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The Synthesis of Some 7α- and 7β-Methyl Steroid Hormones[1]

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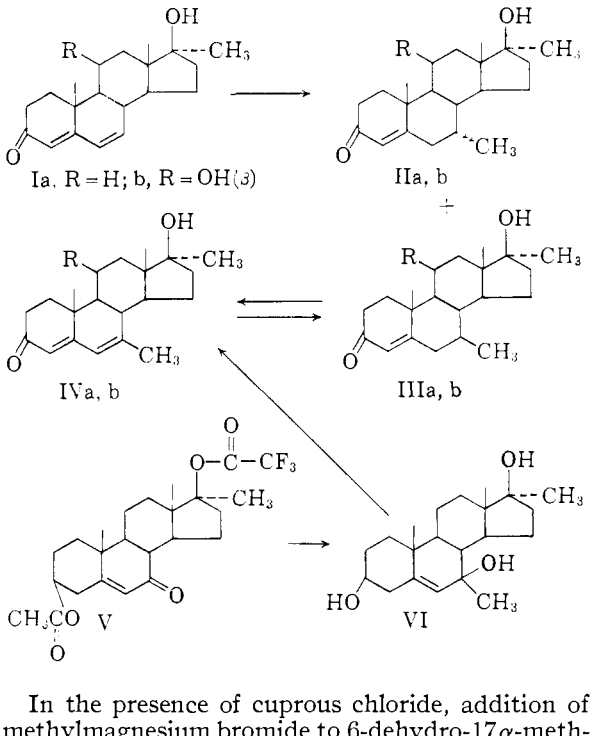
7-Methyl derivatives of the androstane and pregnane series have been prepared by 1,6-addition of methylmagnesium bromide to steroidal $\Delta^{4,6}$-3-ketones. The 7-methyl derivatives of hydrocortisone acetate, progesterone, testosterone, 17-methyltestosterone and 11β-hydroxy-17-methyltestosterone are described.

During the past two decades efforts to alter the properties of hormones by unnatural modifications of the steroid nucleus have led to the introduction of methyl groups[2] at the 1-, 2-, 3-,[2a] 4-, 6-,[2b] 9-,[2c] 11-,[2d] 14-, 16- and 17-positions. We now wish to report on some of our work on the preparation of 7-methyl derivatives in the androstane and pregnane series.

When treated with methylmagnesium bromide in the presence of cuprous chloride $\Delta^{4,6}$-3-keto steroids readily undergo 1,6-addition[3] and afford the 7-methyl-Δ^4-3-ketones. Both the 7α- and 7β-methyl epimers ordinarily are produced, but the relative amounts vary markedly according to the structure of the dienone. While back side attack to produce the 7α-methyl derivative is normally the preferred mode of addition, the 11β-hydroxy steroids studied to date have yielded mainly the 7β-epimers. It thus appears that addition from the β-side can be brought about by a neighboring group which may complex with and orient the Grignard reagent to the front of the molecule.

The first indication for the introduction of the 7-methyl group during the Grignard reaction was the shift in the ultraviolet absorption maximum from 284 to 244 mμ. Further evidence was obtained by dehydrogenation of the product with chloranil[4] in boiling *t*-butyl alcohol. The 7-methyl-$\Delta^{4,6}$-3-keto steroids thus produced exhibited an ultraviolet absorption maximum at 296 mμ, about 10–12 mμ higher than the parent 6-dehydro derivative.[5] During the study of the chloranil dehydrogenation it was observed that whereas the 7β-methyl compounds were dehydrogenated readily, the epimeric 7α-methyl derivatives reacted very slowly, if at all. The mechanism of the dehydrogenation of the Δ^4-3-keto steroids with *p*-quinones[6] appears to involve a hydride shift from C-7 of the Δ^4-3-ketones or their enols[4] to the quinone from the back side. The failure of the 7α-methyl compounds to undergo dehydrogenation is therefore not surprising because the hydrogen on C-7 is β (equatorial) and back side approach is hindered by the axial methyl group.

CHART I



In the presence of cuprous chloride, addition of methylmagnesium bromide to 6-dehydro-17α-methyltestosterone (Ia) gave, after chromatography, a broad melting product with an ultraviolet absorption maximum at 244 mμ. The crude product, which consisted mainly of 7α,17α-dimethyltestosterone and a small amount of the 7β-epimer, was not separated readily by chromatography on Florisil or by paper-chromatographic techniques. After treatment of the total material with chloranil, however, the minor component was dehydrogenated. Chromatography then readily afforded unchanged 7α,17α-dimethyltestosterone (IIa, λ_{max} 244 mμ) and a small amount of 6-dehydro-7,17α-dimethyltestosterone (IVa, λ_{max} 296 mμ).

The epimeric 7β-methyl compound IIIa could be regenerated by reduction of 6-dehydro-7,17α-dimethyltestosterone (IVa) with lithium in ammonia in the absence of alcohol. Metal–ammonia reduction of a $\Delta^{4,6}$-3-ketosteroid had been accomplished

(1) After this manuscript was submitted for publication three articles describing some 7β-methyl steroids appeared in print: (a) C. H. Robinson, O. Gnoj, W. Charney, M. L. Gilmore and E. P. Oliveto, THIS JOURNAL, **81**, 408 (1959); (b) C. H. Robinson, O. Gnoj and E. P. Oliveto, *J. Org. Chem.*, **24**, 121 (1959); and (c) J. A. Zderic, H. Carpio and H. J. Ringold, THIS JOURNAL, **81**, 432 (1959).

