and dried ($MgSO_4$). The Et_2O solution was saturated with anhydrous HCl and evaporated to dryness *in vacuo* to yield 1.2 g (76%) of crude α-(±)-methadol hydrochloride (**10**). The nmr spectrum of crude **10** was identical with an nmr spectrum of an authentic sample of **10**.[5] The crude product **10** was recrystallized with MeOH–EtOAc to yield 1 g (64%) of **10**: mp 199–200° (lit.[12] mp 200–203°).

Acknowledgments. The authors thank Dr. S. Smits and Dr. R. Nickander for biological testing, Ms. R. Billings who initially identified the primary amine metabolite, Mr. D. Cline and Mr. G. Maciak for microanalysis, and Dr. G. Wallace and staff for spectral data. The authors are especially indebted to Dr. N. Kornblum for stimulating discussions concerning formation and identification of the nitroalkane.

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Synthesis of 15-Keto-6β,7β-methyleneprogesterone. Effect of the 6β,7β-Methylene Group on Mineralocorticoid Activity†

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Received October 15, 1974

15-Ketoprogesterone is as active as spironolactone in blocking the mineralocorticoid effect of deoxycorticosterone acetate. This activity is reduced when a methylene group is attached to the 6β,7β position. The title compound was prepared from 15α-acetoxy-6-dehydroprogesterone. Methylenation of the Δ^6 double bond with dimethyloxosulfonium methylide proceeds stereoselectively from the β side of the molecule.

Information gained from metabolic and pharmacokinetic studies[1] and knowledge of the characteristics of various substituents[2] have proved useful in the design of new drugs. By altering the biotransformation of a substance through structural changes, compounds with differing profiles of activity can be obtained.

In seeking to develop more potent blockers of aldosterone, we have applied the knowledge acquired from the studies on the spirolactones to the development of antagonists which are structurally more closely related to progesterone. The latter substance had been shown by Landau, *et al.*, to block the activity of aldosterone when administered at a high dose.[3] Subsequently, Tweit and Kagawa showed that the antialdosterone effect of progesterone can be notably enhanced by introduction of an oxygen function at C-15, either in the form of a keto or a β-hydroxy group, and by insertion of a Δ^1 or Δ^6 double bond (**1a**,b).[4]

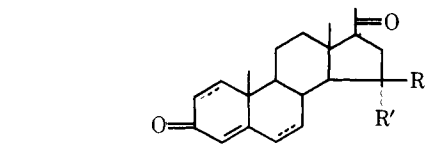
This report is concerned with the attachment of a methylene group to the 6,7 position of 15-oxygenated progesterone derivatives and the effect which this group has on antimineralocorticoid activity. Earlier we had found that the spirolactone with a β-methylene group at the 6,7 position (**2**) has an activity somewhat greater than that of spironolactone (**3a**).[5] Recently, it was reported that an inactive metabolite of spironolactone contains a hydroxyl group at the 6β position (**3b**).[6] Attachment of a β substituent to C-6 would, of course, prevent hydroxylation from occurring at this site. Hence, the 6β,7β-methylene group could be expected to produce a desirable effect by this means. Alternatively, this effect could be produced by π-complex formation with the receptor site as a consequence of the unique electronic characteristic of the cyclopropane ring. Such a process had previously been proposed by Wolff, *et al.*, to account for the androgenic effects of certain 2,3-methyleneandrostanes.[7] It was our hope that the present study would provide some insight as to whether either of these processes is involved in blocking the effect of the mineralocorticoids.

