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THE FORMATION OF STEROID ENOLATE ANIONS BY REDUCTIVE PROCEDURES

THE SYNTHESIS OF 17-ALKYLPROGESTERONES[1]

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Abstract—Treatment of a 16-dehydro, 17-acetoxy, 17-hydroxy or 17-bromopregn-20-one with a liquid ammonia solution of lithium, barium or calcium (and in at least one instance sodium) afforded an intermediate 17-enolate anion, which on reaction with the appropriate alkyl, allyl and benzyl halide furnished the corresponding 17-alkyl, allyl and benzyl-pregn-20-one. A very useful liquid–liquid partition column chromatographic procedure is described.

ALTHOUGH the enhanced progestational activity of 17-methylprogesterone has been known for over a decade,[2] the compounds of this class have not been extensively investigated. One apparent reason for the neglect of this interesting group of compounds was the relative inaccessibility of the 17-methylpregn-20-ones, which hitherto have been prepared by a complex sequence involving the Favorski rearrangement of a 17- or 21-halo-20-ketone and subsequent re-elaboration of the acetyl side chain from the intermediate etianic ester.[3] Furthermore, application of this process to the preparation of the higher 17-alkyl derivatives would be even more complex and to our knowledge has never been reported. We now describe a convenient procedure for the preparation of 17-alkylpregn-20-ones (V) and the use of this procedure for the synthesis of a series of biologically important 17-alkylprogesterone derivatives. This process involves alkylation of an intermediate pregn-20-one 17-enolate anion (II) developed by treatment of a 16-dehydro (I), 17-acetoxy (III), 17-hydroxy (IV), or 17-bromopregn-20-one (VI)[5] with a liquid ammonia solution of lithium, barium, calcium or sodium and is an extension of a procedure previously reported[7] from our laboratory for the C_4-alkylation of a 5α-3-keto steroid *via* a Δ^4-3-ketone.[8]

[1] A portion of this work has been reported in a preliminary communication: M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr. and C. J. Coscia, *Chem. & Ind.* 118 (1963).

[2] H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *Helv. Chim. Acta* **33**, 2229 (1950).

[3] For a review of this procedure see L. F. Fieser and M. Fieser, *Steroids* p. 560. Reinhold, New York, N.Y. (1959). An improvement on this method has been reported recently.[4]

[4] R. Deghenghi and R. Gaudry, *J. Amer. Chem. Soc.* **83**, 4668 (1961).

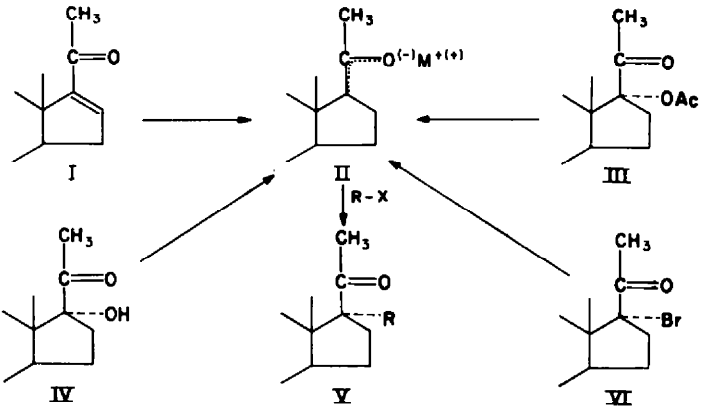
[5] That the normal" sterochemistry at C_{17} is not required is indicated by the syntheses of XVa and b; also see ref. 6.

[6] J. S. Mills, H. J. Ringold and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 6118 (1958).

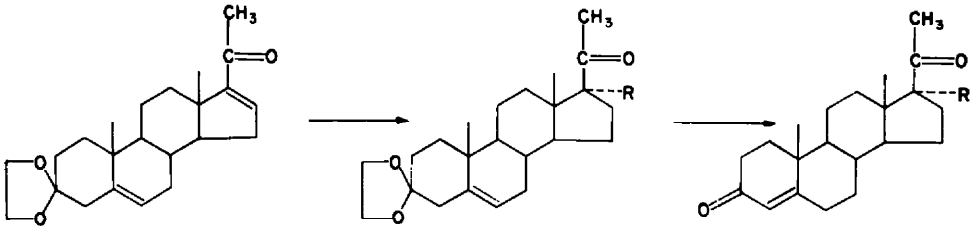
[7] R. E. Schaub and M. J. Weiss, *Chem. & Ind.* 2003 (1961). Similar observations with the *trans*-2-decalone system have been reported by G. Stork, P. Rosen and N. L. Goldman, *J. Amer. Chem. Soc.* **83**, 2965 (1961). See also P. J. Hamrick, Jr. and C. R. Hauser, *Ibid.* **81**, 493 (1959).

[8] Deghenghi *et al.*[8a] also have reported the synthesis of several 17-alkylprogesterone derivatives *via* a 17-enolate anion developed by treatment of a 16-dehydro-20-ketone with lithium-liquid ammonia.

[8a] R. Deghenghi and R. Gaudry, *Tetrahedron Letters* No. 11, 489 (1962);
[8b] R. Deghenghi, C. Revesz and R. Gaudry, *J. Med. Chem.* **6**, 301 (1963).



Most of the alkylations in this study were carried out with enolate anions formed by the interaction of lithium in liquid ammonia with the 16-dehydro-20-keto system, which consumes approximately two equivalents of lithium per mole. Since preliminary experiments with 16-dehydroprogesterone indicated that reaction with lithium in liquid ammonia proceeded without any substantial selectivity for the 16-dehydro-20-keto function, it was necessary to protect the Δ^4-3-keto system. The 3-ethylene ketal VII[10] of 16-dehydroprogesterone thus served as a suitable starting material. Development of the enolate anion II from VII was accomplished simply by addition of a tetrahydrofuran solution of VII to a lithium-liquid ammonia solution to the point of color discharge. Treatment of this anion with the appropriate halide then gave the corresponding 17-alkyl-3-ethylenedioxypregn-20-one VIII (Table 1),[11] ketal hydrolysis of which furnished the desired 17-alkylprogesterone IX (Table 3). In this way, the 17-methyl, ethyl, propyl, butyl, hexyl, octyl, decyl, allyl, and benzyl derivatives of progesterone were obtained.[12]



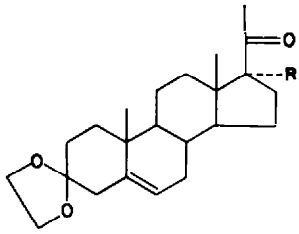
Although the addition of the 16-dehydro derivative to lithium-liquid ammonia usually proceeded smoothly to an essentially colorless end point, occasionally the pale blue color, characteristic of the latter stages of titration, would not discharge (possibly an artifact). In one instance (ethylation) a 50% excess of the 16-dehydro

[10] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 192 (1955).

[11] At least in the instance tried (ethylation to give VIII, R = C_2H_5) the reaction also could be affected, albeit in apparently lower yield, when barium or calcium was substituted for lithium.

[12] Several of the compounds of this study wherein the alkyl group is hexyl or higher could not be crystallized despite intensive efforts at purification. Nevertheless, on the basis of combustion and spectral analyses, we consider most of these products to be of relatively good quality.

TABLE 1. 17-SUBSTITUTED-3-ETHYLENEDIOXYPREGN-5-EN-20-ONES



R[a]	Yield, %	M.P., °C[b]	$[\alpha]_D$, °c	Molecular formula	Analysis			
					C		H	
					Calcd.	Found	Calcd.	Found
Methyl	65[d]	167–170 (A–B)	−32	$C_{24}H_{36}O_3$	77·37	77·30	9·74	10·16
Ethyl	43	164–167 (E–B)	· 11	$C_{25}H_{38}O_3$	77·67	77·59	9·91	9·92
Propyl	21	148–150[e] (F–C)	−43	$C_{26}H_{40}O_3$	77·95	77·81	10·07	10·33
Butyl[f]	7	96–102[g,g] (G)						
Hexyl	20	85–86[h] (G–D)	−43	$C_{28}H_{44}O_3$	78·68	78·83	10·47	10·51
Octyl	24	93–95[i] (G)	−35	$C_{31}H_{50}O_3$	79·10	79·27	10·71	10·81
Allyl	17	108–117[h,j] (G)						
Benzyl	16	175–180[h] (E–B)	−26	$C_{30}H_{40}O_3$	80·31	80·67	8·99	8·90

[a] The decyl derivative was also prepared from VII. The crude product was an oil which was not characterized, but used directly in the ketal hydrolysis step to give the corresponding product of Table 3

[b] Recrystallization solvents: A = acetone, B = pet ether (60–70°), C = pet ether (30–60°), D = pet ether (20–40°), E = ether, F = methylene chloride, G = methanol.