(2) See footnote 1a for references as well as (a) L. Ruzicka, M. W. Goldberg and J. Meyer, *Helv. Chim. Acta*, **18**, 994 (1935), and D. H. R. Barton, A. da S. Campos-Neves and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); (b) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *ibid.*, 4092 (1957), and succeeding papers; (c) E. R. H. Jones, E. D. Meakins and J. S Stephenson, *ibid.*, 2156 (1958); (d) J. C. Babcock, presented at the 129th Meeting of the American Chemical Society, Dallas, Tex., 1956.

(3) See M. S. Kharasch and O. Reinmuth, "Grignard Reactions," Prentice–Hall, Inc., New York, N. Y., 1954, p. 234, for discussion of 1,6-addition of Grignard reagents.

(4) E. J. Agnello and G. D. Laubach, THIS JOURNAL, **79**, 1257 (1957); Abstracts of 132nd Meeting of the American Chemical Society, Sept., 1957, p. 23-P.

(5) The rules as stated in Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd ed., 1949, Reinhold Publishing Corp., New York, N. Y., p. 192, predict an increment of 18 mμ for δ-substitution.

(6) L. Mandel, THIS JOURNAL, **78**, 3199 (1956).

earlier by Johnson, *et al.*,[7] who prepared 4,22-ergostadien-3-one by this method. Assignment of the thermodynamically more stable 7β (equatorial) configuration is based on analogy with the known steric course of reduction at the β-position of α,β-unsaturated steroids and on the general concepts developed by Barton and others.[8]

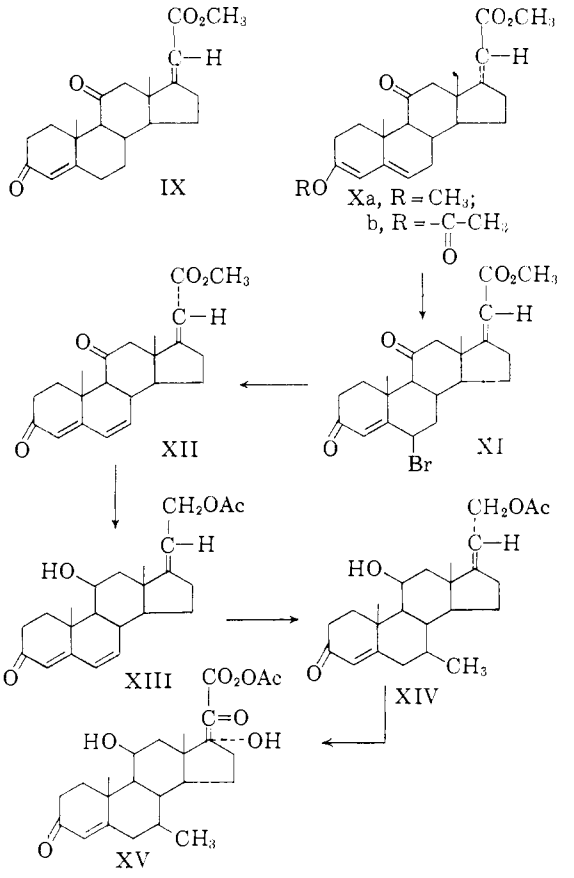
Additional evidence for the structure of the 7-methyl derivatives was obtained by an unequivocal synthesis. Thus, 3β,17β-dihydroxy-17α-methyl-5-androsten-7-one 3-acetate 17-trifluoroacetate (V), recently described by Marshall, *et al.*,[9] reacted with methyllithium to afford the 7-methylcarbinol VI[10] which was transparent to ultraviolet light. This product may have been a solvate or a mixture of epimers at C-7 since it resisted purification. Under conditions of the Oppenauer oxidation the unpurified material underwent oxidation and dehydration to produce 6-dehydro-7,17α-dimethyltestosterone (IVa) identical with that obtained previously.

When 6-dehydro-11β-hydroxy-17α-methyltestosterone (Ib), readily prepared by chloranil dehydrogenation of 11β-hydroxy-17α-methyltestosterone,[11] was treated with methylmagnesium bromide and chromatographed, a broad melting material with an ultraviolet absorption maximum at 244 mμ was obtained. Several recrystallizations from both acetone and methanol afforded pure 7β,17α-dimethyl-11β-hydroxytestosterone (IIIb). The 7α-methyl epimer could not be isolated by direct chromatography so the mixture was treated with chloranil, converting the 7β-methyl compound to the 6-dehydro derivative and leaving the 7α-methyl epimer unchanged. Chromatography through Florisil and crystallization then afforded 6-dehydro-11β-hydroxy-7,17α-dimethyltestosterone (IVb). 11β-Hydroxy-7α,17α-dimethyltestosterone (IIb) was obtained after further chromatography through a Darco column.

To prepare 7-methylprogesterone, methylmagnesium bromide was added to 20-hydroxy-4,6-pregnadien-3-one (from dehydrogenation of 20-hydroxy-4-pregnen-3-one[12]) as described above to produce the 7-methyl compound (λ_{max} 243 mμ). Oxidation of the 20-hydroxyl group with sodium dichromate in acetic acid afforded 7α-methylprogesterone (VII). In the same way 7α-methyltestosterone (VIII) was prepared from 6-dehydrotestosterone.[13]

To prepare 7β-methylhydrocortisone acetate (XV), methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate (IX)[14] was converted to its enol ether Xa with methyl orthoformate in methanol. The product crystallized from the reaction mixture in 85% yield. The enol ether Xa and the corresponding enol acetate Xb added the elements of hypobromous acid equally well using modifications of the Inhoffen procedures[15,16] to give the 6-bromo-Δ^4-3-ketone XI. The bromo compound was smoothly dehydrobrominated with collidine to give the corresponding 6-dehydro compound (XII, λ_{max} 284 mμ) which was formed in 64% yield from IX. It existed in two crystalline modifications, one melting at 170–173° and the other at 183–185°; a mixture of both forms melted at the higher temperature. On treatment with pyrrolidine it formed the 3,7-bis-pyrrolidinyl-3,5-diene[17] which was not isolated but was reduced directly with lithium aluminum hydride[14] to give, after hydrolysis and acetylation, the key intermediate, 11β,21-dihydroxy-4,6,17(20)-*cis*-pregnatrien-3-one 21-acetate (XIII).

