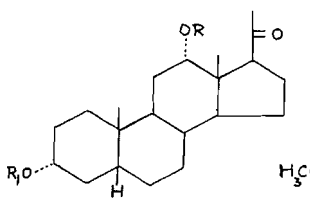
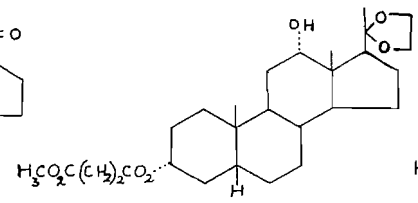


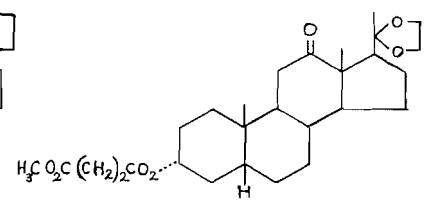
I $R = R_1 = H$

Ia $R = R_1 = COCH_3$

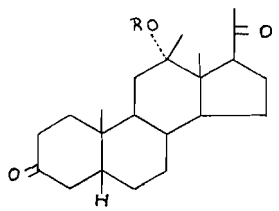
Ib $R = H, R_1 = CO(CH_2)_2CO_2CH_3$



II

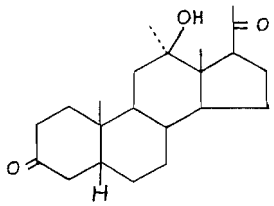


III

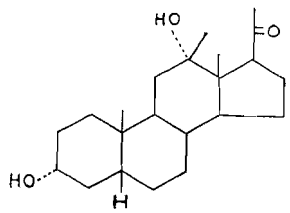


IV $R = H$

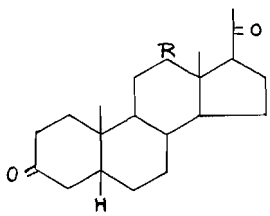
IVa $R = COCH_3$



V

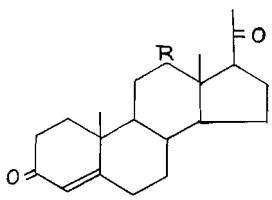


VI



VII $R = =CH_2$

VIIa $R = =O$



VIII $R = \begin{matrix} OH \\ CH_3 \end{matrix}$

VIIIa $R = =CH_2$

VIIIb $R = \begin{matrix} OCOCH_3 \\ CH_3 \end{matrix}$

Dehydration of the epimeric hydroxy ketones IV and V with phosphorus oxychloride and thionyl chloride in pyridine (6, 7) was unsuccessful. However, treatment of the hydroxy ketone V with acetic acid, acetic anhydride, and *p*-toluene sulphonic acid gave a 53% yield of the 12-methylene compound VII. It had been observed that the epimeric hydroxy ketone IV under similar reaction conditions also affords a 53% yield of the exo olefin VII (2).

Since $\Delta''$-dehydroprogesterone exhibits high progestational activity (8), the effect of the incorporation of a 12,12*a*-double bond by introduction of a methylene group at $C_{12}$ to the parent hormone seemed a worth-while investigation. Consequently, the progesterone

analogue VIII (1) was dehydrated with acetic acid, acetic anhydride, and *p*-toluene sulphonic acid to 12-methyleneprogesterone, VIII*a*. A minor product was obtained as an oil and it was assigned the 12$\alpha$-acetoxy-12$\beta$-methylprogesterone configuration VIII*b* since its infrared spectrum showed absorption bands characteristic of an acetate group, and also because the analogous reaction of 12$\alpha$-hydroxy-12$\beta$-methylpregnane-3,20-dione (IV) with acetic acid, acetic anhydride, and *p*-toluene sulphonic acid gave the exo olefin VII and the 12$\alpha$-acetate IV*a* (2).