Methylenation at the 6,7 position of a steroid is generally achieved by the addition of dimethyloxosulfonium methylide to a 3-keto-$\Delta^{4,6}$-dienone system. Previous investigators had shown that the methylenation of 6-dehydrotestosterone acetate by this procedure furnishes a pair of stereoisomers, **4** and **5**, of which the one possessing the methylene group in the β configuration (**4**) predominates, the ratio of the β/α isomers being about 1.5:1.[8,9]

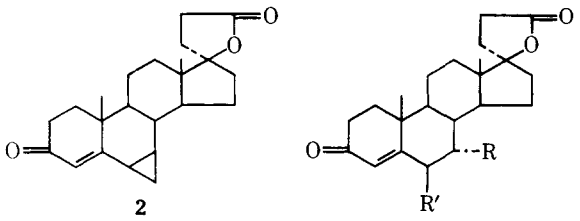
The starting material for our study was 15α-acetoxy-6-dehydroprogesterone (**6**). Addition of dimethyloxosulfonium methylide results not only in methylenation of the 6,7 double bond but also in oxirane formation at C-20. Oxirane formation can readily be discerned from the upfield shift of the C-21 methyl group and the accompanying downfield shift of the C-18 methyl group in the nmr spectrum. To prevent formation of the oxirane, the 20-carbonyl group of **6** was reduced with lithium tri-*tert*-butoxyaluminum hydride. Although the reduction was conducted at 0°, some reduction of the 3-keto group occurred. The allylic hydroxyl group at C-3 was selectively converted back to the keto group by means of dichlorodicyanobenzoquinone (DDQ).

Treatment of the product (**7**) with dimethyloxosulfon-

†Presented in part at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., 1974.



1a, R = OH; R′ = H
b, R, R′ = O



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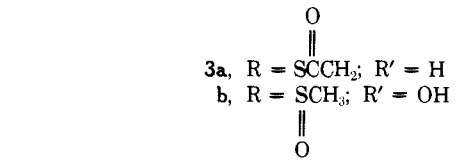
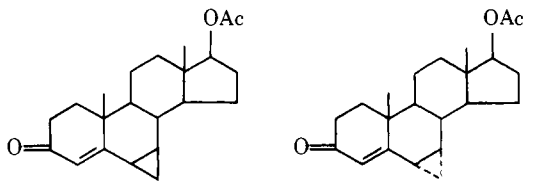


3a, R = SCCH$_2$; R′ = H
b, R = SCH$_3$; R′ = OH



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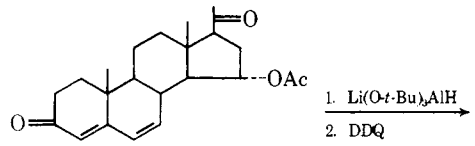

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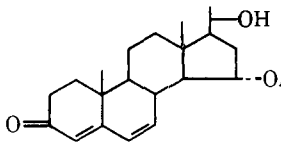

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ium methylide affords a mixture in which one product (8) is in preponderance according to gas–liquid chromatography. Passage of the crude methylenated mixture through a column of alumina removes the highly polar by-products. Oxidation of the chromatographed mixture with Jones reagent at room temperature furnishes a product (9) in which the 20-carbonyl group is regenerated. Hydrolysis of the acetoxy group occurs readily with sodium carbonate in aqueous methanol. Oxidation of the resultant 15α-hydroxy compound 10 with Jones reagent at 0° affords the 3,15,20-trione 11. The double bond at the 1,2 position can be introduced into 15α-acetoxy-6,7-methyleneprogesterone (9) with the aid of DDQ. Successive hydrolysis and oxidation as before yields the cross-conjugated dienone (14) with a keto group at C-15 and a methylene group at C-6 and -7.

The methylene group in this series of compounds was assigned the β configuration on the basis of spectral and molecular rotation data (Tables I and II). In the 6-dehydrotestosterore series, the 6β,7β-methylene derivative 4 absorbs uv light maximally at 263 nm, and its C-4 proton signal appears at 361 Hz in the nmr spectrum. The corresponding values for the 6α,7α-methylene isomer 5 are 259 nm and 357 Hz.[8] The uv absorption maximum of 11 is 263 nm, and the chemical shift of the C-4 proton appears at 360.5 Hz. These results are consistent with the 6,7-methylene group of 11 having the β configuration. Molecular rotation differences are also in accord with this conclusion. In the 6-dehydrotestosterone series, the introduction of a 6β,7β-methylene group results in a substantial negative shift (ΔMD −703) in the molecular rotation while a positive shift (ΔMD +287) is observed when the methylene group is attached to the 6α,7α position.[8] The difference in molecular rotation between 11 and the corresponding 6-dehydro compound 15 is −765.