CHART II



On treatment with methylmagnesium bromide and cuprous chloride followed by acetylation and chromatography, both XIII and its free alcohol gave 7β-methyl-Δ^4-3-ketone (XIV, λ_{max} 245 mμ) in 13–20% yield. Introduction of the cortical side chain was accomplished with either phenyl iodosoacetate and osmium tetroxide[18] or with N-methylmorpholine oxide peroxide and osmium tetroxide[19] to pro-

(7) F. Johnson, G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1302 (1954).

(8) D. H. R. Barton and C. H. Robinson, *ibid.*, 3045 (1954), and references cited therein.

(9) C. W. Marshall, R. E. Ray, I. Laos and B. Riegel, THIS JOURNAL, **79**, 6308 (1957).

(10) Compare with B. Bonn, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 1274 (1936).

(11) M. E. Herr, J. A. Hogg and R. H. Levin, THIS JOURNAL, **78**, 500 (1956).

(12) A. Butenandt and J. Schmidt, *Ber.*, **67**, 2092 (1934).

(13) A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

(14) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, THIS JOURNAL, **77**, 4436 (1955).

(15) H. H. Inhoffen, *Ber.*, **69**, 2141 (1936).

(16) H. H. Inhoffen, G. Stoeck, G. Kolling and U. Stoeck, *Ann.*, **568**, 52 (1950).

(17) J. L. Johnson, M. E. Herr, J. C. Babcock, R. P. Holysz, A. E. Fonken, J. E. Stafford and F. W. Heyl, THIS JOURNAL, **78**, 432 (1956).

(18) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(19) W. P. Schneider and A. R. Hanze, U. S. Patent 2,769,823 (Nov. 6, 1956); see also G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958).

duce 7β-methylhydrocortisone acetate. The infrared and ultraviolet absorption spectra were in accord with the proposed structure.

Assignments of configuration to the epimeric 7-methyl steroids were based on the ease of chloranil dehydrogenation of the 7β-methyl compounds, the formation of the equatorial 7β-methyl derivatives in the lithium–ammonia reduction and the characteristic differences in rotation and rotatory dispersion between the C_7-epimers and the corresponding compounds without the methyl group (see Table I and Fig. 1).

TABLE I

Name	[α]D (CHCl3) 7-H	7α-CH3	7β-CH3
17α-Methyltestosterone	+ 85	+ 90	+ 57
11β-Hydroxy-17α-methyltestosterone	+132	+131	+105
Testosterone	+109 (alc.)	+111 (109 alc.)	
Progesterone	+202	+197	
11β,21-Dihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-acetate	+151		+140
Hydrocortisone acetate	+147 (acetone)		+121 (acetone)

The rotatory dispersion curves for the 7α- and 7β-methyl derivatives described in this paper have the same general shape (see, for example, Fig. 1) as the corresponding compounds without the methyl group,[20] but are sufficiently displaced in relative magnitude above and below the parent curve to permit assignments of configuration.

Acknowledgment.—The authors gratefully acknowledge the services of J. L. Johnson and W. A. Struck and associates for the analyses, rotations, ultraviolet and infrared spectra.

Experimental[21]

6-Dehydro-17α-methyltestosterone (Ia).—A solution of 98 g. of methyltestosterone, 88 g. of chloranil and 1.7 l. of *t*-butyl alcohol was refluxed for 0.5 hour, then concentrated during an additional 0.5 hour under vacuum. The resulting residue was taken up in methylene chloride and, after filtering through 500 g. of Florisil, was washed with dilute sodium hydroxide and twice with water. Filtration through Celite was necessary to break emulsions during the sodium hydroxide wash. After removal of the solvent the residue was recrystallized from acetone to yield 51.5 g., m.p. 191–195°. A sample was prepared for analysis by recrystallization from acetone, m.p. 193–196°, $[\alpha]_D$ +35°, λ_{max}^{alc} 285 mμ, a_M 26,850.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.18; H, 9.50.

7α,17α-Dimethyltestosterone (IIa) and 6-Dehydro-7,17α-dimethyltestosterone (IVa).—To a solution of 100 ml. of commercial 3 *M* ethereal methylmagnesium bromide in 200 ml. of tetrahydrofuran, cooled in an ice-bath and stirred under nitrogen, was added 1.6 g. of cuprous chloride followed by 9.8 g. of 6-dehydromethyltestosterone (Ia) and a small amount of cuprous chloride in 130 ml. of tetrahydrofuran. After removal of the cooling bath, the mixture was stirred for 25 minutes and was poured into ether–ice–dilute hydrochloric acid saturated with sodium chloride. The ether phase was separated and washed with dilute hydrochloric acid saturated with sodium chloride, saturated sodium chloride, dilute sodium hydroxide saturated with sodium chloride and twice with saturated sodium chloride. Each aqueous phase was back extracted with ether. The extracts were combined, dried ($MgSO_4$), and the solvent removed. The residue was chromatographed through a column of Florisil. The 7α,17α- and 7β,17α-dimethyltestosterones were eluted together with 6–8% acetone in Skellysolve B. The combined fractions were triturated with ether to give 2.8 g., m.p. about 120–140°, λ_{max}^{alc} 243 mμ, a_M 15,300. This mixture of 7,17α-dimethyltestosterones (2.8 g.) was treated with chloranil (2.8 g.) in boiling *t*-butyl alcohol (80 ml.) for 1 hr. and 40 min. The usual work-up (see preparation of Ia above) gave a crude product with only a small amount of 290 mμ absorbing material. On chromatography through Florisil, 7α,17α-dimethyltestosterone (IIa) was eluted with 5% acetone in Skellysolve B. Two recrystallizations from acetone gave the pure product, m.p. 163–165°, $[\alpha]_D$ +90°, λ_{max}^{alc} 243 mμ, a_M 16,250.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.22; H, 9.91.