Preliminary biological tests of the two progesterone analogues VIII*a* and VIII*b* did not exhibit any notable progestational, androgenic, diuretic, hypotensive, or anabolic properties.[1]

## EXPERIMENTAL[2, 3, 4, 5]

*3α,12α-Dihydroxypregnan-20-one 3-Methyl Succinate (Ib) (4)*

To a solution of the diol I (12.2 g, m.p. 164–167°; crude product obtained by alkaline hydrolysis of 15.0 g of the diacetate I*a*) in pyridine (125 ml) was added succinic anhydride (32.5 g); the resulting solution was heated at 90° for 2 hours and left at room temperature for 12 hours. The reaction mixture was extracted with ether. The organic layer was washed with 2 *N* hydrochloric acid, water, and then dried over magnesium sulphate. The ethereal solution was methylated with diazomethane. Crystallization from acetone–hexane afforded 13.427 g of the methyl succinate I*b* (4), m.p. 125–127° (yield 84%).

*3α,12α-Dihydroxy-20-pregnanone Ethylene Ketal 3-Methyl Succinate (II)*

To a solution of 8.99 g of the methyl succinate I*b* in absolute benzene (200 ml) was added ethylene glycol (20 ml) and *p*-toluene sulphonic acid (100 mg), and the reaction mixture was heated at reflux temperature for 12 hours. The water that formed during the reaction was continuously removed. The reaction mixture was extracted with ether, the ethereal layer washed with sodium bicarbonate solution and then with water, until the washings were neutral, and dried over magnesium sulphate. Repeated crystallizations from ether–hexane afforded 3.92 g of broad needles of the ketal II, m.p. 181–184° (yield 40%).

Two crystallizations from ether–hexane raised the melting point of II to 182–184°, $[\alpha]_D^{27}$ 57° (*c* 1.01 in $CHCl_3$). Calc. for $C_{28}H_{44}O_7$: C 68.26, H 9.00; found: C 68.40, H 9.07.

*3α-Hydroxy-12,20-pregnandione 20-Ethylene Ketal 3-Methyl Succinate (III)*

A solution of 3.2 g of the ketal II in pyridine (36 ml) was added to a slurry of chromium trioxide (3.2 g) in pyridine (32 ml) with stirring and left at room temperature for 16 hours (5). The reaction mixture was poured into 500 ml of water and extracted with chloroform. The organic layer was washed with iced 2 *N* hydrochloric acid, 5% sodium bicarbonate solution, and water, until the washings were neutral. The chloroform solution was dried over magnesium sulphate and evaporated to about 40 ml. On addition of 20 ml of hexane, the ketone III crystallized as needles, 2.404 g, m.p. 239–240°. The mother liquors on crystallization from methylene chloride – hexane afforded 0.364 g, m.p. 237–239° (yield 98%).

Recrystallization of the ketone III for analysis did not raise the melting point, $[\alpha]_D^{27}$ 96° (*c* 0.78 in $CHCl_3$). Calc. for $C_{28}H_{42}O_7$: C 68.55, H 8.63; found: C 68.64, H 8.65.

*Reaction of Methyl Magnesium Iodide with 3α-Hydroxy-12,20-pregnandione 20-Ethylene Ketal 3-Methyl Succinate (III)*

To 300 ml of an ethereal solution of methyl magnesium iodide (from 700 mg of magnesium and 2.0 ml of methyl iodide) was added with stirring a solution of 1.0 g of the ketone III in benzene, and the resulting mixture was heated at reflux temperature for 18 hours. A solution of ammonium chloride (20 g) in water (500 ml) was added to the reaction mixture. The usual extraction procedure afforded 930 mg of an oil.