[c] The optical rotary dispersion curve for each of the entries in this table showed a positive Cotton effect as does progesterone 3-ethylene ketal (see ref. 24). The curves for these compounds and for progesterone-ethylene ketal were all very similar. In all instances a peak at 317–319 mμ (benzyl: 320 mμ, allyl: 325 mμ) and in most instances a second peak at 308–310 mμ was observed. Whereas [M] 308–310, 317–319 for the methyl and ethyl derivatives were 1690°, 1730° and 1950°, 2250°, respectively, these values for the higher alkyl derivatives were in the ranges 2600–2970° and 2600–3350°.

[d] Prepared in 21% yield with calcium and in 6% yield with barium.

[e] Product isolated by elution with benzene from a Florisil column.

[f] Progesterone 3-ethylene ketal (m.p. 170–173°, ca 5%) also was isolated on elution of the chromatographic column with 2% ether-in-benzene.

[g] Better quality material (m.p. 122–123°) was obtained by ketalization of the corresponding ketone (see experimental).

[h] Product isolated by elution with benzene-ether (95:1, hexyl member 99:1) from silica gel.

[i] Product isolated by partition chromatography, HBV 0·42; PMR: C_{21}-methyl peak at 124 C.P.S.

[j] Crude product, not further purified, but used directly in the hydrolysis step to give 17-allyl progesterone (see Table 3).

TABLE 2. ALKYLATIONS VIA METAL-AMMONIA TREATMENT OF VARIOUS 17-ACETOXY-, HYDROXY- AND BROMOPREGN-20-ONES[a]

Reactants	Products	Yield %	Chromatography		M.p., °C
			Adsorbent	Eluting Solvent	
17-Acetoxy-3 methoxy-pregna-3,5-dien-20-one[a] Na, CH_3I	17-Methyl-3-methoxy-pregna-3,5-dien-20-one[b,c]	22			120–125[d]
17-Hydroxy-3-methoxy-pregna-3,5-dien-20-one[e] Li, C_2H_5I	17-Ethyl-3-methoxy-pregna-3,5-dien-20-one[b]	45			133–143[d]
17-Acetoxy-3-methoxy-pregna-3,5-dien-20-one Ba, C_2H_5I	17-Ethyl-3-methoxy-pregna-3,5-dien-20-one[b]	52			130–140[d]
17-Acetoxy-3-methoxy-pregna-3,5-dien-20-one Ca, C_2H_5I	17-Ethyl-3-methoxy-pregna-3,5-dien-20-one[b]	47			125–132[d]
17-Bromopregnenolone acetate,[f] Ba, CH_3I	17-Methylpregnenolone[g,h] + Pregnenolone acetate	7	Florisil	Benzene–ether —95:5—	179–183 148–158
17-Bromopregnenolone acetate, Li, CH_3I	17-Methylpregnenolone[g] + Pregnenolone	9 24	Silica gel	Benzene–ether —9:1— —95:5—	174–177 149–153
17-Hydroxy-3 methoxy-6-methylpregna-3,5-dien-20-one, Ba, C_2H_5I	17-Ethyl-6α-methyl-progesterone[i,j]	trace	Silica gel	Benzene ether —95:5—	133–141
17-Acetoxy-3-methoxy-pregna-3,5-dien-20-one Ca, C_4H_9I	17-Butylprogesterone[i]	16	Celite	HBV 2·05	114–116

[a] See ref. 20.

[b] For characterization and preparation from corresponding Δ^4-3-ketone see experimental.

[c] Obtained by methanol crystallization of the residue remaining on removal of extraction solvent.

[d] In general, the melting points of the enol ethers were a poor criterion of purity. Melting usually occurred over a wide range, even after repeated recrystallizations.

[e] In our earlier communication (ref. 1) we erroneously reported the preparation of the 17-methyl derivative from this compound.

[f] See ref. 22.

[g] See ref. 23. The PMR spectrum of our sample showed methyl peaks at 42 (C_{18}), 63(C_{17}), 69(C_{19}) and 128 c.p.s. (C_{21}) and a vinyl proton as a multiplet centered at 327 c.p.s. The mass spectrum showed a major peak at 330 (theoretical M.W.: 330). The ORD curve showed a positive Cotton effect with peaks at 318 and 310 mμ (see Table 1, footnote *c*).

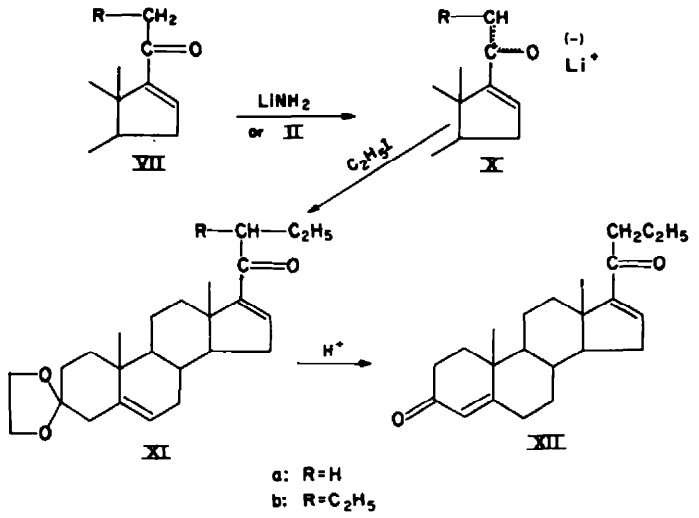
[h] Also prepared in 9% yield from 16-dehydropregnenolone acetate and lithium; also see ref. 9.

[i] After acid hydrolysis according to the procedure given in the experimental section for the formation of 17-ethylprogesterone from its 3-methyl enol ether.

[j] A superior procedure from the 16-dehydro-6-methyl enol is given in the experimental section.

ketal VII was added without causing total discharge of this color. This experiment afforded, in addition to a low yield of the 17-ethyl derivative, the products of 21-mono and bisalkylation (XI), also in low yield. Ketal hydrolysis of the monoalkylated XIa gave XII. The 21-ethyl derivatives XI presumably are formed *via* the C_{21} enolate anion X, developed by ionization of VII by lithium amide or by the C_{17} enolate anion II. (However, in the latter circumstance, the resulting progesterone 3-ketal would consume lithium, if in fact the metal were present.)

The possibility exists that this course of reaction may proceed to a significant extent even in the presence of unconsumed metal—in particular towards the end of



the titration when the concentration of metal is relatively low and the concentration of metal amide and C_{17} enolate ion II is relatively high. This, of course, would explain the over-titration experiments and the fact that many of our preparations were contaminated, often heavily, with an unidentified substance apparently containing the Δ^{16}-20-keto moiety, despite titration to an essentially colorless end point. In view of this possibility, it was conceivable that 21-alkylation might be minimized if the reaction were carried out in the presence of a substantial excess of lithium. However, from one such experiment (100% excess lithium) no 17-ethylprogesterone 3-ketal could be isolated.

The requisite 17-enolate anion II can also be produced by similar treatment of pregn-20-ones substituted at C-17 with the acetoxy,[13] hydroxy[15] or bromo group.[18,19]

[13] The deacetoxylation of several 17β-acetoxy-17α-pregn-20-ones *via* treatment with calcium or lithium in liquid ammonia[6] and the deacetoxylation of certain 12α- and 12β-acetoxy-11-keto derivatives with calcium, barium or lithium in liquid ammonia[14] have been reported. Questions concerning the mechanism of the former reaction (ref. 3, p. 631) would appear to be resolved by the present work. Thus, this deacetoxylation is an α-side protonation of the intermediate enolate anion II. A similar mechanism has already been suggested for the ring C deacetoxylation.[14]

[14] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).

[15] The ability of the 17-hydroxy-20-ketone to generate the 17-enolate anion is of some interest because of the alternate possibility that the hydroxy ketone on treatment with metal-ammonia would preferentially form an oxygen anion, which would be expected to resist further reaction to the enolate anion. Thus, unsuccessful attempts to effect the dehydroxylation of a 12β-hydroxy-11-ketone with calcium-liquid ammonia have been reported, the major product being an 11α,12β-diol.[16] On the other hand, dehydroxylation with lithium-liquid ammonia of 6β-hydroxytestosterone[16] and the conversion of 3β,5α-dihydroxyergosta-7,9(11),22-trien-6-one to 3β,6α-dihyroxyergost-22-ene[17] were successful.