Later fractions from the column contained the 6-dehydro derivative IVa presumably arising from the β-epimer. It crystallized as a hydrate (intense band at 1640 $cm.^{-1}$) from aqueous ethanol (52 mg.). Several recrystallizations from aqueous ethanol gave m.p. 95–101°, $[\alpha]_D$ +96°, λ_{max}^{alc} 296.5 mμ, a_M 27,700.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.71; H, 9.96.

7β,17α-Dimethyltestosterone (IIIa).—To about 40 ml. of ammonia cooled in a Dry Ice–acetone-bath was added about 4 mg. of lithium followed by 0.3 g. of 6-dehydro-7,17α-dimethyltestosterone (IVa) in 10 ml. of tetrahydrofuran. An additional 32 mg. of lithium in small pieces was added over a period of about 15 minutes. The ammonia was allowed to evaporate and the solution then was concentrated under vacuum then diluted with water. The product, after extraction with ether, was chromatographed through a column of 75 g. of Florisil. 7β,17α-Dimethyltestosterone (IIIa), eluted with 6% acetone in Skellysolve B, was recrystallized from acetone–Skellysolve B to give 48 mg., m.p. 127–129°, $[\alpha]_D$ +57°, λ_{max}^{alc} 243 mμ, a_M 16,650.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.63; H, 9.89.

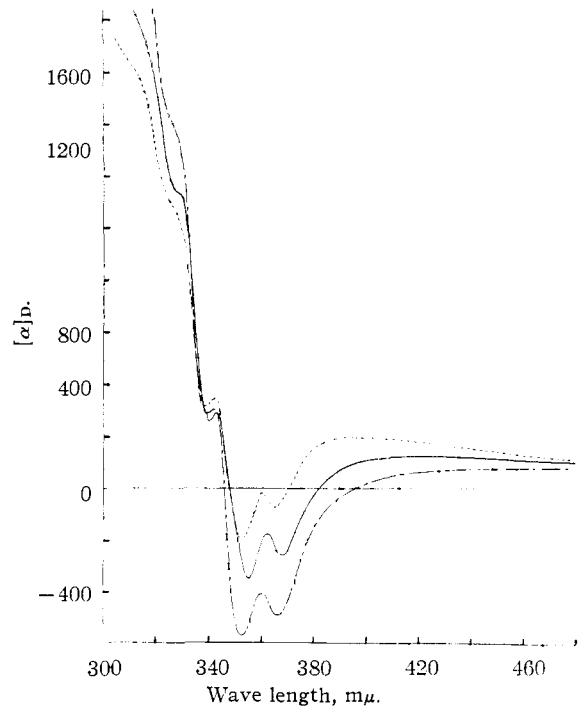


Fig. 1.—Optical rotatory dispersion curves (dioxane solution): ———, 17α-methyltestosterone; – – – –, 7α,17α-dimethyltestosterone (IIa); — — — — —, 7β,17α-dimethyltestosterone (IIIa).

(20) We are grateful to R. L. Houtman and W. A. Struck for permission to publish these results which are not in complete accord with similar structures briefly reported by C. Djerassi, O. Halpern, V. Halpern and R. Riniker, THIS JOURNAL, **80**, 4001 (1958).

(21) Melting points were determined on a Kofler block. The infrared spectra were determined as Nujol mulls, ultraviolet spectra in 95% ethanol and rotations in chloroform in 1-dcm. tubes at concentrations of 0.8–1.2 mg./ml. unless otherwise specified. The tetrahydrofuran used throughout was freshly distilled from lithium aluminum hydride. Skellysolve B is a commercial hexane fraction, b.p. 60–90°, made by the Skelly Oil Co.

7,17-Dimethyl-5-androstene-3β,7,17β-triol (VI).—To a solution of 10 g. of 17α-methyl-17β,3β-dihydroxy-5-androsten-7-one 3-acetate 17-trifluoroacetate (V, m.p. 139–142°, $[\alpha]_D$ −108°, λ_{max}^{alc} 235 mμ, a_M 13,150) described as an oil by Marshall, *et al.*,[17] and 500 ml. of ether was added, with slight cooling, a solution of about 5 equivalents methyllithium in 200 ml. of ether over a period of about 10 minutes. After 2 hours, 50 ml. of methanol was added. The solution was washed 3 times with water, concentrated to about 50 ml., and diluted with 25 ml. of water. The precipitate was collected, washed with fresh ether, and dried to yield 6.3 g. This product was not nicely crystalline, and attempts to purify it failed.

One gram was acetylated with pyridine–acetic anhydride, chromatographed through Florisil and crystallized from acetone–Skellysolve B to give the 3-acetate, m.p. 164–173°, $[\alpha]_D$ −83°, which, however, was still not nicely crystalline.

Anal. Calcd. for $C_{24}H_{40}O_4$: C, 73.36; H, 9.64. Found: C, 73.55; H, 9.76.