To a solution of the Grignard adduct (930 mg of oil) in 50 ml of acetone was added with stirring 75 mg of *p*-toluene sulphonic acid and the reaction mixture left at room temperature for 22 hours. Ether extraction afforded 884 mg of an oil. An infrared spectrum analysis of the oil showed a strong absorption band at 1707 $cm^{-1}$ ($C_{20}$-ketone), and a weak absorption band at 1725 $cm^{-1}$ ($C_3$-methyl succinate).

A solution of this oil in 25 ml of 5% methanolic potassium hydroxide was heated at reflux temperature for 45 minutes. The usual extraction procedure afforded 735 mg of foam. It was dissolved in 10 ml of acetic

[1]*Biological tests were carried out by Drs. C. I. Chappel and C. Revesz of Messrs. Ayerst, McKenna and Harrison Ltd., Montreal, Que.*

[2]*All melting points are corrected.*

[3]*Only the best yields obtained were reported.*

[4]*The commercially available aluminum oxide (Woelm) was used for chromatography.*

[5]*The microanalyses were carried out by Dr. A. Bernhardt, Mülheim, Germany, and Dr. C. Daessle, 5757 Decelles St., Montreal, Que.*

acid, and to it was added with stirring a solution of 250 mg of chromium trioxide in 3 ml of 90% acetic acid. The reaction mixture was left at room temperature for 12 hours. Ether extraction afforded 740 mg of oil, and it was chromatographed on 23 g of alumina (4.5% water).

The hexane–benzene (1:1) eluates on crystallization from acetone–hexane afforded 106 mg of the trione VII*a* (1, 9), m.p. 197–199°, identified by mixed melting point and comparison of infrared spectra with an authentic sample. Crystallization of mother liquors from acetone–hexane gave 21 mg, m.p. 192–197°.

The first half of the benzene fractions on crystallization from ether–hexane afforded 67 mg of the hydroxy ketone V, m.p. 123–124°.

The rest of the benzene eluates and the benzene–ether (9:1, 4:1) fractions on crystallization from acetone–hexane afforded 80 mg of the hydroxy ketone IV, m.p. 187–188°. Crystallization of mother liquors gave 29 mg, m.p. 184–187°.

The ether–methanol (9:1) eluates on crystallization from acetone–hexane afforded 34 mg of needles of 3$\alpha$,12$\alpha$-dihydroxy-12$\beta$-methylpregnan-20-one (VI), m.p. 225–259°. Recrystallization from acetone–hexane raised the melting point to 228–230°, $[\alpha]_D^{27}$ 106° (*c* 0.74 in $CHCl_3$). Calc. for $C_{22}H_{36}O_3$: C 75.80, H 10.41; found: C 75.96, H 10.07.

Chromium trioxide oxidation of the hydroxy ketone VI (10 mg) afforded 3 mg of the hydroxy ketone IV, m.p. 186–188°, identified by mixed melting point and comparison of infrared spectra with an authentic sample (1).

Taking into consideration the unreacted ketone III (isolated as the trione VII*a*), the yields of 12$\alpha$-alcohol IV and 12$\beta$-alcohol V were 25% and 12% respectively.

*12-Methylenepregnan-3,20-dione (VII) from 12α-Methyl-12β-hydroxypregnan-3,20-dione (V)*

To a solution of 330 mg of the hydroxy ketone V in 25 ml of acetic acid were added 5 ml of acetic anhydride and 330 mg of *p*-toluene sulphonic acid monohydrate (10), and the suspension was stirred until the solid dissolved. The reaction mixture was left at room temperature for 4 hours, then poured into 500 ml of iced water. After 30 minutes, the usual extraction procedure afforded 390 mg of an oil which showed absorption bands in the infrared at 3080 $cm^{-1}$, 1645 $cm^{-1}$, 890 $cm^{-1}$ ($\diagdown\!\!\diagup C{=}CH_2$) (11); 1755 $cm^{-1}$, 1218 $cm^{-1}$ ($\Delta^{17(20)}$-enol acetate) (12); 1713 $cm^{-1}$ (3-ketone). Under the above reaction conditions the $\Delta^{17(20)}$-enol acetate is known to be formed (2, 13). The enol acetate (390 mg of oil) was converted to the $C_{20}$-ketone by heating a solution of it in 30 ml of methanol and 700 mg of potassium carbonate in 10 ml of water at reflux temperature for 2 hours. Ether extraction afforded 360 mg of product showing no bands at 1750 $cm^{-1}$ and 1218 $cm^{-1}$ characteristic of enol acetates, and it was chromatographed on 10 g of alumina (4.5% water). The hexane–benzene (4:1, 1:1) eluates containing the olefin VII[6] crystallized from ether–hexane as needles, 134 mg, m.p. 89–90°. Crystallization of mother liquors afforded 33 mg, m.p. 89–90° (yield 53.4%).