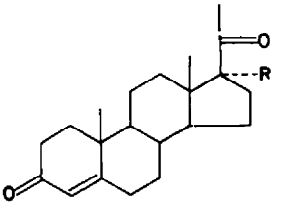
[16] C. Amendolla, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.* 1226 (1954).

[17] A. Zürcher, H. Heusser, O. Jeger, and P. Geistlich, *Helv. Chim. Acta.* 37, 1562 (1954).

[18] The amount of metal consumed by the 17-substituted-20-ketone was variable; however, usually two-four equivalents were required (also see ref. 14).

[19] Several attempts to effect 17-methylation of a 17-hydrogen-pregn-20-one with potassium or lithium t-butoxide did not give significant amounts of 17-methyl derivative. In contrast, compare the successful introduction of the 17-hydroxy group *via* potassium t-butoxide treatment of such a pregn-20-one [E. J. Bailey, D. H. R. Barton, J. Elks and J. F. Templeton, *J. Chem. Soc.* 1578 (1962)].

TABLE 3. 17-SUBSTITUTED PROGESTERONE;



R	Yield, %[a]	M.p., °C[b]	$[\alpha]_D$,	$\lambda_{max}^{CCl_4}$, μ 20C = 0	Δμ (17-R–17-H)	Molecular formula	Analysis C Calc.	C Found	H Calc.	H Found
Methyl	82	131–138[c,d] (A–B)	- 112[c]			$C_{22}H_{32}O_2$[e]	80·44	80·08	9·83	10·03
Ethyl	95	148–149[f,g] (D–B)	+ 97[f]	5·88	0·04	$C_{23}H_{34}O_2$[e]	80·65	80·41	10·01	10·13
Propyl	62	150–151[h] (A–C)	+ 92	5·88	0·04	$C_{24}H_{36}O_2$[e]	80·85	80·25	10·18	10·35
Butyl	32	114–115[i] (C)	+ 93	5·89	0·05	$C_{25}H_{38}O_2$	81·03	81·39	10·34	10·44
Hexyl	88	Syrup[k]	+ 93	5·87	0·03	$C_{27}H_{42}O_2$	81·03	80·02	10·15	10·64
Octyl	70	Syrup[l]	+ 63	5·87	0·03	$C_{29}H_{46}O_2$	81·63	81·97	10·87	11·14
Decyl	38[m]	Syrup[n]	+ 51			$C_{31}H_{50}O_2$	81·88	81·32	11·08	10·97
Allyl	36	150–152[o] (E–F)	+ 84	5·87	0·03	$C_{24}H_{34}O_2$[e]	81·31	80·14	9·67	9·59
Benzyl	98	194–196 (D)	- 26			$C_{28}H_{36}O_2$	83·12	82·55	8·97	9·28

[a] Represents yield of material with sufficient purity for further transformations.

[b] Analytical melting point. The ultraviolet maxima of these products were in the 240–242 mμ range (ε15,300–17,000). Recrystallization solvents: A = ether, B = pet. ether (b.p. 60–70°), C = pet. ether (30–60°), D = acetone, E = ethanol, F = water.

[c] Reported (ref. 23) m.p. 129–130°, $[\alpha]_D$ + 102·5°.

[d] PMR: methyl peaks at 43(C_{18}), 67(C_{19}), 72(C_{18}) and 127 c.p.s. (C_{21}); vinyl proton at 344 c.p.s.

[e] The mass spectrum showed a major peak corresponding to theoretical molecular weight.

[f] Reported (ref. 9) m.p. 148–150°, $[\alpha]_D$ + 93°.

[g] PMR: methyl peaks at 42(C_{18}), 73(C_{19}) and 128(C_{21}) c.p.s., a peak at 52 and a shoulder at 44 c.p.s. (not shown by progesterone, probably methyl of 17-ethyl); vinyl proton at 350 c.p.s.

[h] PMR: methyl peaks at 42(C_{18}), 73(C_{19}) and 127 c.p.s. (C_{21}); enhanced absorption[4] centered at 56 c.p.s. probably methyl of 17-propyl); vinyl proton at 348 c.p.s.

[i] Compared to that shown by progesterone in the 40–72 c.p.s. region.

[j] PMR: methyl peaks at 42(C_{18}), 73(C_{19}) and 128 c.p.s. (C_{21}); enhanced absorption[4] centered at 57 c.p.s. (probably methyl of 17-butyl); vinyl proton at 349 c.p.s.

[k] PMR: methyl peaks at 41(C_{18}), 72(C_{19}) and 125 c.p.s. (C_{21}); enhanced absorbtion[4] centered at 54 c.p.s. (probably methyl of 17-hexyl); vinyl proton at 345 c.p.s.

[l] Eluted from silica gel by 5% ether-in-benzene.

[m] Overall yield based on 16-dehydroprogesterone 3-ketal (VII) used in the alkylation step.

[n] Isolated by partition chromatography, HBV 0·90.

[o] PMR: methyl peaks at 47(C_{18}), 72(C_{19}) and 128 c.p.s. (C_{21}); no enhanced absorption[4] between 47 and 72 c.p.s.; C_4 vinyl proton at 348 c.p.s. and side-chain vinyl protons present as complex multiplets centered at 316 c.p.s. (integral ratio of 316 multiplet to 348 peak: 2·8:1).

Thus, 17-acetoxy-3-methoxypregna-3,5-dien-20-one[20] was converted to 17-methylprogesterone on treatment with sodim[21] in liquid ammonia followed by methylation and enol ether hydrolysis, and similarly, to 17-ethylprogesterone (calcium or barium) and 17-butylprogesterone (calcium). 17-Hydroxy-3-methoxypregna-3,5-dien-20-one afforded 17-ethylprogesterone (lithium), and 17-bromopregnenolone acetate[22] gave

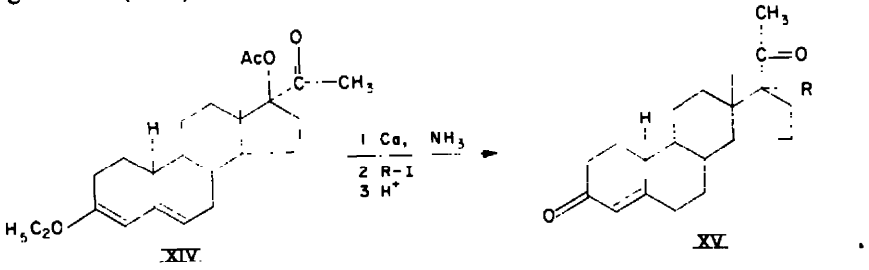
[20] J. P. Dusza, J. P. Joseph and S. Bernstein, *J. Org. Chem.* **28**, 92 (1963).

[21] However, in general, sodium does not appear to be as useful for these reactions as lithium, calcium or barium.

[22] P. L. Julian and W. J. Karpel, *J. Amer. Chem. Soc.* **72**, 362 (1950).

17-methylpregnenolone[23] (barium or lithium) which was also prepared from 16-dehydropregnenolone acetate (lithium).

Further utility of this alkylation procedure was demonstrated in the important 6-methyl and 19-nor series. Thus, lithium-ammonia treatment of 6-methyl-16-dehydroprogesterone 3-methyl enol ether followed by appropriate alkylation afforded, after acid hydrolysis, 6α-methyl-17-ethylprogesterone and 6α-methyl-17-propylprogesterone. The former product was also obtained, although in very poor yield, *via* barium-ammonia treatment of 6-methyl-17-hydroxyprogesterone 3-methyl enol ether. Additionally, 17-ethyl-6-methylpregnenolone was obtained via ethylation of the tetrahydropyranyl ether or acetate ester of 6-methyl-16-dehydropregnenolone. In the 19-nor series, treatment of XIV with calcium in liquid ammonia[13] followed by alkylation and enol ether hydrolysis afforded 17-methyl (XVa)[23a] and 17-ethyl-19-norprogesterone (XVb).