Of particular interest is the stereoselectivity observed in the addition of dimethyloxosulfonium methylide to the 15α-acetoxy-3-keto-Δ^{4,6} steroid. Although the yield in the methylenation process is only of the order of 35%, we believe our results do accurately reflect the effect which the 15α-acetoxy group has on the process; *viz.*, it causes methylenation to proceed preferentially from the β side of the molecule.

An effort was made to isolate the 6α,7α-methylene isomer but to no avail. Gas–liquid chromatography of the

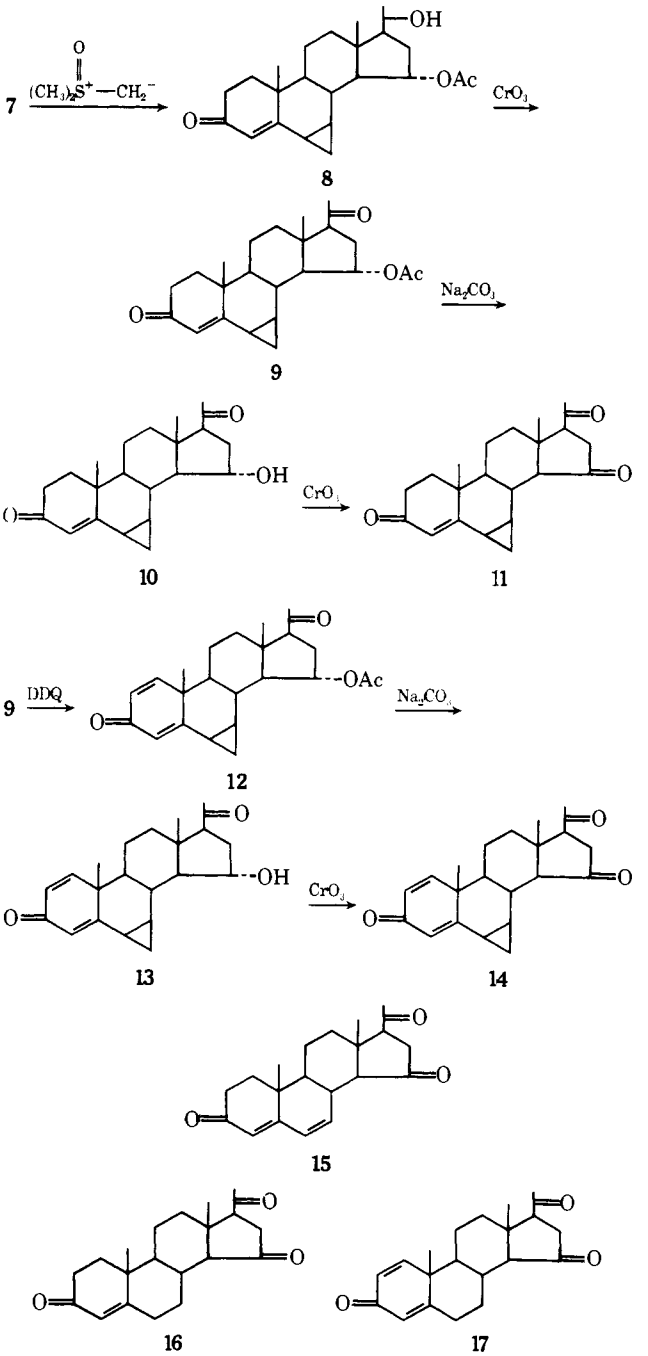

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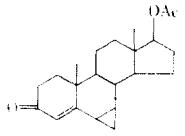
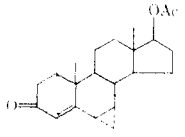
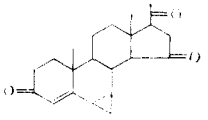
Table I. Spectral Characteristics

Structure	λ_{max} (MeOH), nm	4-H, nmr, Hz ($CDCl_3$)
	263[a] 264[b]	361[a] 360[b]
	259[c] 262[b]	357[c] 356[b]
	263	360.5

[a] See ref 8a. [b] See ref 8b. [c] See ref 8c.

methylenation reaction mixture revealed that if the 6α,7α-methylene isomer was present in the mixture, it was present only to a small extent.