A portion of the olefin VII was recrystallized from ether–hexane for analysis, m.p. 89–90°, $[\alpha]_D^{27}$ 133° (*c* 1.02 in $CHCl_3$), $\nu_{max}^{CS_2}$ 3075 $cm^{-1}$, 1645 $cm^{-1}$, 888 $cm^{-1}$ ($\diagdown\!\!\diagup C{=}CH_2$); 1713 $cm^{-1}$ (3,20-ketone). Calc. for $C_{22}H_{32}O_2$: C 80.41, H 9.82; found: C 80.18, H 9.84.

The benzene and benzene–ether eluates on crystallization from acetone–hexane afforded 56 mg of leaflets of IV*a* (1), m.p. 175–176° (yield 15.1%).

*12-Methyleneprogesterone (VIIIa) and 12β-Methyl-12α-acetoxyprogesterone (VIIIb)*

According to the procedure previously described by us (1), 900 mg of the hydroxy ketone IV was transformed to the progesterone analogue VIII. Crystallization from ether–hexane afforded 330 mg of VIII, m.p. 152–153°. The mother liquors (590 mg) were chromatographed on 17 g of alumina (4.5% water). The benzene and benzene–ether eluates on crystallization from ether–hexane afforded 160 mg of the progesterone analogue VIII, m.p. 152–153°. Crystallization of mother liquors afforded 51 mg, m.p. 135–142° (yield 61%).

In a solution of the progesterone analogue VIII (475 mg, m.p. 152–153°) in 25 ml of acetic acid and 5 ml of acetic anhydride was dissolved 475 mg of *p*-toluene sulphonic acid with stirring. The reaction mixture was left at room temperature for 2 hours. Ether extraction afforded 540 mg of an oil, and it was dissolved in 25 ml of methanol. To the methanol solution was added 750 mg of potassium carbonate dissolved in 10 ml of water and the reaction mixture was heated at reflux temperature for 2 hours. The usual extraction procedure afforded 520 mg of an oil, which was chromatographed on 15 g of alumina (4.5% water). The

[6]*In our previous publication it was concluded that the compound with m.p. 100–101° was the olefin VII and the compound with m.p. 73–74° contained mainly the exo olefin with probably traces of the endo olefin (2). It now seems that all the three forms melting at 73–74°, 89–90°, and 100–101° are different polymorphic forms of the olefin VII on the basis of the following evidence: A mixed melting point of the two forms of olefin VII melting at 73–74° and 89–90° on a Kofler block showed the form melting at 73–74° melted at the latter temperature, but crystallized on further raising the temperature, and the whole mass melted at 89–90°. The two forms of olefin melting at 89–90° and 100–101° were melted side by side, and the molten mass was seeded with a crystal of the form melting at 89–90°, and cooled. The whole mass melted at 89–90°. Furthermore, the infrared spectra and the rotations of the three forms were identical within experimental error.*

