂₀+11790. PMR (δ): 0.75 (s, 3, Me), 4.06 (s, 6, SO₂Me), 3.56 (s, Wh/2=3.5 Hz, 1, 10-H), 4.01 (m, 4, ketal-CH₂), 5.73 (m, 1, 11-H). Anal. Calcd. for C₂₀H₃₀O₁₄S₂: C, 53.71; H, 6.51; S, 15.93. Found: C, 53.51; H, 6.63; S, 15.65.

**Desulfurization of 24** — a) To a stirred solution of 1.25 g of Na in 100 ml of liquid ammonia was added 360 mg of 24 as crystals, mp 157-157.5°, which was characterized by mixed mp and comparison of the IR spectrum. b) To a suspension of 24 (392 mg) in 7 ml of MeOH was added 92 mg of NaBH₄ and the mixture was stirred for 30 min at room temperature. The resulting clear solution was poured into ice water and extracted with CH₂Cl₂, leaving 415 mg of a crystalline material. This substance dissolved in 6 ml of dry THF was allowed to stand for 18 hr at room temperature. After the excess of Na had been decomposed by addition of EtOH, the mixture was extracted with CH₂Cl₂. Work-up in the usual way gave 5.3 g of the product which was found to be a mixture of the desired 25 and the reagent, phenyl methyl sulfone. Purification of a part of this material (ca. 20 mg) by preparative TLC (cyclohexane:AcOEt= 1:1) gave 11 mg of pure 25, which could not be crystallized from any solvent. A solution of the remainder of the material and 86 mg of p-TsOH-H₂O in 80 ml of ethylene glycol was slowly distilled at 3-5 mmHg for 5 hr during which period 50 ml of distillate was removed. Work-up as described above gave ca. 5 g of a material from which 26 was separated by dry column chromatography on 350 g of silica gel (CH₂Cl₂:AcOEt=1:1). Crystallization of the fraction corresponding to 26 from ether afforded 2.971 g (69.9%) of 26 as crystals, mp 180-182°; [α]D +163.7±2.1° (c=0.957). IR νmax cm⁻¹: 1710 (C=O), 1645

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No. 2 343
(C=O), 1586, 755, 686 (C=H), 1479, 1404 (SO2H). IR \( \nu \text{max} \text{ cm}^{-1} \): 3273 (\( \text{\textbeta}\text{CH}\)), 2113, 1372 (C=O), 1316, 1104 (SO2), 1077 (ketal), 934. PMR (\( \delta \)): 0.78 (s, 3, Me), 3.07 (s, 3, OMe), 3.62 (m, 3, ketal-CH2), 3.90 (m, 2, C6H5-H), (C6D6): 0.99 (s, 3, Me), 3.05 (br s, \( WH/2=3.3 \text{ Hz} \), 1, 10-H), 7.52 (m, 3, C6H5-H), 7.05 (br s, 2, C6H5-H), (C6D6): 0.98 (s, 3, Me), 3.00 (br s, \( WH/2=4.1 \text{ Hz} \), 1, 10-H), 7.52 (m, 3, C6H5-H), 7.05 (br s, 2, C6H5-H). Mass Spectrum \( \text{m/e} \): 614 (M+, 1%), 473 (M+,SO2C6H5, 16%), 328 (M+,SO2C6H5, 4%), 99 (O+O, 100%).

**Desulfurization of 26** —— A stirred solution of 1.724 g of Na in 500 ml of redistilled liquid ammonia was added dropwise during 15 min. The mixture was stirred for 4 hr, allowed to stand overnight at room temperature, and treated as described above. The product (2.65 g) was further treated with 1.32 ml of 70% HClO4 in 26.5 ml of 70% acetone aq. for 2.5 hr. Subsequent oxidation with Jones reagent in 22 ml of acetone gave 2.2 g of an oily material, which was purified by chromatography on 220 g of silica gel (CH2Cl2:AcOEt=3:1). Recrystallization from ether—petroleum ether yielded 1.605 g (70.0%) of 27, mp 80—81°.