Recently, Arth, *et al.*, proposed that relief of torsional strain is likely to be the key factor in determining the stereochemistry of the methylenated product rather than steric approach control.[9] Our present study suggests, however, that in some instances steric hindrance to the approach of the nucleophile can be a critical factor.

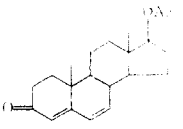
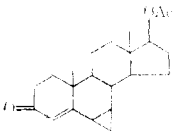
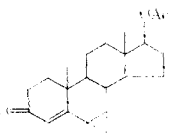
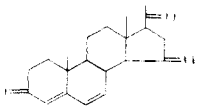
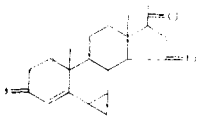
The antimineralocorticoid effect of 15-keto-6β,7β-methyleneprogesterone (**11**) and 15-keto-6β,7β-methylene-1-dehydroprogesterone (**14**) was determined in a standard test employing deoxycorticosterone acetate as the mineralocorticoid.[12] Both **11** and **14** were found to possess antimineralocorticoid activity when given subcutaneously (MED 1.1 mg). The activity was 30% that of spironolactone (MED 0.33 mg). Compounds **11** and **14** were also tested orally but were found to be inactive (MED > 2.4 mg). In contrast, the corresponding compounds in which the methylene group at the 6β,7β position is absent, *viz.*, **16** and **17**, have activities which are comparable to that of spironolactone (subcutaneous MED 0.44 and 0.23 mg, respectively).[4]

In view of the low order of activity of **11** and **14**, the possibility that epimerization had occurred at C-14 and -17 was considered. Precedence for inversion of these two centers of asymmetry without abolishing biological activity is found in the work of Ehrenstein, *et al.*, who showed that the 19-norprogesterone and the 19-nordeoxycorticosterone prepared from strophanthidin and which possess progestational and mineralocorticoid activities, respectively, actually have the 14β,17α configuration.[13]

In our study, epimerization at C-14, and possibly at C-17, would have had to occur during the oxidation of the 15α-hydroxyl group. The conditions employed (Jones reagent at 0°) were exceedingly mild. It appears unlikely that oxidation and epimerization could have occurred to give not a complex mixture but a single product isolated in 80% yield. Moreover, the excellent correlation between the values of 15-keto-6β,7β-methyleneprogesterone (**11**) and those of 6β,7β-methylenetestosterone acetate (**4**) (Tables I and II) would provide an additional argument against inversion at C-14 and -17.

In contradistinction to the spirolactone analog, 15-keto-progesterone with a 6β,7β-methylene group (**11**) is considerably less active than the corresponding compound lacking this group. This suggests that π-complex formation involving the cyclopropane ring, if it does occur, does not contribute significantly to antimineralocorticoid activity. Blockage of hydroxylation at the 6β position conceivably could be the process by which the 6β,7β-methylene group exerts its beneficial effect in the spirolactone compound, but this remains to be determined.

Table II. Molecular Rotation Differences

Structure	$[\alpha]_D$ ($CHCl_3$), deg	M_D	ΔM_D ($M_{D,\text{product}} - M_{D,\text{substr}}$)
	−36[a]	−118	
	−171[b] −179[c]	−585 −614	−703 −732
	−118[d] −133[e]	−405 −455	−287 −337
	−161[f]	−525	
	−71	−240	−765

[a] See ref 10. [b] See ref 8a. [c] See ref 8b. [d] See ref 8c. [e] See ref 11.

