Treatment of I in cold chloroform with gaseous hydrogen sulfide and hydrogen chloride gave a mixture of two bases which could be separated by repeated extraction with boiling methanol. The methanol-insoluble fraction, on recrystallization from acetone, gave colorless crystals which did not melt below 300°. The method of preparation and the elemental analysis, the latter in excellent agreement with the formula $[C_{18}H_{21}NO_3S]_n$, suggest that II is the expected thioketone corresponding to I; it is undoubtedly present in the usual polymerized form.[3] While a few examples of dimeric thioketones are known,[4] trimer formation is the rule, so that n in the formula is assumed to be 3. The insolubility of the compound prevented experimental investigation of its molecular weight.

The second compound, present in the methanol-soluble fraction of the crude reaction product, was obtained pure by recrystallization from boiling methanol. It forms colorless leaflets melting at 231–233° to a pink liquid. The substance contains N and S in the ratio 2:1; it is thus undoubtedly sulfide III. Formation of compounds of this type (*e.g.*, IVa and b) has been studied by Campaigne and co-workers.[5] Elemental analysis of III is in satisfactory agreement with this formulation; while it does not with certainty exclude the possibility that III might be a sulfoxide rather than a sulfide, such an interpretation is unlikely because of the absence from the infrared spectrum of III of the characteristic intense sulfoxide band[6] at 1040 cm.$^{-1}$. Possibilities of acid-catalyzed O-demethylation or cleavage of the oxygen bridge, likewise not precluded by the elemental analysis, may be dismissed because of the lack of phenolic properties.

Pharmacological tests (hot plate method in mice)[7] indicate that III has a relatively weak analgesic action, significantly less than that of codeine. Compound II, on the other hand, is about comparable to codeine, with a similar time of onset but later peaking of effect and much longer duration of action. The prolonged action of II, if confirmed in man, might be of significance in the treatment of chronic pain. The comparative data are given in Table I.

TABLE I

ANALGESIC ACTIVITIES

	ED_{50}, mg./kg., s.c.	Onset, min.	Peak, min.	Duration, min.
Codeine	14.2	7.0	18	67
III	90.2	13.0	60	171
II	10.2	9.2	55	257
Morphine	2.1	13.0	34	129

Experimental

Microanalyses are by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Reaction of 14-Hydroxydihydrocodeinone with Hydrogen Sulfide and Hydrogen Chloride.—A solution of 9.1 g. of I in 400 ml. of chloroform was cooled to −10° and saturated with gaseous hydrogen chloride for about 30 min. Regardless of the formation of a white precipitate of the hydrochloride of I, streams of hydrogen chloride and hydrogen sulfide were passed simultaneously through the liquid for about 6 hr., while the temperature of the liquid was kept at about 0°. Excess hydrogen chloride and hydrogen sulfide were next removed by a stream of nitrogen, and the reaction mixture was extracted repeatedly with water. Addition of ammonia to the combined aqueous extracts precipitated a white amorphous mixture of bases. Extraction with chloroform yielded a greenish solution, part of the solid remaining undissolved. Evaporation of the filtered chloroform extracts *in vacuo* gave 7.0 g. of a white residue, which was boiled out repeatedly with methanol. The extracts were combined with the methanol solution of the original chloroform-insoluble solid, concentrated *in vacuo* to a small volume, and allowed to crystallize, yielding 1 g. of crude III. The methanol-insoluble portion of the crude bases, recrystallized from acetone, gave 6.4 g. of crude II.

Repeated recrystallization of the crude II from acetone or benzene gave the pure compound as colorless crystals which did not melt below 300° and decomposed on further heating.

Anal. Calcd. for $C_{18}H_{21}NO_3S$: N, 4.23; S, 9.68. Found: N, 4.14; S, 9.73; ratio N:S, 0.98.

Compound III, purified by several recrystallizations from boiling methanol, melted at 231–233° to a pink liquid. The product is insoluble in aqueous alkali and does not give any color with ferric chloride.

Anal. Calcd. for $C_{36}H_{36}N_2O_6S$: C, 68.76; H, 6.41; N, 4.46; O, 15.27; S, 5.09; mol. wt., 628.76. Found: C, 68.51; H, 6.00; N, 3.93; O, 16.3 (direct determination); S, 4.75; mol. wt. (Rast), 566; ratio N:S, 1.89.

Work on these compounds had to be terminated for external reasons before a detailed study of the most suitable procedures for their preparation and isolation had been carried out.

Acknowledgment.—The authors are much indebted to Dr. N. B. Eddy for permission to quote his findings on the pharmacologic action of the compounds.