**5-Pyrrolidyl-des-A-19-norpregna-5(10),9(11)-dien-20-one (31)** —— To a chilled solution of 27 (2.184 g) in 4.4 ml of MeOH was added 8.75 ml of pyrrolidine and the mixture was allowed to stand at room temperature for 20 min. The mixture was stirred overnight at room temperature and treated as described above. The product (2.65 g) was further treated with 1.32 ml of 70% HClO4 in 26.5 ml of 70% acetone aq. for 2.5 hr. Subsequent oxidation with Jones reagent in 22 ml of acetone gave 2.2 g of an oily material, which was purified by chromatography on 220 g of silica gel (CH2Cl2:AcOEt=3:1). Recrystallization from ether—petroleum ether yielded 1.605 g (70.0%) of 27, mp 80—81°.

**10-Propargyl-des-A-19-norpregn-9(10)-ene-5,20-dione (32)** —— A stirred mixture of 31 (2.188 g) and 0.61 ml of propargyl bromide in 32 ml of HMFA was allowed to stand in the dark for 25 hr then heated at 100—110° for 1.5 hr. After 26 ml of water had been added, the mixture was heated at 110° for 2 hr. After dilution with water, extraction with CH2Cl2 gave 2.2 g of an oily material, which was purified by preparative TLC (cyclohexane:AcOEt=1:1). The less polar fraction gave 161 mg (8.9%) of recovered 27, mp 80—81°. The more polar fraction afforded 1.102 g (53.1%) of 32, which was recrystallized from ether—petroleum ether to give the pure sample, mp 122—124°. [\( \epsilon \)24 D +27080. Anal. Calcd. for C20H29ON: C, 78.64; H, 9.79; N, 4.59. Found: C, 78.59; H, 9.60; N, 4.50.

**10-Propargyl-des-A-19-norpregn-9(10)-ene-5,20-dione (32)** —— A stirred mixture of 31 (2.188 g) and 0.61 ml of propargyl bromide in 32 ml of HMFA was allowed to stand in the dark for 25 hr then heated at 100—110° for 1.5 hr. After 26 ml of water had been added, the mixture was heated at 110° for 2 hr. After dilution with water, extraction with CH2Cl2 gave 2.2 g of an oily material, which was purified by preparative TLC (cyclohexane:AcOEt=1:1). The less polar fraction gave 161 mg (8.9%) of recovered 27, mp 80—81°. The more polar fraction afforded 1.102 g (53.1%) of 32, which was recrystallized from ether—petroleum ether to give the pure sample, mp 122—124°. [\( \epsilon \)24 D +27080. Anal. Calcd. for C20H29ON: C, 78.64; H, 9.79; N, 4.59. Found: C, 78.59; H, 9.60; N, 4.50.

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**10-Propargyl-des-A-19-norpregn-9(10)-ene-5,20-dione (32)** —— A stirred mixture of 31 (2.188 g) and 0.61 ml of propargyl bromide in 32 ml of HMFA was allowed to stand in the dark for 25 hr then heated at 100—110° for 1.5 hr. After 26 ml of water had been added, the mixture was heated at 110° for 2 hr. After dilution with water, extraction with CH2Cl2 gave 2.2 g of an oily material, which was purified by preparative TLC (cyclohexane:AcOEt=1:1). The less polar fraction gave 161 mg (8.9%) of recovered 27, mp 80—81°. The more polar fraction afforded 1.102 g (53.1%) of 32, which was recrystallized from ether—petroleum ether to give the pure sample, mp 122—124°. [\( \epsilon \)24 D +27080. Anal. Calcd. for C20H29ON: C, 78.64; H, 9.79; N, 4.59. Found: C, 78.59; H, 9.60; N, 4.50.
with 140 ml of ice water and extracted with CH₂Cl₂. The organic layer was washed with Na₂CO₃ aq. and dried over Na₂SO₄. Removal of the solvent in vacuo gave 939 mg of a crystalline residue, recrystallization of which from acetone-hexane yielded 910 mg (97.8%) of 33, mp 110-111.5°. [α]D₂5 +26.3° (c=0.391). IR νmax cm⁻¹: 1717, 1700 (C=O), 1659, 1610 (C=C-C=O), 1199, 1153. UV λmax nm (ε): 248 (14640). CD (in MeOH): [θ]237 -876, [θ]265.5 +14200, [θ]240 -31380, [θ]262.5 +14920. PMR (δ): 0.81 (s, 3, Me), 2.12 (s, 3, COMe), 3.51 (s, Wh/2=3.4 Hz, 2, C-CH₂-C). Anal. Calcd. for C₁₉H₂₆O₃: C, 75.46; H, 8.67. Found: C, 75.74; H, 8.42.