hexane–benzene (4:1, 1:1) and benzene eluates on crystallization from ether–hexane afforded 121 mg of cubic crystals of 12-methyleneprogesterone, VIII*a*,[7] m.p. 104–105° (yield 27%). Two recrystallizations from ether–hexane raised the melting point to 105–106°, $[\alpha]_D^{27}$ 189° (*c* 0.92 in $CHCl_3$), $\lambda_{max}^{EtOH}$ 240 mμ (ε 18,500). $\nu_{max}^{CCl_4}$ 3070 cm$^{-1}$, 1643 cm$^{-1}$, 890 cm$^{-1}$ (>CH=CH$_2$); 1707 cm$^{-1}$ (20-ketone); 1675 cm$^{-1}$, 1617 cm$^{-1}$ ($\Delta^4$-3-ketone). Calc. for $C_{22}H_{30}O_2$: C 80.91, H 9.25; found: C 80.70, H 9.05.

The benzene–ether eluates afforded 210 mg of an oil which resisted crystallization. Its infrared spectrum showed absorption bands at 1727 cm$^{-1}$ (12-acetate); 1705 cm$^{-1}$ (20-ketone); 1675 cm$^{-1}$, 1617 cm$^{-1}$ ($\Delta^4$-3-ketone). It was tentatively assigned the 12β-methyl-12α-acetoxyprogesterone configuration VIII*b* on the basis of its infrared spectrum, and from the analogous reaction that 12β-methyl-12α-hydroxypregnan-3,20-dione with acetic acid, acetic anhydride, and *p*-toluene sulphonic acid gives 12β-methyl-12α-acetoxypregnan-3,20-dione as the minor product of the reaction (2).

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1. G. Just and R. Nagarajan. Can. J. Chem. **39**, 548 (1961).
2. R. Nagarajan and G. Just. Can. J. Chem. **39**, 1274 (1961).
3. E. Schwenk, B. Riegel, R. B. Moffett, and E. Stahl. J. Am. Chem. Soc. **65**, 549 (1943). M. Sorkin and T. Reichstein. Helv. Chim. Acta, **29**, 1218 (1946).
4. Ch. R. Engel and W. W. Huculak. Can. J. Chem. **37**, 2031 (1959).
5. G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett. J. Am. Chem. Soc. **75**, 422 (1953).
6. P. Bladon and W. McMeekin. J. Chem. Soc. 2191 (1960).
7. S. G. Levine and M. E. Wall. J. Am. Chem. Soc. **82**, 3391 (1960).
8. P. Hegner and T. Reichstein. Helv. Chim. Acta, **26**, 715 (1943). J. von Euw and T. Reichstein. Helv. Chim. Acta, **29**, 654 (1946).
9. T. Reichstein and E. v. Arx. Helv. Chim. Acta, **23**, 747 (1940).
10. R. B. Turner. J. Am. Chem. Soc. **75**, 3489 (1953).
11. L. J. Bellamy. The infrared spectra of complex molecules. John Wiley and Sons, Inc., New York. 1958. p. 34.
12. H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher. J. Am. Chem. Soc. 74, 2810 (1952).
13. P. Z. Bedoukian. J. Am. Chem. Soc. **67**, 1430 (1945). C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher. J. Am. Chem. Soc. **70**, 1837 (1948).

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## PREPARATION OF ALUMINUM *tert*-ALKOXIDES

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The alcohol interchange method for the preparation of aluminum alkoxides has been mentioned by various workers (1, 2) and was used elegantly by Mehrotra (3, 4) in preparing pure primary and secondary aluminum alkoxides for studying their physical properties. It was claimed that repeated attempts to obtain aluminum *tert*-butoxide and aluminum *tert*-amyloxide from aluminum isopropoxide by the interchange method failed since the third isopropoxide group did not interchange. Steric hindrance was considered the main cause for this failure of complete interchange and consequently for steric reasons the dimeric nature of these mixed alkoxides was proposed through isopropoxide bridges as

[7]*The progesterone derivative VIIIa was obtained in another polymorphic modification as needles, m.p. 135–136°.*

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