XIV XV

a: R = CH_3
b: R = C_2H_5

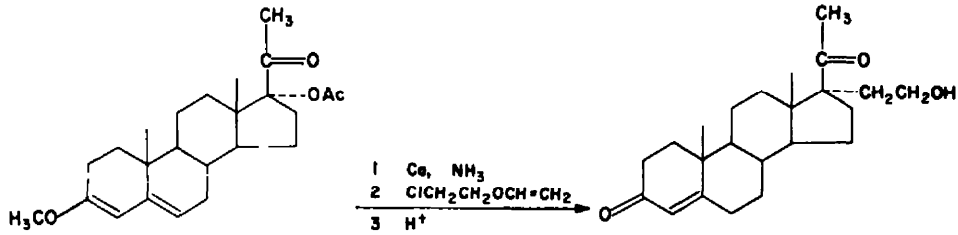
In general, the yields for the alkylation process were in the 15–50% range and the products usually required chromatography for purification. (We call attention to the detailed partition chromatography procedures developed by one of us (C.P.) and described in the experimental section.) Best yields were obtained on alkylation with methyl and ethyl iodide. Proton magnetic resonance, optical rotary dispersion and infrared studies, as well as molecular weight determination by mass spectroscopy, support the structural assignments. In particular, mass spectroscopic data and PMR measurements afforded confirming evidence for the introduction of the appropriate alkyl group (microanalytical data was equivocal). Moreover the PMR spectra showed a peak at about 125 c.p.s. ascribable to the unsubstituted C_{21} methyl group and thereby placing the introduced alkyl group at C_{17}. That this group occupied the α-position was indicated by the positive Cotton effect observed in the ORD curves of the alkylated 3-ketals.[24] Finally, it is of interest to note that in the infrared the presence of a 17-alkyl group usually results in a bathochromic shift of 0·03–0·05 μ in the position of the 20-carbonyl band (see Table 3).

[23] Pl. A. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta.* **32**, 270 (1949).

[23a] *Note added in proof.* A synthesis of 17-methyl-19-norprogesterone has also been reported by Petrow and coworkers [*J. Chem. Soc.* 4242 (1963)]. However, the reported physical constants are not in agreement with those determined from our sample and we have since learned from Dr. Petrow that the BDH product is not 17-methyl-19-norprogesterone. He and his colleagues will report on this matter at a latter date.

[24] Progesterone 3-ethylene ketal also gives a positive Cotton effect. On the other hand, several 17α-pregn-20-ones have been reported to show negative Cotton effect (C. Djerassi, *Optical Rotary Dispersion* p. 51. McGraw-Hill, New York, N.Y. (1960). W. A. Struek and R. L. Houtman, *J. Org. Chem.* **26**, (1961).

Preliminary attempts to alkylate with the secondary halide, isopropyl bromide, and with the branched chain primary halide, isoamyl bromide, failed and progesterone was isolated after ketal hydrolysis. Also unsuccessful were preliminary efforts to effect reaction with 2-chloropyridine, methylene dichloride, ethylene dichloride, acrylonitrile, chloroacetonitrile, chloromethyl ether and propargyl chloride. However, alkylation of the enolate anion developed by calcium-liquid ammonia treatment of XVI with 2-chloroethyl vinyl ether gave the 2'-hydroxyethyl derivative XVII, in low yield after concomitant enol and vinyl ether hydrolysis. An attempt to acylate this alcohol with acetic anhydride in pyridine was ineffective.



XVI XVII

Finally, some comment concerning the general effect of the 17-alkyl group on the C_{17} side chain is in order. Hinderance by the 17-methyl group to reaction of the 20-carbonyl group with Grignard or Girard reagents has already been noted.[25] We also have observed the inability of a 17-alkyl-20-ketone to react with a Girard reagent and in the experimental section we describe the use of this reagent for the clean separation of 17-ethylprogesterone 3-ethylene ketal from a mixture with 16-dehydroprogesterone 3-ethylene ketal. This steric effect also allows preferential formation of the 3-ketal derivative of a 17-alkylpregn-4-en-3,20-dione under conditions[26] which, in the absence of hindrance,[27] affords 3,20-*bis*-ketals; thus, the preferential 3-ketalization of 17-butylprogesterone, 17-ethyl-6α-methylprogesterone and 6α-methyl-17-propylprogesterone.

The preparation of several highly active oral progestins from certain of these 17-alkylprogesterone derivatives has been described elsewhere.[1,9b,25,30] In addition, appropriate dehydrogenation procedures have given 17-ethyl-6α-methylpregna-1,4-diene-3,20-dione, 17-ethyl-6-methylpregna-1,4,6-triene-3,20-dione and 6-methyl-17-propylpregna-4,6-diene-3,20-dione, all of biological interest.

EXPERIMENTAL

General M.ps. were determined in open capillary tubes and are uncorrected. Optical rotations were measured at 25° in $CHCl_3$ at concentrations of 0·6–1·0%. UV spectra were determined in methanol solution on a Cary recording spectrophotometer. Except where otherwise noted, IR spectra were determined (KBr discs) on a Perkin-Elmer spectrophotometer (Model 21). PMR spectra were measured on a Varian Model A-60 spectrophotometer in deuterochloroform solution using tetramethylsilane as an internal standard. Mass spectrometric analysis for mol. wt. was carried out with

[25] R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand and R. Gaudry, *Tetrahedron* **19**, 289 (1963).
[26] R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1341 (1952).
[27] The presence of acetoxy groups at C_{17}[28] or at C_{21}[29] also hinder 20-ketalization.
[28] C. W. Marshall, R. E. Ray, I. Laos and B. Riegel, *J. Amer. Chem. Soc.* **79**, 6303 (1957).
[29] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953).
[30] M. J. Weiss, R. E. Schaub, J. F. Poletto, G. R. Allen, Jr. and C. Pidacks, *Steroids* **1**, 608 (1963).

a consolidated Electrodynamics model 21–103 mass spectrometer at 70 volts and an inlet temp of 200°. All evaporations were carried out at red. press. Unless otherwise stated, the petroleum ether used was that fraction boiling at 60–70°. The optical rotary dispersion curves were determined with a Perkin Elmer ORD attachment to a Cary model 14 spectrophotometer at 25° in dioxane solution at concentrations of about 2% (see Table 1, footnote *c*).

Liquid-liquid partition column chromatography (by C.P.). The chromatography of these non-polar steroids was readily accomplished by using a heptane: 2-methoxyethanol partition system. The columns were prepared by the dry-pack method[81] with HCl washed Celite 545[83] diatomaceous silica as the inert support for the stationary (the more-polar[82]) phase. This phase was thoroughly mixed (0·75 ml per g) with the Celite, and the mix was packed into columns in small uniform increments. The volume of mobile phase, V_m, in the column (also referred to as the hold back volume or HBV) is that volume of mobile phase necessary to completely fill the dry-packed column. This volume will vary with the tightness of the pack. The volume of stationary phase, V_s, in the column is that volume, of solvent which was mixed with Celite and packed into the column.

The position of the product peak in the eluate from the partition column is a function of the distribution coefficient, which is a constant,[84] and the ratio of mobile phase to stationary phase, V_m/V_s. Therefore, it is necessary for comparison purposes to report the position of the product peak corrected to a specified V_m/V_s ratio. For example, in a 1·2 cm I.D. × 35 cm column packed with

Compound[a]	HBV[b]
Progesterone	4·23
17-Benzylprogesterone	3·88
17-Ethylprogesterone	2·80
17-Propylprogesterone	2·46
17-Butylprogesterone	2·05
17-Hexylprogesterone	1·67
17-Octylprogesterone	1·44
17-Decylprogesterone	0·90
19-Norprogesterone	5·35
17-Methyl-19-norprogesterone	4·82
17-Ethyl-19-norprogesterone	3·96
17-Ethyl-6α-methylprogesterone	2·41
17-Propyl-6α-methylprogesterone	2·19
1-Dehydro-17-ethyl-6α-methylprogesterone	5·15
6-Dehydro-17-ethyl-6-methylprogesterone[c]	2·14
6-Chloro-6-dehydro-17-ethylprogesterone[c]	3·61
6-Fluro-6-dehydro-17-ethylprogesterone[c]	4·57
6-Dehydro-17-hexylprogesterone[c]	2·30
6-Dehydro-17-octylprogesterone[c]	1·50
1-Dehydro-17-ethylprogesterone[d]	5·22

[a] For a similar study with the 6-chloro-6-dehydro-17-alkylprogesterone series see ref. 30. [b] Peak position of product-containing fraction. [c] Ref. 30. [d] Ref. 1.

[81] C. Pidacks, Instrument Society of America, *Proceedings* 1961 *National Symposium on Instrumental Methods of Analysis* 7, 199 (1961).

[83] Celite is the trademark of Johns-Manville Co. for diatomaceous silica products.

[82] Celite 545, when treated with dichlorodimethylsilane, will retain the less polar phase of the solvent system for a reverse-phase partition column.

[84] Although the distribution coefficient of a number of compounds is known to change with concentration, we have assumed that this coefficient remains constant under the conditions and concentrations of these partition columns.