Hydrogenation of 33—Compound (33) (866 mg) dissolved in 27 ml of AcOEt and 1.1 ml of Et₃N was hydrogenated over 200 mg of prereduced 10% Pd-C. After uptake of hydrogen ceased (ca. 96 ml of H₂), the mixture was worked up in the usual way. Recrystallization of the product from acetone-hexane gave 675 mg of 34a, mp 127-128.5°. [α]D₂5 +65.9° (c=0.340). IR νmax cm⁻¹: 1712, 1706 (C=O), 1205, 1194, 1173, 1149. CD (in CHCl₃): [θ]310sh +3130, [θ]292.5 +4290, [θ]292 -5790. PMR (δ): 0.71 (s, 3, Me), 2.10 (s, 3, COMe), 2.22 (s, 3, COMe). Anal. Calcd. for C₁₉H₂₈O₃: C, 74.96; H, 9.27. Found: C, 75.21; H, 9.35.

The mother liquor was concentrated to dryness in vacuo, and the residue (240 mg) was subjected to preparative TLC (cyclohexane:AcOEt=1:1). In order of their decreasing mobility, the fractions afforded 98 mg of 34a; 58 mg (5.1%) of 34b, which was recrystallized from acetone-hexane to yield the pure sample, mp 111-111.5°. [α]D₂5 +88.1° (c=0.256). IR νmax cm⁻¹: 1349 (OH), 1707 sh, 1692 (C=O), 1196, 1154. CD (in CHCl₃): [θ]310sh +3130, [θ]292.5 +4290, [θ]292 -5790. PMR (δ): 0.68 (s, 3, Me), 2.11 (s, 3, COMe), 2.16 (s, 3, COMe). Anal. Calcd. for C₁₉H₂₈O₃: C, 74.96; H, 9.27. Found: C, 74.72; H, 9.28; and 13 mg (1.3%) of 35, which on recrystallization from acetone-hexane gave the pure sample, mp 119-121°. [α]D₂5 +98.1° (c=0.268). IR νmax cm⁻¹: 1710, 1705 (C=O), 1230, 1196. CD (in CHCl₃): [θ]310sh +3130, [θ]292.5 +4290, [θ]292 -5790. PMR (δ): 0.63 (s, 3, Me), 2.09 (s, 3, COMe), 2.12 (s, 3, COMe), 3.26 (dt, J5a:6a=4.5 Hz, J5a 6=10=14.5 Hz, 1, 5α-H). Anal. Calcd. for C₁₉H₃₀O₃: C, 74.74; H, 9.87. Found: C, 74.74; H, 9.52. The combined yield of 34a was 773 mg (88.7%). Jones oxidation of 35 (6.5 mg) in the usual way gave 6 mg of 34a, which was identified with the sample prepared above by mixed mp, comparison of the IR spectrum and TLC.

2-Methyl-3-oxa-4,19-bisnorpregna-1,5(10)-dien-20-one (36)—A solution of 34a (719 mg) and 85 mg of p-TsOH·H₂O in 72 ml of benzene was refluxed for 30 min with azeotropic removal of the formed water. The cooled mixture was poured into iced Na₂CO₃ aq. and extracted with CH₂Cl₂. Recrystallization of the product from aqueous acetone afforded 582 mg (86.0%) of 36, mp 111-112°. [α]D₂5 +125.9° (c=0.351). IR νmax cm⁻¹: 1699 (C=O), 1658, 1630, 1574, 949, 812 (furan). UV λmax nm (ε): 226 (7760). CD (in isooctane): [θ]298 O, [θ]292 +9600, [θ]282 +9120, [θ]271.5 O, [θ]260 -12640, [θ]250 +9920, [θ]250 -6400. PMR (δ): 0.66 (s, 3, Me), 2.12 (s, 3, COMe), 2.24 (s, Wh/2=2.6 Hz, 3, furan-Me), 5.82 (s, Wh/2=2.3 Hz, 1, 1-H). Mass Spectrum m/e: 286 (M+, 100%). Anal. Calcd. for C₁₉H₂₆O₂: C, 79.68; H, 9.15. Found: C, 79.75; H, 9.14. The same treatment of 34b (20 mg) with acid as described above gave 17 mg of a compound identical with 36.

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