6-Dehydro-7,17α-dimethyltestosterone from VI.—A solution of 5 g. of the methylcarbinol VI, 50 ml. of cyclohexanone and 300 ml. of toluene was boiled to remove all traces of water and 5 g. of aluminum *t*-butoxide was added. After refluxing for 3 hours the solution was concentrated to about 175 ml., washed with dilute sodium hydroxide and water, dried, and filtered. The filtrate was chromatographed through Florisil. The product (2.7 g.), which was eluted as an oil with 8% acetone in Skellysolve B, was crystallized by trituration with wet ether. Recrystallization from aqueous ethanol gave IVa, m.p. 91–102°, identical in all respects to the product described previously.

6-Dehydro-11β-hydroxy-17α-methyltestosterone (Ib).—A solution of 5.0 g. of 11β-hydroxy-17α-methyltestosterone and 4.0 g. of recrystallized chloranil in 300 ml. of *t*-butyl alcohol was stirred and heated at reflux for 1 hour. The mixture was concentrated on a rotary evaporator near room temperature, and was diluted with methylene chloride, shaken with dilute sodium hydroxide, and filtered through a bed of Celite (to break the emulsion and remove a greenish-brown sludge). The filtrate was separated and the methylene chloride layer was washed with water and concentrated to about 25 ml. to crystallize. The product was collected and washed with ether to yield 3.5 g., m.p. 254–257°, $[\alpha]_D$ +148°, λ_{max}^{alc} 284 mμ, a_M 25,800.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.97; H, 9.13.

7α- and 7β,17α-Dimethyl-11β-hydroxytestosterone (IIb, IIIb) and 6-Dihydro-7,17-dimethyl-11β-hydroxytestosterone (IVb).—To a solution prepared by the addition of 1.6 g. of cuprous chloride in 100 ml. of ethanol, 3 *M* methylmagnesium bromide and 240 ml. of tetrahydrofuran was added a solution of 8.0 g. of 6-dehydro-11β-hydroxymethyltestosterone (Ib) and 0.8 g. of cuprous chloride (not completely dissolved) in 300 ml. of tetrahydrofuran under nitrogen and with stirring and cooling in an ice–salt-bath. After 15 minutes the reaction mixture was poured into dilute hydrochloric acid–ice–ether saturated with sodium chloride. The ether phase was washed with brine, dilute sodium hydroxide saturated with salt, and again with brine, dried over magnesium sulfate, filtered, and concentrated to dryness. The residue was dissolved in methylene chloride and poured on a 250-g. Florisil chromatographic column. The column was washed with increasing amounts of acetone in methylene chloride. Fractions eluted with 4–10% acetone in methylene chloride were combined and triturated with acetone–Skellysolve B to give 3.2 g., m.p. 218–224°, $[\alpha]_D$ +102°, λ_{max}^{alc} 243 mμ, a_M 15,175. This product, although it shows only one spot by papergram analysis, is still a mixture of the 7α- and 7β-methyl epimers.

The β-isomer IIIb was obtained by repeated recrystallizations from acetone and methanol, yielding 200 mg., m.p. 242–246°, $[\alpha]_D$ +105°, λ_{max}^{alc} 244 mμ, a_M 15,175.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.59; H, 10.04.

This compound was the 7β-methyl derivative since on treatment with chloranil in boiling *t*-butyl alcohol it was converted completely to the Δ^6-compound (IVb, λ_{max}^{alc} 296 mμ).

To obtain the 7α-isomer Vb 1.0 g. of the crude mixture of epimers and 1.0 g. of recrystallized chloranil was boiled in 80 ml. of *t*-butyl alcohol under nitrogen for 2.5 hours. Aliquots taken during the reaction showed that after about 1 hour the relative intensities at 245 and 290 mμ did not change. The *t*-butyl alcohol was removed under a stream of nitrogen and the residue was taken up in methylene chloride, shaken with dilute sodium hydroxide, and filtered through a bed of Celite. The methylene chloride phase was washed with water, dried, concentrated, and chromatographed through Florisil.

The first crystalline fractions, eluted with 7% acetone in methylene chloride, contained both 245 mμ and 296 mμ absorbing materials. These fractions were combined and rechromatographed through a 1:1 mixture of activated carbon (Darco) and Celite. Those fractions (eluted with 1:1 methanol–acetone) which were free from 296 mμ absorbing material were recrystallized from acetone to give 60 mg. of IIIb, m.p. 227–229° (with presoftening), $[\alpha]_D$ +131°, λ_{max}^{alc} 243 mμ, a_M 15,825.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.65; H, 9.96.

The later fractions were free of 245 mμ absorbing material and gave, after recrystallization from acetone, 100 mg. of IVb, m.p. 242–244° dec., $[\alpha]_D$ +310°, λ_{max}^{alc} 296 mμ, a_M 23,250.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.49; H, 9.53.

7α-Methyltestosterone (VIII).—To a solution of 100 ml. of ethereal 3 *M* methylmagnesium bromide and 200 ml. of tetrahydrofuran was added 1.6 g. of cuprous chloride and 10 g. of 6-dehydrotestosterone in 200 ml. of tetrahydrofuran with cooling in an ice-bath and vigorous stirring. The cooling bath was removed and, after an additional 0.5 hour, the mixture was poured into a mixture of ether–dilute hydrochloric acid saturated with salt. The ether phase, after washing with dilute sodium hydroxide saturated with salt and twice with brine, was dried ($MgSO_4$) and concentrated to dryness. The residue was recrystallized three times from acetone to give 1.4 g., m.p. 211–214°, $[\alpha]_D$ +111°, λ_{max}^{alc} 242 mμ, a_M 16,050.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.62; H, 10.00. Found: C, 79.37; H, 10.03.