12 g Celite wetted with 6 ml stationary phase, one may obtain an HBV of 14 to 20 ml. The V_m/V_s ratio will therefore vary from 14/6 to 20/6 and the position of the product peak will also vary, eluting earlier with the larger V_m/V_s ratio. Since the position of the product peak (reported in HBV) is inversely proportional to the V_m/V_s ratio, it is possible to compare peak positions in different columns regardless of the tightness with which they may have been packed. Thus, an observed ratio of 2·0 and a peak position of product-containing fraction at 2·2 HBV on correction for standard V_m/V_s ratio of 1·8 gives an HBV value of 2·45, the reported figure. In the data to follow, the position of the product peak will be reported in HBV corrected to a V_m/V_s ratio of 1·80.

Since all of the steroids in question have absorption in the UV, the effluent from the chromatographic columns was monitored continuously at an appropriate wave length. The instrument used was a Beckman DU spectrophotometer fitted with a variable-space flow cell[35] in a modified cell housing. The output of the instrument was recorded on a 50 mv. stripchart recorder.

It is interesting to note the regularity observed in the elution positions of a series of 17-substituted progesterones.

General procedure for the alkylation of anions derived by reduction with the metal-ammonia system

Conversion of 3-*ethylenedioxypregna*-5,16-*dien*-20-*one* (VII) *to* 3-*ethylenedioxy*-17-*methylpregn*-5-*en*-20-*one* (VIII). The following preparation serves to illustrate the general alkylation procedure with the Δ^{16} or the various 17-substituted 20-ketones. It should be noted that 3-ethylenedioxypregna-5,16-dien-20-one (VII) has only limited solubility in tetrahydrofuran. However, the other substrates are considerably more soluble in tetrahydrofuran and less solvent was necessary. The 16-dehydro-20-keto system consumed approximately 2 equivs. of metal, whereas the 17-substituted derivatives consumed about 2–4 equivs. The various 17-alkyl-3-ethylenedioxypregn-5-en-20-ones prepared by this procedure are listed in Table 1. The alkylation results with the various 17-substituted derivatives and with 16-dehydropregenolone are given in Table 2.

A solution of 40 g 3-ethylenedioxypregna-5,16-dien-20-one (VII)[10] in 750 ml purified tetrahydrofuran was added to a stirred solution of 1·55 g Li in approximately 2 l. liquid NH_3 (dried by prior addition of minimum pieces of Li until the blue color was retained for at least 15 min). Toward the end of the addition the blue color gradually faded and at the end of the addition this color was completely discharged. (Usually the color was discharged before the addition of the "theoretical" amount of steroid, in which case the addition was then stopped. Usually at least 70–80% of the "theoretical" amount was required to cause color discharge.) To the milky solution was added, dropwise, a solution of 40 ml methyl iodide in 70 ml tetrahydrofuran and stirring was continued for 1 hr after which time an additional 40 ml methyl iodide was added. The resulting mixture was stirred for 18 hr. Ammonium chloride (20 g) was added followed by 1 l. water and 1 l. ether. The aqueous layer was extracted further with ether, and removal of the solvent from the combined ethereal solutions gave a residue, which on recrystallization from acetone furnished, in two crops, 27 g (65%) 3-ethylenedioxy-17-methylpregn-5-en-20-one, m.p. 157–162°. Further characterization of this substance is given in Table 1.

From the 16-dehydro-3-ketal (VII) only this derivative and the corresponding 17-ethyl compound could be isolated by direct crystallization. Details of the chromatography for the other 17-substituted ketals prepared from VII may be found above and in Table 1. Allyl and benzyl chloride and the required alkyl iodides were used for the preparation of the compounds in Table 1.

General procedure for the hydrolysis of the 17-*substituted* 3-*ketals* (VIII) *to the* 17-*substituted progesterones* (IX)

The following procedure for the preparation of 17-*methylprogesterone* serves to illustrate this method. The various 17-substituted progesterones are listed in Table 3.

A solution of 3-ethylenedioxy-17-methylpregn-5-en-20-one (15·0 g) in 950 ml methanol containing 93 ml 8% H_2SO_4 was heated at reflux temp for 45 min. The solution was then concentrated to turbidity, diluted with 200 ml water, and the product isolated with methylene chloride. Recrystallization of the residue from acetone–pet. ether gave 10·9 g (82%) 17-methylprogesterone, m.p. 120–125°. Further characterization of this substance is given in Table 3.

[35] A product of Research and Industrial Instrument Co., 557 Post Road, Darien, Conn.

17-Hydroxy-3-methoxypregna-3,5-dien-20-one

A solution of 7·93 g 17-hydroxyprogesterone, 211 mg *p*-toluenesulfonic acid monohydrate, 66 ml 2,2-dimethoxypropane,[86] 66 ml dimethylformamide and 2·64 ml methanol was heated at reflux temp for 3 hr. Sodium bicarbonate was added to the cooled solution which then was poured, with stirring, into a large volume water. The resulting solid was collected by filtration and recrystallized from methanol containing a trace of pyridine to give 6·10 g (74%) white crystals, m.p. 145–156°; $[\alpha]_D$ −122°; λ_{max} 2·87, 5·86, 6·00, 6·10 μ; 239 mμ (ϵ 19,800). (Found: C, 76·31; H, 9·52; Calc. for $C_{22}H_{32}O_3$ (344·48): C, 76·70; H, 9·36%).

3-Methoxy-17-methylpregna-3,5-dien-20-one

To a solution of 17-methylprogesterone (5·0 g) in 50 ml purified dioxane containing 1·5 ml methyl alcohol and 20 ml methyl orthoformate was added 1·3 ml 5% solution of H_2SO_4 in dioxane. After 15 min at room temp, the solution was treated with 10 ml pyridine and poured into 350 ml water. The crude product was isolated with methylene chloride and crystallization was induced by trituration with methanol, yielding 3·88 g (75%) crystals, m.p. 132–137°.

In a pilot run, material was obtained as white needles, m.p. 138–144°; $[\alpha]_D$ −40°; λ_{max} 5·89, 6·04, 6·13 μ; 239 mμ (ϵ 21,400). (Found: C, 80·71; H, 10·21; Calc for $C_{23}H_{34}O_2$ (342·50): C, 80·65; H, 10·01%).

The preparation of this compound by the reaction of 17-acetoxy-3-methoxypregna-3,5-dien-20-one[80] with Na in liquid NH_3 followed by methyl iodide treatment is noted in Table 2.

17-Ethyl-3-methoxypregn-3,5-dien-20-one

In the manner described above for the 17-methyl derivative, 2·00 g 17-ethylprogesterone afforded, after recrystallization from methanol, 1·41 g (68%) crystals, m.p. 131–136°. A sample recrystallized for analysis had m.p. 132–136°; $[\alpha]_D$ −26°; λ_{max} 5·86, 6·00, 6·08 μ; 239 mμ (ϵ 16,000). (Found: C, 81·12; H, 10·36; Calc. for $C_{24}H_{36}O_2$ (356·53): C, 80·85; H, 10·18%).

The preparation of this compound by ethylation of the reaction product obtained from 17-hydroxy-3-methoxypregna-3,5-dien-20-one and Li, and from 17-acetoxy-3-methoxypregna-3,5-dien-20-one and Ba or Ca is noted in Table 2.

Formation of 17-ethylprogesterone by hydrolysis of 17-ethyl-3-methoxypregna-3,5-dien-20-one

A solution of 2·40 g 17-ethyl-3-methoxypregna-3,5-dien-20-one, the preparation of which by various alkylation experiments is noted in Table 2, in 100 ml methanol and 25 ml 3N HCl solution was heated at reflux temp for 40 min. The solution was concentrated to turbidity, diluted with water, and the product isolated with methylene chloride. Recrystallization from methanol gave 805 gm (35%) white crystals, m.p. 146–147°.

Formation of 17-methylprogesterone by hydrolysis of 3-methoxy-17-methyl-pregna-3,5-dien-20-one

This experiment was carried out in the manner described immediately above for the 17-ethyl derivative the product was recrystallized from acetone–pet. ether and then from ether–pet. ether to give material with m.p. 132–134°; no depression on admixture with an authentic sample.