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4,4,6,16α-Tetramethyl-5-androstenes[1]

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Received May 20, 1963

Utilization of methyl iodide–potassium *t*-butoxide–*t*-butyl alcohol system for the conversion of Δ^4-3-keto steroids into 4,4-dimethyl-Δ^5-3-ketones[2] has been demonstrated, and recently Ringold and Malhotra[3] revealed the mechanism of such reaction.

Substitution at position 6 as well as 16 of steroids often results in significant enhancement of biological activities. It is, therefore, of considerable interest to investigate the effects of such substitutions of the 4,4-dimethyl-Δ^5-steroids.

Selective 4,4-dimethylation was carried out by promoting conjugated anion formation under Ringold

(1) GMI Journal Series Number 340.

(2) (a) G. Cooley, B. Ellis, and V. Petrow, *J. Chem. Soc.*, 2998 (1955); (b) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *ibid.*, 4490 (1956); (c) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, 602 (1957); (d) F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.*, **79**, 2906 (1957); (e) A. Bowers and H. J. Ringold, *ibid.*, **81**, 424 (1959); (f) N. W. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, L. N. Nysted, and P. B. Sollman, *J. Org. Chem.*, **26**, 3077 (1961); N. W. Atwater, *J. Am. Chem. Soc.*, **82**, 2847 (1960).

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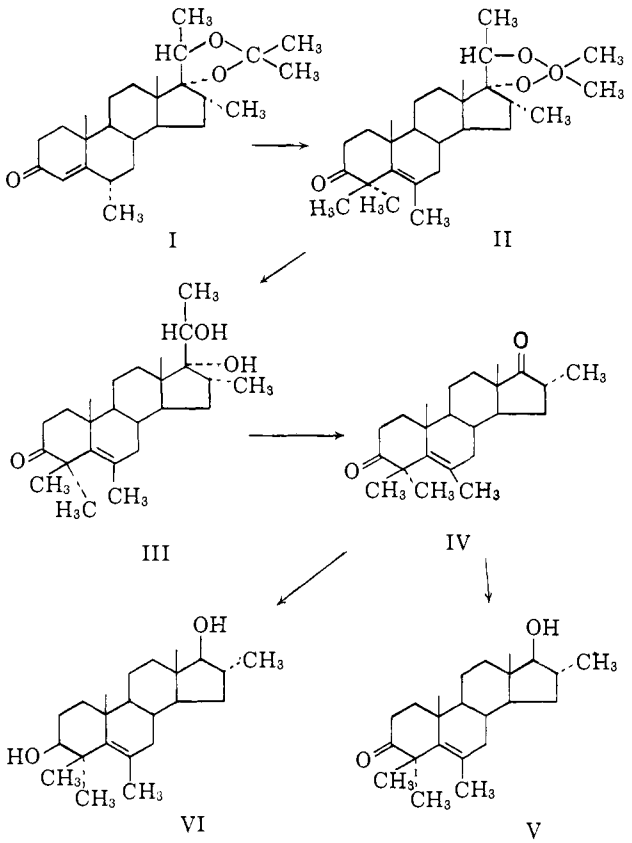

conditions.[3] Thus, 17α,20β-isopropylidenedioxy-6α,-16α-dimethyl-4-pregnene-3-one[4] (I) was converted to the 4,4-dimethyl derivative II which was treated subsequently with aqueous acetic acid to give the 17α,20β-diol derivative III. Periodic acid treatment[5] of III yielded the corresponding 3,17-dione IV. Selective reduction with sodium borohydride converted IV to 4,4,6,16α-tetramethyl-5-androsten-17β-ol-3-one (V), whereas lithium aluminum hydride gave the 3β,17β-diol VI.

Mass spectroscopy studies carried out in these laboratories on compounds II, III, IV, V, and VI support the specific structure herein presented.

It is possible that oxidation of III may result in equilibration at C-16 to give substantial amounts of the 16β-epimer.[2f,6,7] On reduction with hydride the 16α-epimer might also be expected to give two products,[2f,6,7] due to an attack from the top as well as the now more hindered underside of the molecule (by virtue of the 16α-substituent). The assumption that no inversion occurred at C-16 was based on infrared and n.m.r. studies. The infrared absorption study on 16α-fluoro-4-androstene-3,17-dione[8,9] and 16β-fluoro-4-androstene-3,17-dione[9] showed distinct differences in the characteristic vibrations of ring-breathing frequency.[10] The 16β-fluoro-17-ketone system showed peaks at 977 cm.$^{-1}$ (a strong peak) and at 742 cm.$^{-1}$ (a weaker peak), whereas the 16α-fluoro epimer was lacking these peaks. The similar relationships have been observed between 16α-methyl-5-androstene-3β-ol-17-one 3-acetate[11] and 16β-methyl-5-androstene-3β-ol-17-one 3-acetate.[11] The 16α-methyl-17-ketone system showed very weak peaks at 977 cm.$^{-1}$ and 742 cm.$^{-1}$, while 16β-methyl-17-ketone showed a strong peak at 977 cm.$^{-1}$ and medium absorption at 742 cm.$^{-1}$. The infrared absorption spectra of compounds IV, V, and VI showed a very weak or no peak at 977 cm.$^{-1}$. The n.m.r. studies on C-16, β-H, and C-16, α-H, have been described by Lavie, *et al.*[12] Similar observations were obtained on IV, V, and VI. For example, in IV, the C-16,β proton couples its spin with the C-15,β and C-15,α protons, giving the coupling constant values of 7.7 c.p.s. and 2.6 c.p.s., respectively.