7α-Methylprogesterone (VII).—A solution of 12 g. of 20-hydroxy-4-pregnen-3-one[12] (a mixture of epimers at C-20) and 10 g. of chloranil in 500 ml. of acetone was stirred under nitrogen and heated at reflux for 4.5 hours. The solvent was removed under vacuum and the residue was dissolved in methylene chloride and washed as described for other chloranil dehydrogenations. Removal of the methylene chloride and trituration with ether gave 7.0 g. of 20-hydroxy-4,6-pregnadien-3-one (also a mixture of epimers at C-20), λ_{max}^{alc} 287 mμ. Without further purification this product was dissolved in 200 ml. of tetrahydrofuran and added to a stirred solution of 100 ml. of 3 *M* ethereal methylmagnesium bromide and 1.6 g. of cuprous chloride in 200 ml. of tetrahydrofuran while cooling in an ice-bath. The cooling bath was removed and after 25 minutes the reaction mixture was worked up as described for the previous runs. The crude product (λ_{max} 244 mμ) was oxidized with 7 g. of sodium dichromate in 50 ml. of acetic acid for 5 hours. The product was isolated with ether and chromatographed through a column of 200 g. of Florisil. 7α-Methylprogesterone was eluted with 6–7% acetone in Skellysolve B. Two recrystallizations from acetone–Skellysolve B gave 0.45 g., m.p. 191–199°, $[\alpha]_D$ +197°, λ_{max}^{alc} 242 mμ, a_M 16,900.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.08; H, 9.81.

Methyl 3-Methoxy-11-keto-3,5,17(20)-*cis*-pregnatrien-21-oate (Xa).—To a slurry of 54 g. of finely ground methyl 3,11-diketo-4,17(20)-*cis*-pregnadien-21-oate (IX),[14] 325 ml. of absolute methanol and 75 ml. of methyl orthoformate was added with stirring 30 drops of concentrated sulfuric acid. The enol ether began to precipitate before all the starting material dissolved. The mixture was stirred at room temperature for about 30 minutes. It then was cooled for 2–3 hours and the precipitate of enol ether collected and washed well with cold methanol, yield 48.3 g. (86%), m.p. 179–183°, λ_{max}^{alc} 235 mμ, a_M 27,075. Recrystallization from ethyl acetate did not raise the m.p.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.62; H, 8.06.

Methyl 3-Acetoxy-11-keto-3,5,17(20)-*cis*-pregnatrien-21-oate (Xb).—A solution of 7.2 g. of methyl 3,11-diketo-4,17-(20)-*cis*-pregnadien-21-oate (IX), 200 mg. of *p*-toluenesulfonic acid and 50 ml. of acetic anhydride was heated under reflux for 4 hours with nitrogen bubbling through the reaction mixture. The solvent was removed under vacuum, and the residue triturated with ethyl acetate. The insoluble material was recrystallized from ethyl acetate with a Darco treatment to give 2.2 g. of the enol acetate, m.p. 150–170° (mostly 150–155°), λ_{max}^{alc} 238 mμ, a_M 28,850.

Methyl 3,11-Diketo-4,6,17(20)-*cis*-pregnatrien-21-oate (XII). a. **From the Enol Ether (Xa).**—To a solution of 30 g. of the enol ether in 1700 ml. of acetone was added a solution of 36.0 g. of sodium acetate trihydrate, 33 ml. of acetic acid, 33 g. of N-bromoacetamide in 300 ml. of water slowly with stirring and with sufficient cooling to keep the temperature below 23°. After stirring 1.5 hours the reaction mixture was concentrated at 22–25° under vacuum to half the original volume, and was diluted with water and extracted with ether. The ether extract was washed with sodium carbonate and water, dried ($MgSO_4$), filtered and concentrated to dryness.

Anal. Calcd. for $C_{22}H_{27}BrO_4$: Br, 18.5. Found: Br, 21.5.

Without purification the 6-bromo compound XI was dissolved in 250 ml. of collidine and refluxed under a slow stream of nitrogen for 45 minutes. The mixture was cooled and the collidine hydrobromide separated by filtration. The filtrate was made slightly acidic with 6 *N* hydrochloric acid and extracted with methylene chloride. The extract was washed with dilute hydrochloric acid, water, dilute sodium hydroxide and again with water until the washings were neutral, dried over magnesium sulfate, and filtered through a bed of Florisil to remove a considerable amount of black material. The filtrate was concentrated to dryness and the dark residue was triturated with ether. The insoluble material was recrystallized from methanol to give 13.6 g., m.p. 180–182°, of the desired compound. The liquors were combined, concentrated to dryness, and chromatographed through 200 g. of Florisil. The desired product, 8.0 g., was eluted with 9 to 13% acetone in Skellysolve B. This material was combined with the 13.6 g. of product which was obtained by direct crystallization and recrystallized from acetone–ether (Darco), yield 15.5 g., m.p. 170–173°. A second crop, 3.75 g., m.p. 169–172°, was obtained after two Darco treatments. The yield from IX was 64%. An analytical sample was obtained by recrystallization from acetone, m.p. 183–185° (there are two crystal forms of this compound, one melting at 170–174° and the other at 183–185°), $[\alpha]_D$ +228° (acetone), λ_{max}^{alc} 224 and 282 mμ, a_M 12,650 and 26,500.

Anal. Calcd. for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.53; H, 7.12.

b. **From the Enol Acetate Xb.**—To a solution of 2.1 g. of the enol acetate in 230 ml. of acetone was added dropwise with cooling in a cold water-bath a solution of 2.2 g. of N-bromoacetamide, 2.0 g. of sodium acetate trihydrate and 2.2 ml. of acetic acid in 40 ml. of water. The water-bath was removed and, after 3 hours, the solution was concentrated to dryness under vacuum below room temperature. The product was dissolved in ether and washed as described in part a. The crude product XI, showed m.p. 133–140°, λ_{max}^{alc} 232 mμ, a_M 20,300. The infrared spectrum was identical with that of the bromo compound described in part a.