Treatment of 3-ethylenedioxypregna-5,16-dien-20-one (VII) (50% *excess*) *with lithium followed by ethylation*

Isolation of 17-ethyl-3-ethylenedioxypregn-5-en-20-one, 21-ethyl-3-ethylenedioxypregna-5,16-dien-20-one (XIa), *and of 21, 21-diethyl-3-ethylenedioxypregna-5,16-dien-20-one* (XIb). In the manner of the General alkylation procedure (above) 3-ethylenedioxypregna-5,16-dien-20-one (VII; 105 g, 0·294 mole), dissolved in 2,870 ml tetrahydrofuran, was added to a solution of Li (2·7 g, 0·388 g-atom) in about 5 l. dried liquid NH_3. Complete discharge of the final milky-blue color was not observed. Ethyl iodide (100 ml) was added and after stirring overnight, the reaction mixture treated as described above. Evaporation of the extraction solvent (ether) gave a viscous,

[86] Procedure of A. L. Nussbaum, E. Yuan, D. Dincer and E. P. Oliveto, *J.Org.Chem.*, **26**, 3925 (1961).

yellow oil which on treatment with acetone (350 ml) and chilling afforded 27·2 g of recovered 3-ethylenedioxypregna-5,16-dien-20-one (VII; m.p. 220–230°). Concentration of the acetone mother liquor to dryness gave a viscous residue which was rubbed with isopropyl ether until crystallization commenced. After chilling, 35·5 g (m.p. 135–145°) of crystalline material was obtained and an additional 11·5 g was isolated by concentration of the mother liquor. Repeated recrystallizations of this 47 g from acetone, ether and isopropyl ether resulted in the isolation of 6·1 g (m.p. 167–172°) of *17-ethyl-3-ethylenedioxypregn-5-en-20-one* and of 7·2 g (m.p. 175–180°) of the less soluble *21-ethyl-3-ethylenedioxypregna-5,16-dien-20-one* (XIa). The latter substance (XIa) was then recrystallized from acetone to a constant m.p. (m.p. 192–195° corr.); $[\alpha]_D$ −15·1°; λ_{max} 6·0 (s), 6·12 (w sh), 6·28 (m)μ; 240 mμ (ϵ 8,250); PMR: 48,55 (sh), 63 (sh) possible triplet corresponding to methyl of 21-ethyl group), 57 (C_{18}–CH_3), 65 (C_{19}–CH_3), 242 (O—CH_2—CH_2—O), multiplet centered at 330 (C_6—H), triplet centered at 412 c.p.s. (J = 3 c.p.s., C_{16}—H); the C_{21}—CH_3 peak of a 21-acetyl side chain at about 117 c.p.s. was missing; integral ratio of 48–65 c.p.s. area: 242 c.p.s. peak was 9·1:4. (Found: C, 77·68, 77·55; H, 8·98, 9·42; mol. wt. (mass. spec.), 384; Calc. for $C_{25}H_{36}O_3$ (384·54): C, 78·08; H, 9·44%).

The mother liquors (above) from the recrystallizations which afforded 6·1 g of the 17-ethyl derivative and 7·2 g of the 21-ethyl- Δ^{16}-derivative were concentrated to dryness. Of the residual 29 g, 27 g was treated with Girard T reagent (27 g) for 1·5 hr, in the manner described near the conclusion of this section for the separation of the 17-ethyl 3-ketal from a mixture with 16-dehydroprogesterone 3-ketal, to give 14 g unreacted material. Treatment again with Girard T reagent (14 g) gave 8 g unreacted material, crystallization of which from ether furnished an additional 4·8 g *17-ethyl-3-ethylenedioxypregn-5-en-20-one* (m.p. 160–170°, total yield 10·9 g). Partial concentration of the ether filtrate and dilution with pentane then afforded 1·9 g of a mixture (m.p. 105–130°), which was submitted to partition chromatography on Celite with the heptane-2-methoxyethanol system. An additional 473 mg impure 17-ethylprogesterone 3-ketal (m.p. 145–165°) was obtained and from the fraction with peak at HBV 1·15 900 mg of *21,21-diethyl-3-ethylenedioxypregna-5,16-dien-20-one* (XIb) (m.p. 130–137°) was isolated. Several recrystallizations from hexane gave material m.p. 137–140°; $[\alpha]_D$ −39·2°; λ_{max} 6·02(s), 6·15(w), 6·28(m), 9·20(s) μ; 240 mμ (ϵ 9,900); PMR 42,49,55(sh) (CH_3 of 21-ethyl groups), 57(C_{18}—CH_3), 65(C_{19}—CH_3), 238(O—CH_2—CH_2—O), multiplet centered at 323 (C_6—H), triplet centered at 403 c.p.s. (C_{16}—H); the C_{21}—CH_3 peak of a 21-acetyl side chain usually observed at about 117 c.p.s. was missing; integral ratio of 42–59 c.p.s. area (C_{16}—CH_3 + 2CH_3 from 2 C_{21}—C_2H_5): 238 c.p.s. peak was 9·4:4. Analysis indicated a hemihydrate and the sample was dried *in vacuo* over P_2O_5 at 100° for 2 hr, m.p. 139–141°. (Found: C, 78·73; H, 9·69; mol. wt. (mass spec.): 412; Calc. for $C_{27}H_{40}O_3$(412·59): C, 78·59; H, 9·77%).

21-Ethylpregna-4,16-diene-3,20-dione (XII).

21-Ethyl-3-ethylenedioxypregna-5,16-dien-20-one (XIa, 1·0 g, 2·6 mmole; m.p. 180–188°) was hydrolyzed with H_2SO_4 in acetone in the manner described above. Evaporation of the extraction solvent (methylene chloride) gave 0·85 g (92%) product XI, m.p. 135–145°. Recrystallization to constant m.p. from methylene chloride–ether gave material, m.p. 151–153° corr., $[\alpha]_D$ +153°; λ_{max} 5·96, 6·01, 6·18, 6·30 μ; 238 mμ (ϵ 27,000). (Found: C, 81·46; H, 9·69; Calc. for $C_{23}H_{32}O_2$(340·49): C, 81·13; H, 9·47%).

3-Methoxy-6-methylpregna-3,5,16-trien-20-one

A solution containing 24·0 g (0·074 mole) 6α-methylpregna-4,16-diene-3,20-dione[37] and 640 mg *p*-toluenesulfonic acid monohydrate in 200 ml 2,2-dimethoxypropane,[38] 200 ml dimethylformamide and 8 ml methanol was heated at reflux temp for 3 hr. The cooled solution was treated with 3·60 g $NaHCO_3$ and poured onto cracked ice. The crude solid was recrystallized from methanol, containing a trace of pyridine, to give 19·0 g (76%) crystals, m.p. 134–144°. A sample recrystallized twice from the same solvents had m.p. 130–148°; $[\alpha]_D^{25}$ −35°(*c* 1·0, $CHCl_3$); λ_{max} 5·99, 6·02, 6·13, 6·29 μ; 242 mμ (ϵ 22,000). (Found: C, 80·71; H, 9·62; Calc. for $C_{23}H_{32}O_2$ (340·49): C, 81·13; H, 9·47%).

[37] D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957).

17-Hydroxy-3-methoxy-6-methylpregn-3,5-dien-20-one

In the manner described immediately above, 17-hydroxy-6α-methylprogesterone[38] (3·00 g., 8·7 mmoles) was converted into the methyl enol ether. The product (2·09 g, 67%) was obtained, after recrystallization from methanol containing a trace of pyridine, as crystals, m.p. 130–145°. Material from a similar experiment was recrystallized 3 times from methanol containing a trace of pyridine to give white needles, m.p. 146–152°; $[\alpha]_D$ −187°; λ_{max} 2·83, 5·87, 6·02, 6·12 μ; 245 mμ (ε 18,700). (Found: C, 76·88; H, 9·64; Calc. for $C_{23}H_{34}O_2$ (358·50): C, 77·05; H, 9·56%).

6-Methyl-3β-(2'-tetrahydropyranyloxy)pregna-5,16-dien-20-one

A solution containing 7·60 g (20 mmoles) 6-methyl-16-dehydropregnenolone,[37] 1·68 g dihydropyran and 500 mg *p*-toluenesulfonic acid hydrate in 100 ml benzene was mechanically stirred at room temp for 24 hr. The solvent was removed, and the residual gum was chromatographed on Florisil[39] magnesia–silica gel. The material eluted with benzene was crystallized from methanol to give 3·75 g (45%) white crystals, m.p. 122–125°; $[\alpha]_D$ −10°; λ_{max} 6·00, 6·30, 9·70 μ; 240 mμ (ε 8,670). (Found: C, 78·44; H, 9·97; Calc. for $C_{27}H_{40}O_3$ (412·59): C, 78·59; H, 9·77%).