Experimental Section

Melting points were determined on a Fisher-Johns melting block and are uncorrected. Nmr spectra were taker on a Varian A-60 instrument in deuteriochloroform with tetramethylsilane as an internal standard (s = singlet, br= broad, d = doublet, dd = doublet of doublets). Optical rotations were determined in $CHCl_3$.

15α,20ξ-Dihydroxypregna-4,6-dien-3-one 15-Acetate (7). A mixture of 1.5 g of 15α-acetoxy-6-dehydroprogesterone (**6**),[4] 15 ml of THF, and 1.5 g of lithium tri-*tert*-butoxyaluminum hydride was allowed to stand in an ice bath for 2 hr after which time it was poured into a mixture of ice and water. The resultant mixture was made slightly acidic with 5% HCl and then extracted with C_6H_6. The C_6H_6 extract (*ca.* 300 ml) was washed with H_2O, dried (Na_2SO_4), and concentrated to *ca.* 250 ml by distillation at atmospheric pressure. The residue was treated with 300 mg of dichlorodicyanobenzoquinone, and the reaction mixture was heated under reflux for 1 hr. The cooled mixture was washed successively with dilute NaOH and H_2O, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford 1.2 g of **7** as a semisolid: λ_{max} (MeOH) 282 nm (ε 22,500); nmr (Hz) 369 (s, 2, 6-H, 7-H), 342.5 (s, 1, 4-H), ~298 (br, 1, 15-H), ~227 (br, 1, 20-H), 124 [s, 3, -OC(=O)CH_3], 69 (d, 3, J = 6 Hz, 20-CH_3), 68 (s, 3, 10-CH_3), 55 (s, 3, 13-CH_3); ν (KBr) 3470, 1744, 1668, 1655, 1622, 1590 cm^{-1}.

15α,20ξ-Dihydroxy-6β,7β-methylenepregn-4-en-3-one 15-Acetate (8). a. To 1.2 g of **7** was added 20 ml of 0.5 *M* dimethyloxosulfonium methylide in DMSO.[14] The reaction mixture was allowed to stand at room temperature for 25 hr. Then it was diluted with ice water and acidified with 5% HCl. The resultant mixture was extracted with EtOAc. The EtOAc extract was washed with H_2O, dried (Na_2SO_4), and distilled to dryness under reduced pressure to afford a viscous yellow oil. The oil was chromatographed on

10 g of Al_2O_3 (Woelm neutral). The column was eluted first with C_6H_6 and then successively with 5 and 10% EtOAc in C_6H_6. The products obtained from the 5 and 10% EtOAc–C_6H_6 eluents were combined: yield 479 mg. A sample of this mixture was analyzed by glc. The results indicated that starting material **7** was present in a yield of 14.4% and the desired product **8** in 81.7% yield. Three other products were present in yields of 3.1, 0.3, and 0.5%.

A 425-mg sample of this mixture was oxidized with Jones reagent at room temperature (*vide infra*). Dilution of the reaction mixture with water gave 294 mg of a crystalline product: mp 200–205°. Glc of this product revealed the presence of 15α-acetoxy-6-dehydroprogesterone (**6**) and 15α-acetoxy-6β,7β-methyleneprogesterone (**9**) in yields of 13.4 and 86.2%, respectively. Two other substances were present in yields of 0.3 and 0.7%.

b. To 8.0 g of **7** was added 60 ml of 1.1 *M* dimethyloxosulfonium methylide in DMSO. The reaction mixture was allowed to stand at room temperature in a nitrogen atmosphere for 18 hr. The reaction mixture was worked up as described above. The oil obtained from the EtOAc extract was chromatographed on 50 g of Al_2O_3 (Woelm neutral). The column was eluted first with C_6H_6 and then with varying proportions of EtOAc in C_6H_6, up to 5% EtOAc in C_6H_6. The solid fractions were combined and crystallized from EtOAc to afford 2.2 g of **8**: mp 242–245°; nmr (Hz) 358 (s, 1, 4-H), ~300 (br, 1, 15-H), ~224 (br, 1, 20-H), 120 [s, 3, $-OC(=O)CH_3$], 68.5 (d, 3, J = 6 Hz, 20-CH_3), 65.5 (s, 3, 10-CH_3), 50 (s, 3, 13-CH_3); ν (KBr) 3545, 1745, 1673, 1613 cm^{-1}; λ_{max} (MeOH) 263–265 nm (ε 18,200). *Anal.* ($C_{24}H_{34}O_4$) C, H.