Anal. Calcd. for $C_{22}H_{27}O_4Br$: Br, 18.5. Found: Br, 18.91.

Without further purification it was heated in 25 ml. of collidine at reflux for 45 minutes. The product XII was isolated as in part a, and recrystallized from acetone–ether; yield, 1st crop, 0.8 g., m.p. 182–184°; 2nd crop, 0.1 g., m.p. 180–183°.

11β,21-Dihydroxy-4,6,17(20)-*cis*-pregnatrien-3-one 21-Acetate (XIII).—A solution of 19.0 g. of the $\Delta^{4,6}$-3-ketone XII, 50 mg. of *p*-toluenesulfonic acid, 69 ml. of methylene chloride and 19 ml. of pyrrolidine was allowed to stand at room temperature under nitrogen for 40 minutes. The solvent was removed under vacuum, and the residue was slurried with a small amount of methanol and the methanol removed under vacuum. A small amount of ether was added to disperse the ball of gummy product and removed under vacuum and the residue was dried under high vacuum for about 3 hours. The crude enamine (λ_{max}^{alc} 324 mμ, λ_{max}^{ether} 284 mμ) was dissolved in about 1 l. of dry ether and 9 g. of lithium aluminum hydride was added. The solution was stirred for 75 minutes and 60 ml. of ethyl acetate was added slowly, followed by 60 ml. of water. Heat was evolved and the solution boiled. The vapor was allowed to escape. To the concentrate was added 400 ml. of methanol and 50 ml. of 10% sodium hydroxide. The solution was kept at 40° for about 15 minutes then 25 ml. of acetic acid was added. After about 1 hour the solution was made acidic with dilute hydrochloric acid and extracted well with methylene chloride. The combined extracts were washed with dilute sodium hydroxide and water, dried over magnesium sulfate, filtered and concentrated to dryness (14.1 g.). It was dissolved in 20 ml. of pyridine and 15 ml. of acetic anhydride and heated at 40° for 4 hours. The solution was cooled and diluted slowly with water. The precipitate was collected, washed well with water, dried (10.4 g.), and crystallized from acetone to give 7.1 g. of XIII, m.p. 177–181°. An analytical sample had m.p. 180–182°, $[\alpha]_D$ +105° (acetone), λ_{max}^{alc} 286 mμ, a_M 26,350.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.58; H, 8.16. Found: C, 74.88; H, 8.22.

11β,21-Dihydroxy-4,6,17(20)-*cis*-pregnatrien-3-one.—A solution of 3.0 g. of 11β,21-dihydroxy-4,6,17(20)-*cis*-pregnatrien-3-one 21-acetate (XIII) in 90 ml. of 5% potassium carbonate in 80% methanol was heated under reflux for 2 hours with nitrogen bubbling through. About half of the solvent was removed under vacuum. The concentrate was diluted with water and extracted with methylene chloride. The extracts were washed with water, dried ($MgSO_4$), filtered and concentrated at atmospheric pressure until crystals began to form. The product, 2.75 g., m.p. 88–90° (with bubbling), λ_{max}^{alc} 286 mμ, a_M 23,400, was solvated with methylene chloride. Drying at temperatures high enough to remove the methylene chloride caused it to decompose.

Anal. Calcd. for $C_{21}H_{28}O_3 \cdot CH_2Cl_2$: C, 63.92; H, 7.31; Cl, 17.15. Found: C, 64.71; H, 7.55; Cl, 16.20.

7β-Methyl-11β,21-dihydroxy-4,17(20)-*cis*-pregnadien-3-one 21-Acetate (XIV).—To a stirred slurry of 1.8 g. of cuprous chloride and 300 ml. of tetrahydrofuran was added with cooling 100 ml. of ethereal 4 *M* methylmagnesium bromide. To this mixture was added with cooling and stirring 0.9 g. of cuprous chloride and 8.7 g. of 11β,21-dihydroxy-4,6,17(20)-*cis*-pregnatrien-3-one 21-acetate (XIII) in 300 ml. of tetrahydrofuran. The thick dark gray reaction mixture was stirred for 4 hours at room temperature and was poured into ice–dilute hydrochloric acid mixture saturated with sodium chloride and extracted with ether. The extracts were washed with dilute hydrochloric acid, dilute sodium hydroxide and water, all saturated with sodium chloride, and dried. The solvent was removed and the residue was acetylated in 15 ml. of pyridine and 10 ml. of acetic anhydride. After standing overnight the excess acetic anhydride was decomposed with a small piece of ice. The mixture was diluted with water and extracted with methylene chloride. The methylene chloride extracts were washed with dilute hydrochloric acid, dilute sodium hydroxide and water, and dried. The solvent was removed and the residue was chromatographed through 150 g. of Florisil. After developing the column with 2, 4 and 6% acetone in Skellysolve B the desired 7-methyl compound (2.7 g., XIV) was eluted with 10% acetone in Skellysolve B. Trituration with ether gave 1.9 g., m.p. 161–170°, $[\alpha]_D$ +140°, λ_{max}^{alc} 244 mμ, a_M 15,825, of XIV

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.51; H, 8.64.