17-Ethyl-6α-methylprogesterone

According to the General alkylation procedure, a solution of 3-methoxy-6-methylpregna-3,5,16-trien-20-one in tetrahydrofuran was added dropwise to a solution of 698 mg (100 mg-atoms) Li in about 1 l. dry liquid NH_3; 14·56 g (42·7 mmoles) steroid was required for color discharge. The crude product was isolated in the previously described manner and hydrolyzed in 350 ml methanol and 100 ml water with 50 ml HCl. The product was isolated with methylene chloride and chromatographed on Celite using a heptane:2-methoxyethanol system; the product was isolated from the fraction with peak at HBV 2·41 and was recrystallized from dil. methanol to give 2·63 g (17%) needles, m.p. 141–143°. Material from a similar experiment had m.p. 142–144°; $[\alpha]_D$ +77·6°; $\lambda_{max}^{CCl_4}$ 5·88 5·94, 6·16 μ; 240 mμ (ε 16,600); PMR: 42 (C_{18}—CH_3), 43 (triplet, J = 7·5 c.p.s.; CH_3 of 17-ethyl), 64 (doublet, J = 6·5 c.p.s.; C_6—CH_3), 72 (C_{19}—CH_3), 127 (C_{21}—CH_3), 352 c.p.s. (doublet J = 2 c.p.s., C_4—H). (Found C, 80·44; H, 10·37; mol. wt. (mass spec.): 356; Calc. for $C_{24}H_{36}O_2$ (356·53): C, 80·85; H, 10·18%).

This product was also prepared, in very poor yield, *via* ethylation of 17-hydroxy-3-methoxy-6-methylpregna-3,5-dien-20-one. (See Table 2).

6α-Methyl-17-propylprogesterone

According to the General alkylation procedure a solution of 1·00 g (0·144 g-atom) Li in approximately 2·5 l. NH_3 was treated with 29·0 g (84·5 mmoles) 3-methoxy-6-methylpregna-3,5,16-trien-20-one in 260 ml tetrahydrofuran; the deep blue color persisted. Nevertheless, addition of 144 ml propyl iodide gave a crude product which was hydrolyzed with HCl. The crude material was chromatographed on Celite, and the product eluted in the fraction with peak at HBV 2·19. The fraction was evaporated, and the residue crystallized with ether to give 8·30 g (26%) crystals, m.p. 165–169°. The material was of suitable purity for the subsequent step. For analysis a sample was recrystallized from acetone–hexane to give white needles, m.p. 167–168°; $[\alpha]_D$ + 73°; λ_{max} 5·90, 5·95, 6·17 μ; 240 mμ (ε 16,300); PMR: 42(C_{18}—CH_3), 56 (ill-defined, probably due to methyl of 17-propyl), 64 (doublet, J = 6·5 c.p.s., C_6—CH_3), 72 (C_{19}—CH_3), 126 (C_{21}—CH_3), 350 c.p.s. (doublet, J = 2 c.p.s., C_4—H). (Found: C, 80·62; H, 10·33; mol. wt. (mass spec.): 370; Calc. for $C_{25}H_{38}O_2$ (370·55): C, 81·03; H, 10·34.

17-Ethyl-6-methylpregnenolone

(A.) To a solution of 61 mg (8·8 mg -atoms) Li in about 200 ml dry liquid NH_3 was added to the point of color discharge a solution of 6-methyl-3β-(2'-tetrahydropyranyloxy)pregna-5,16-dien-20-one in tetrahydrofuran; 2·61 g (6·3 mmoles) steroid was required (see General alkylation procedure). The crude product, isolated in the usual manner, was hydrolyzed in 100 ml boiling methanol with 5 ml 8% H_2SO_4. The product was isolated with methylene chloride, chromatographed on silica gel

[38] J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, *J. Amer. Chem. Soc.* **80**, 2094 (1958).

[39] Florisil is the trademark of the Floridin Co. for a magnesia-silica gel adsorbent.

and the material eluted with a 7·5% ether-in-benzene solution was recrystallized from acetone–pet ether to give 496 mg (31%) white crystals, m.p. 208–217°. The analytical sample had m.p. 217–222°; $[\alpha]_D$ −65°; λ_{max} 2·82, 5·90, 9·37 μ; PMR: 39·5 (C_{18}—CH_3), 44 (triplet, J = 7 c.p.s., CH_3 of 17-ethyl), 60 (C_{19}—CH_3), 127 c.p.s. (C_{21}—CH_3); ORD: positive Cotton effect, peaks at 320 and 312 mμ (see Table 1, footnote *c*). (Found: C, 80·10; H, 10·73; mol. wt. (mass spec.), 358; Calc. for $C_{24}H_{38}O_3$ (358·54): C, 80·39; H, 10·68%).

(B.) In the usual manner (General alkylation procedure) a solution of 6-methyl-16-dehydropregenolone acetate[37] in tetrahydrofuran was added dropwise to a solution of 711 mg (0·102 g -atom) Li in about 1 l. dry liquid NH_3; 11·88 g (0·032 mole) was required for color discharge. The crude product was chromatographed on silica gel and the material eluted with benzene–ether (93:7 and 9:1) was recrystallized from acetone–hexane to give 1·55 g (13%) white crystals, m.p. 210–218°. This material was identical, by the usual criteria, with that obtained in A directly above.

17-*Methyl*-19-*norprogesterone* (XVa)[23a]

According to General alkylation procedure, a solution of 17β-acetoxy-3-ethoxy-19-nor-17α-pregna-3,5-dien-20-one (XIV)[6,13] in tetrahydrofuran was added to a solution of 183 mg (4·56 mg -atoms) Ca in about 250 ml liquid NH_3; 1·00 g (2·60 mmoles) of steroid was required to discharge the blue color. The resulting mixture was treated with 10 ml methyl iodide and stirred at room temp for 18·5 hr. The product was isolated with ether and hydrolyzed with 75 ml methanol, 30 ml water and 15 ml 37% HCl. The crude product, isolated with methylene chloride, was chromatographed on Celite with the heptane:2-methoxyethanol system. The product was isolated from the fraction with peak at HBV 4·82 and was recrystallized from hexane to give 50 mg (6%) white crystals, m.p. 142–144°. A mixture with 19-norprogesterone melted at 110–117°. The compound had $[\alpha]_D$ +58°; λ_{max} 5·89, 5·97, 6·15 μ; 240 mμ (ϵ 18,700); PMR: methyl peaks at 44 (C_{18}), 69 (C_{17}) and 128 c.p.s. (C_{21}); vinyl proton peak at 351 c.p.s.; ORD (0·67% dioxane): positive Cotton effect, $[M]_{308,352,365,400}$ +11,200°, −610°, −740°, +190°. (Found: C, 79·62; H, 9·10; Calc. for $C_{21}H_{30}O_2$ (314·45); C, 80·21; H, 9·62%).

17-*Ethyl*-19-*norprogesterone* (XVb)

According to the General alkylation procedure, a solution of 17β-acetoxy-3-ethoxy-19-nor-17α-pregna-3,5-dien-20-one (XIV)[6,13] in tetrahydrofuran was added to a solution of 183 mg (4·56 mg atoms) Ca in about 250 ml liquid NH_3; 938 mg (2·44 mmoles) steroid was required to obtain discharge of the blue color. The resulting mixture was treated with 10 ml ethyl iodide and stirred at room temp for 4·5 hr. The mixture was then kept at room temp for about 17 hr, and the crude product isolated with ether. The residue remaining after evaporation of the extraction solvent was hydrolyzed. with 50 ml water, 20 ml water and 10 ml 37% HCl. The crude product, isolated with methylene chloride, was subjected to partition chromatography on Celite using heptane-2-methoxyethanol. The product was isolated from the fraction with peak at HBV 3·96 and was crystallized from ether-hexane to give 118 mg (15% yield) white crystals, m.p. 121–123°. A mixture with 19-norprogesterone melted at 92–107°; recrystallization from hexane gave crystals, m.p. 122–123°; $[\alpha]_D$ +44°; $\lambda_{max}^{CCl_4}$ 5·88, 5·95, 6·16 μ; 239 mμ (ϵ 17,700); PMR: methyl peaks at 39 (C_{18}) and 128 c.p.s. (C_{21}), enhanced absorption at 34–55 c.p.s. on comparison with the PMR spectrum of 19-norprogesterone (probably methyl of 17-ethyl); vinyl proton peak at 356 c.p.s.; ORD (0·88% dioxane): positive Cotton effect, $[M]_{302,352,364,400}$ +8,500°, −750°, −970°, +95°. (Found: C, 80·26; H, 9·87; Calc. for $C_{22}H_{32}O_2$ (328·48): C, 80·44; H, 9·83%).

The material eluted from the fraction with peak at HBV 5·32 was crystallized from acetone–hexane to give 80 mg (11% yield) 19-norprogesterone as white crystals, m.p. 140–142°, reported[6] m.p. 144–145°, $\lambda_{max}^{CCl_4}$ 5·84; 5·94; 6·15μ; ORD (0·60% dioxane): positive Cotton effect, $[M]_{309,352,366,385}$ +12,090°, +420°, 0°, +570°.