15α-Acetoxy-6β,7β-methyleneprogesterone (9). A 1.4-g sample of **8** was dissolved in 60 ml of redistilled acetone. To this solution, cooled in an ice bath, was added 1.3 ml of Jones reagent (8 *N* CrO_3 in acetone and H_2SO_4). The reaction mixture was allowed to stand at room temperature for 0.5 hr. Then it was treated with a few drops of *i*-PrOH and diluted with H_2O. The resultant mixture was concentrated under reduced pressure whereupon a crystalline product separated out. The solid was collected: yield 1.2 g; mp 220–222°. Crystallization from ethyl acetate raised the mp to 230–233°. Glc indicated the product to be pure: nmr (Hz) 361.5 (s, 1, 4-H), ~305 (br, 1, 15-H), 128.5 [s, 3, $-C(=O)CH_3$], 121 [s, 3, $-OC(=O)CH_3$], 66 (s, 3, 10-CH_3), 43.5 (s, 3, 13-CH_3); ν (KBr) 1738, 1715, 1660, 1602 cm^{-1}; λ_{max} (MeOH) 263 nm (ε 18,450); $[\alpha]D$ −45.8° (*c* 1.00). *Anal.* ($C_{24}H_{32}O_4$) C, H.

15α-Hydroxy-6β,7β-methyleneprogesterone (10). A mixture of 1.2 g of **9**, 40 ml of MeOH, 1.0 g of Na_2CO_3, and 4 ml of H_2O was stirred at room temperature for 6 hr. MeOH was evaporated from the mixture. The residue was diluted with H_2O. The residue was extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried ($MgSO_4$) and then evaporated to dryness under reduced pressure. The residue was crystallized from EtOAc–ether to afford 900 mg of **10**: mp 110–112°; resolidified and remelted at 133–135°; nmr (Hz) 361 (s, 1, 4-H), 128 [s, 3, $-C(=O)CH_3$], 66 (s, 3, 10-CH_3), 45.5 (s, 3, 13-CH_3); ν (KBr) 3510, 1705, 1650, 1590 cm^{-1}; λ_{max} (MeOH) 265 nm (ε 18,800); $[\alpha]D$ −51.6° (*c* 0.09). *Anal.* Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.70; H, 8.90.

15-Keto-6β,7β-methyleneprogesterone (11). To a solution of 850 mg of **10** in 40 ml of redistilled acetone was added 0.8 ml of Jones reagent. The reaction mixture was allowed to stand in the ice bath for 0.5 hr after which time it was treated with a few drops of *i*-PrOH and diluted with water. Acetone was removed by evaporation under reduced pressure. The crystalline product thus formed was collected, washed with H_2O, and dried. Crystallization from ethyl acetate afforded 700 mg of **11**: mp 180–182°; nmr (Hz) 360.5 (s, 1, 4-H), 133.5 [s, 3, $-C(=O)CH_3$], 65.5 (s, 3, 10-CH_3), 43 (s, 3, 13-CH_3); ν (KBr) 1742, 1712, 1678, 1605 cm^{-1}; λ_{max} (MeOH) 263 nm (ε 18,800); $[\alpha]D$ −70.6° (*c* 0.43). *Anal.* ($C_{22}H_{28}O_3$) C, H.