7β-Methylhydrocortisone Acetate (XV).—To a solution of 1.0 g. of XIV in 50 ml. of *t*-butyl alcohol, 3.5 ml. of pyridine and 0.8 ml. of water cooled to about 10° was added 2.5 g. of phenyl iodosodiacetate and 0.011 g. of osmium tetroxide. The reaction mixture was stirred at 6° for 24 hours and 10 ml. of cold water saturated with sulfur dioxide was added. After 10 minutes the solution was refluxed for 20 minutes, diluted with Skellysolve B and washed several times with brine. The solvent was removed and the residue was chromatographed through Florisil and recrystallized

from acetone to give 7β-methylhydrocortisone acetate, m.p. 193–196°. An analytical sample had m.p. 198–200°, $[\alpha]D$ +121° (acetone), λ_{max}^{ale} 245 mμ, a_M 16,425.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.05; H, 8.30.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

The Relative Stabilities of *cis* and *trans* Isomers. V. The Bicyclo[5.2.0]nonanes. An Extension of the Conformational Rule[1,2]

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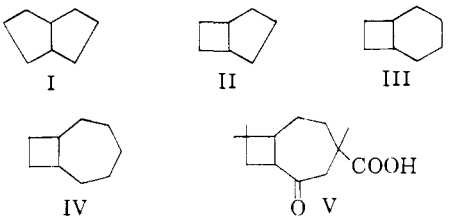
Pure *cis*- and *trans*-bicyclo[5.2.0]nonane have been prepared by unequivocal methods. The equilibrium between the isomers could not be established by heating with palladium catalyst, apparently because of the ease of rupture of the four-membered ring under these conditions. Application of the conformational rule led to the conclusion that the heat contents of the isomers are similar, that of the *trans* isomer probably being somewhat lower.

Introduction

Fused ring systems of the decalin and hydrindane types have been examined with respect to the relative stabilities of *cis* and *trans* ring junctures in considerable detail while systems containing larger rings, although well known in other respects, have not been studied previously in this regard.

It seems clear that a simple decalin system is more stable[3] in the *trans* form and this case is well understood in terms of conformational analysis.[4] The available evidence indicates that in the hydrindane system the heat contents are more nearly equal than in the decalins, and for some substituted hydrindanes the *cis* isomer is more stable.[4] The six-membered ring in hydrindane would have a lower energy if the attached groups were equatorial, but in opposition to this effect, a five-membered ring tends to be more nearly planar than does a six.[5] Since it is energetically more economical to decrease a dihedral angle between an axial and an equatorial bond in a six-membered ring than between two equatorial bonds,[6] this strain energy is greater in the *trans*-hydrindane than in the *cis* and just about cancels the tendency for the six-membered ring to prefer equatorial substituents.

When two five-membered rings are fused together (I), the *cis* isomer appears to be of lower free energy,[7] and the four-membered ring must be even more nearly planar than the five.[8] When a second ring is fused to a cyclobutane ring in the 1,2-position, it is clear that if the second ring is sufficiently small the *cis* isomer will be of lower heat content, while if the second ring is sufficiently large, the *trans* isomer will be so favored. Since I appears to be more stable in the *cis* form, it appears certain that the same will be true for II. In going up the homologous series of compounds II, III, IV and so on, it cannot be unambiguously predicted where the crossover point will be. As



soon as the second ring contains seven atoms (IV) the 1,2-*trans*-(di-pseudoequatorial) positions in this ring are on the average closer together than the corresponding *cis* positions, and therefore it might be predicted that the *trans* isomer of IV will have the more negative heat content. It probably also will have the more negative entropy,[4a,9] and a prediction as to the relative free energies would seem hazardous. Barton and his co-workers[10] have, however, made a tentative assignment of *cis* and *trans* ring junctures of V on the basis of stability. The bicyclo[5.2.0]nonane ring system (IV) appears to have been found in nature only when part of a larger ring system such as the lumicolchicines.[11]

Discussion

The system chosen for study in the present work was the parent hydrocarbon IV. The introduction of a carbonyl adjacent to the ring juncture would have facilitated isomerization, but would also have

(1) Paper IV, THIS JOURNAL, **81**, 232 (1959).

(2) This work was supported by a Frederick Gardner Cottrell grant from The Research Corporation.

(3) Throughout this paper the expression "stable" refers exclusively to free energy, and not to enthalpy.

(4) For a summary of the evidence and references, see (a) N. L. Allinger, *J. Org. Chem.*, **21**, 915 (1956); (b) W. G. Dauben and K. S. Pitzer, in "Steric Effects in Organic Chemistry," Ed. M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 3.

(5) (a) C. G. LeFèvre and R. J. W. LeFèvre, *Rev. of Pure and Applied Chem.*, **5**, 303 (1955); (b) E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955).

(6) Reference 4b, p. 37.

(7) (a) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436 (1935); (b) L. N. Owen and A. G. Peto, *ibid.*, 2383 (1955).

(8) G. W. Rathjens, Jr., N. Freeman, W. D. Gwinn and K. S. Pitzer, THIS JOURNAL, **75**, 5634 (1953).

(9) This is more likely true in this case than with the decalins. The decalin case was discussed previously (ref. 4a), and subsequently the *cis* isomer was found to have the more positive entropy (T. Miyazawa and K. S. Pitzer, THIS JOURNAL, **80**, 60 (1958), and J. Coke, unpublished results), contrary to earlier work (G. S. Parks and J. A. Hatton, *ibid.*, **71**, 2773 (1949)). With the bicyclo[5.2.0]nonanes the excess entropy of the *cis* form should be due to a greater flexibility, while both of the decalins are now known to be rather rigid, and the entropy difference is due mainly to a difference in symmetry. It has been shown (H. G. Derx, *Rec. trav. chim.*, **41**, 312 (1922)) that the *cis*-cycloheptane-1,2-diol forms a more stable boric acid complex than does the *trans* isomer, but the difference seems small, and the extension to the present case seems uncertain.

(10) D. H. R. Barton, T. Bruun and A. S. Lindsey, *J. Chem. Soc.*, 2210 (1952).

(11) P. D. Gardner, R. L. Brandon and G. R. Haynes, THIS JOURNAL, **79**, 6334 (1957), and references cited.