17-(2′-*Hydroxyethyl*)*progesterone* (XVII)

17-Acetoxy-3-methoxypregna-3,5-dien-20-one (XVI[20]; 7 g) was treated with Ca in liquid NH_3 and then with 2-chlorethyl vinyl ether by the General alkylation procedure. The material obtained on evaporation of extraction solvent was triturated with 50 ml methanol and filtered to give 3·7 g 3-methoxypregna-3,5-dien-20-one. Evaporation of the methanol mother liquor then gave 1·8 g syrup,

which was treated with 65 ml 50% aqueous methanol solution containing 1 ml 37% HCl at reflux for 40 min. The methanolic solution was cooled, diluted with water and extracted with methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The residue was dissolved in acetone and chilled. The supernatant solvent was decanted from the precipitated solid, which was triturated with pet ether containing a few drops acetone and then filtered and dried to give 259 mg crude product (XVII), m.p. 200–210°.

This material was then further purified by chromatography on Florisil. The product was obtained on elution with 15% ether–benzene. After one recrystallization from methylene chloride–ether, the product melted at 227–230°; $[\alpha]_D$ + 95°; λ_{max} 2·86(strong), 5·86, 5·99, 6·18 μ; 241 mμ (ϵ 19,300); PMR (in pyridine): 47(C_{18}—CH_3), 62(C_{19}—CH_3), 88(C_{21}—CH_3), 294 (—OH, disappears on equilibration with D_2O), 357 c.p.s. (C_4—H). (Found: C, 75·60; H, 9·22; H_2O (K—F), 2·24; Calc. for $C_{28}H_{34}O_3$. $\frac{1}{2}H_2O$ (367·5): C, 75·30; H, 9·61; H_2O, 2·45%).

Separation of 17*-ethylprogesterone* 3*-ethylene ketal from a synthetic mixture with* 16*-dehydroprogesterone* 3 *-ethylene ketal by extraction with girard T reagent*

To a solution at reflux temp of Girard T reagent (2·0 g) in abs. ethanol (27 ml) containing glacial acetic acid (3 ml) was added 17-ethylprogesterone 3-ethylene ketal (1·0 g) and 16-dehydroprogesterone 3-ethylene ketal (1·0 g). Heating was continued for 2 hr. The solution then was cooled and added to NaOHaq. (1·9 g in 128 ml). The resulting mixture was extracted with ether (3 × 40 ml) and the combined extracts were washed with water, dil $NaHCO_3$aq and water again. After drying ($MgSO_4$), the solvent was evaporated to give 0·7 g (70% recovery) 17-ethylprogesterone 3-ethylene ketal, m.p. 166–172°; IR analysis showed no Δ^{16}-contaminant.

17*-Butyl*-3*-ethylenedioxypregn*-5*-en*-20*-one*

17-Butylprogesterone (200 mg) was ketalized by the *p*-toluenesulfonic acid–benzene–ethylene glycol procedure.[26] The product (61 mg) was obtained from methanol as white needles, m.p. 122–123°; $[\alpha]_D$ −40°; λ_{max} 5·88, 9·04 μ; no significant UV absorption at 100γ/ml. (Found: C, 78·75; H, 10·15; Calc. for $C_{27}H_{42}O_3$ (414·61): C, 78·21; H, 10·21%).

3*-Ethylenedioxy*-17*-ethyl*-6*-methylpregn*-5*-en*-20*-one*

This compound was prepared from 200 mg 17-ethyl-6α-methylprogesterone using the *p*-toluenesulfonic acid–benzene–ethylene glycol procedure. It was obtained after recrystallization from acetone–hexane and then from methanol as white needles, m.p. 175–177°; $[\alpha]_D$ −52°; no appreciable UV absorption at 20γ/ml.; λ_{max} 5·91, 9·05 μ; ORD: positive Cotton effect, $[M]_{319,410.589}$ +2400°, −270°, −160°. (Found: C, 77·62; H, 10·08; Calc. for $C_{26}H_{40}O_3$ (400·58): C, 77·95; H, 10·07%).

3*-Ethylenedioxy*-6*-methyl*-17*-propylpregn*-5*-en*-20*-one*

This compound was prepared as directly above from 250 mg 6α-methyl-17-propylprogesterone. It was eluted from silica gel with a 1% ether-in-benzene solution and then recrystallized from dil. methanol to give 146 mg white needles, m.p. 116–118°; $[\alpha]_D$ −51°; λ_{max} 5·90, 9·04 μ; ORD: positive cotton effect, $[M]_{277,310,320,589}$ −4320°, +2100°, 2400°, −116°. (Found: C, 78·84: H, 10·34; Calc. for $C_{27}H_{42}O_3$ (414·61): C, 78·21; H, 10·21%).

17*-Ethyl*-6α*-methylpregna*-1,4*-diene*-3,20*-dione*

(A) *Selenium dioxide method.* A magnetically stirred solution containing 600 mg 17-ethyl-6α methylprogesterone and 360 mg selenium dioxide in 30 ml t-butyl alcohol containing 0·1 ml pyridine was heated at reflux temp under nitrogen for 25·5 hr. The hot mixture was filtered through Celite and the residue washed with hot ethyl acetate. The combined filtrate and washings were evaporated and the residue dissolved in methylene chloride. This solution was washed with saline, dried ($MgSO_4$) and evaporated. The residue was partition–chromatographed on Celite using the heptane–2–methoxyethanol system and the product was isolated from the fraction with peak at HBV 5·15. The oily residue obtained on evaporation of solvent was partially crystallized with ether to give 117 mg crystals, m.p. 192–194°. Recrystallization from acetone–hexane gave crystals, m.p. 194–195°; $[\alpha]_D$ +6°; λ_{max} 5·88, 6·03, 6·14, 6·22 μ; 244mμ (ϵ 15,100). (Found: C, 81·15; H, 9·95; Calc. for $C_{24}H_{34}O_2$ (368·50): C,81·31; H, 9·67%).

(B) *2,3-Dichloro-5,6-dicyanobenzoquinone (DDQ) method.*[40] A solution of 500 mg (1·4 mmoles) 17-ethyl-6α-methylprogesterone in 50 ml dioxane was treated with 475 mg (2·1 mmoles) DDQ for 72 hr at reflux temp. The residue remaining after evaporation of the washed extraction solvent was recrystallized from acetone–hexane to give 345 mg (72%) crystals, m.p. 192–193°; identical with the product of Method A.

17-Ethyl-6-methylpregna-1,4,6-triene-3,20-dione

In the manner described above for the preparation of 17-ethyl-6α-methylpregna-1,4-diene-3,20-dione, 160 mg 17-ethyl-6-methylpregna-4,6-diene-3,20-dione[30] was treated with 113 mg DDQ[40] in 10 ml dioxane. The crude product was chromatographed on 3 g Florisil, and the solids eluted with benzene (50 ml), 10% methylene chloride in benzene (50 ml) and methylene chloride (50 ml) were combined and recrystallized from methylene chloride–pet ether (b.p. 30–60°) to give 84 mg (53%) white crystals, m.p. 198–199°; $[\alpha]_D$ −12°; λ_{max} 5·88, 6·04, 6·18, 11·21 μ; 228 (ε 15,200), 255 (ε 10,000) and 303 mμ (ε 14,500). (Found: C, 81·29; H, 9·25; Calc. for $C_{24}H_{32}O_2$: C, 81·77; H, 9·15%).

6-Methyl-17-propylpregna-4,6-diene-3,20-dione

A solution of 7·30 g (19·7 mmoles) 6-methyl-17-propylprogesterone in 220 ml dioxane was saturated with HCl, and 5·10 g (24 mmoles) DDQ was added.[41] Crystals rapidly separated; the mixture was allowed to stand at room temp for 30 min and then filtered. The filtrate was diluted with methylene chloride, and this solution was washed successively with water, 1% NaOHaq., saline and finally water, dried (Na_2SO_4) and evaporated. On trituration with a limited volume of acetone the residue crystallized to give 5·13 g (71%) solid, m.p. 166–170°. This material was recrystallized from ether–pet ether (b.p. 30–60°) to give crystals, m.p. 170·0–170·5°; $[\alpha]_D$ +38°; λ_{max} 5·90, 6·00, 6·14, 6·30 μ; 290 mμ (ε 23,000). (Found: C, 81·48; H, 9·94; Calc. for $C_{25}H_{36}O_2$ (368·54): C, 81·47; H, 9·85%).

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[40] D. Burn, D. N. Kirk and V. Petrow, *Proc. Chem. Soc.* 14 (1960).
[41] Method of H. J. Ringold and A. Turner, *Chem. & Ind.* 211 (1962).