15α-Acetoxy-6β,7β-methylene-1-dehydroprogesterone (12). A mixture of 500 mg of 15α-acetoxy-6β,7β-methyleneprogesterone (**8**), 60 ml of anhydrous C_6H_6, and 370 mg of dichlorodicyanobenzoquinone was heated under reflux in a nitrogen atmosphere for 20 hr. The cooled reaction mixture was diluted with ether. The resultant solution was washed successively with 2% NaOH and H_2O, dried ($MgSO_4$), and distilled to dryness under reduced pressure. The residue was crystallized from EtOAc to yield 350 mg of **12**: mp 231–233°; nmr (Hz) 414 (d, 1, J = 10 Hz, 4-H), 379 (d, 1, J = 1.5 Hz, 1-H), 370 (dd, 1, J = 10, 1.5 Hz, 2-H), ~305 (br, 1, 15-H), 126.5 [s, 3, $-C(=O)CH_3$], 120 [s, 3, $-OC(=O)CH_3$], 67 (s, 3, 10-CH_3), 45.5 (s, 3, 13-CH_3); ν (KBr) 1734, 1694, 1657, 1620, 1590 cm^{-1}; λ_{max} (MeOH) 243–244 nm (ε 14,750), 283–285 (12,600); λ_{min} (MeOH) 263 nm (ε 8250).

15α-Hydroxy-6β,7β-methylene-1-dehydroprogesterone (13). A mixture of 200 mg of **12**, 25 ml of MeOH, 200 mg of Na_2CO_3, and 2 ml of H_2O was stirred at room temperature for 15 hr. The reaction mixture was then concentrated under reduced pressure to remove CH_3OH. The residue was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from EtOAc to yield 140 mg of **13**: mp 246–248°; nmr (Hz) 415.5 (d, 1, J = 10 Hz, 4-H), 379.5 (d, 1, J = 1.5 Hz, 1-H), 370.5 (dd, 1, J = 10, 1.5 Hz, 2-H), ~255 (br, 1, 15-H), 128.5 [s, 3, $-C(=O)CH_3$], 68.5 (s, 3, 10-CH_3), 43 (s, 3, 13-CH_3); ν (KBr) 1709, 1659, 1618, 1583 cm^{-1}; λ_{max} (MeOH) 245 nm (ε 11,240), 287 (9875); $[\alpha]D$ −45.9° (*c* 0.07). *Anal.* ($C_{22}H_{28}O_3$) C, H.

15-Keto-6β,7β-methylene-1-dehydroprogesterone (14). To a stirred solution of 200 mg of **13** in 20 ml of redistilled acetone, cooled in an ice bath, was added 0.18 ml of Jones reagent. The reaction mixture was stirred in the ice bath for 0.5 hr and then at room temperature for an additional 0.5 hr. After 0.2 ml of *i*-PrOH was added, the reaction mixture was diluted with H_2O and then concentrated under reduced pressure to remove the acetone. The solid product present in the residue was collected, washed with H_2O, and dried. Crystallization from CH_2Cl_2–EtOAc afforded 120 mg of **14**: mp 213–215°; nmr (Hz) 413.5 (d, 1, J = 10 Hz, 4-H), 379 (d, 1, J = 1.5 Hz, 1-H), 369.5 (dd, 1, J = 10, 1.5 Hz, 2-H), 131 [s, 3, $-C(=O)CH_3$], 66 (s, 3, 10-CH_3), 43.5 (s, 3, 13-CH_3) Hz; ν (KBr) 1742, 1705, 1657, 1622, 1598 cm^{-1}; λ_{max} (MeOH) 240–241 nm (ε 12,200), 279–280 (10,100); λ_{min} (MeOH) 224–226 nm (ε 9500), 263 (6900); $[\alpha]D$ −75° (*c* 0.1). *Anal.* ($C_{22}H_{26}O_3$) C, H.

Acknowledgment. We gratefully acknowledge the assistance of Mrs. Esther Muir and her staff in performing the biological tests. We thank Dr. R. H. Bible and Messrs. A. J. Damascus and E. Zielinski and their staffs for the analytical results. We are indebted to Dr. J. F. Zawadzki for providing us with the standardized solutions of dimethyloxosulfonium methylide in DMSO.

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