In both compounds V and VI, androgenic properties[13] (ventral prostrate) were of a low order at both 0.14 mg. and 1.4 mg. total dose levels, being about 10% of that of testosterone and similar to the control, while the seminal vesicles weight increase was only about 1.4 times the control and almost no changes of levator ani weight were observed.

Experimental[14]

17α,20β-Isopropylidenedioxy-4,4,6,16α-tetramethyl-5-pregnene-3-one (II).—17α,20β-Isopropylidenedioxy-6α,16α-dimethyl-4-pregnene-3-one (I), m.p. 167–169° (from aqueous acetone); $[\alpha]^{26}D$ −5.7° (*c* 1, $CHCl_3$), λ_{max}^{EtOH} 242 mμ (ε 16,750), λ^{KBr} 5.98, 6.21, 7.90, 8.00, 8.12, 8.26, 8.36, 8.52, 9.11, 9.25, 9.46, 9.61, 9.70, 9.92, and 11.52 μ, was used as the parent diol for preparation of II.

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07. Found: C, 78.14; H, 10.09.

I (12 g.) was dissolved at room temperature in 360 ml. of *tert*-butyl alcohol containing 7 g. of potassium metal and the mixture was stirred for 5 hr. under nitrogen atmosphere. Methyl iodide (30 ml.) was added and the mixture stirred for 10 min. at room temperature and then left standing for 16 hr. under a nitrogen atmosphere at room temperature. After dilution with about 300 ml. of water, excess methyl iodide and some *tert*-butyl alcohol were removed by rotary evaporation (10–12 mm.) for 30 min. The mixture was then diluted further with water and extracted with ether. The etheral solution was washed with water, dried, and concentrated to give 12.31 g. (95%) of II, m.p. 144–155°, λ^{KBr} 2.87, 5.85, 6.88, and 7.22 μ. The mass spectrum[15] showed a strong parent peak corresponding to a molecular weight of 428, and exhibited no distinct absorption in the ultraviolet. Purification by silica gel column chromatography (elutions with 5% ethyl acetate in benzene) gave material with m.p. 187–190°. Recrystallization from hexane–acetone gave an analytical sample of m.p. 190–191°, $[\alpha]^{29}D$ −78.8° (*c* 1, $CHCl_3$), λ^{KBr} 5.86, 6.82, 6.91, 7.26, 7.87, 8.25, 9.12, 9.25, 9.66, 9.92, and 11.52 μ. II did not exhibit any distinct absorption in the ultraviolet.

Anal. Calcd. for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.22; H, 10.32.

4,4,6,16α-Tetramethyl-5-pregnene-17α,20β-diol-3-one (III).—17α,20β-Isopropylidenedioxy-4,4,6,16α-tetramethyl-5-pregnene-3-one (II) (10 g.) was suspended in 350 ml. of acetic acid and 200 ml. of water and the mixture refluxed for 3 hr. During this period, most of the steroid dissolved. Dilution with water gave

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a crystalline material which was filtered, washed well with water, and dried to give III (8.56 g., 94%), m.p. 98–107°. Chromatography on silica gel and recrystallization from methanol gave an analytical sample having m.p. 142–143°, λ^{KBr} 2.85, 5.88, 6.85, 7.22, 9.00, 9.75, 9.98, and 10.23 μ, $[\alpha]D$ −41° (c 1, $CHCl_3$). III exhibited no distinct ultraviolet absorption.

Anal. Calcd. for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.10; H, 10.51.

4,4,6,16α-Tetramethyl-5-androstene-3,17-dione (IV).—4,4,6,-16α-Tetramethyl-5-pregnene-17α,20β-diol-3-one (III) (300 mg.) was dissolved in 30 ml. of methanol and treated with an aqueous solution of 250 mg. of periodic acid in 5 ml. of water at room temperature for 17 hr. On dilution with water, the resultant crystals were collected by filtration, washed well with water, and dried to give 262 mg. of crystals, m.p. 158–160°. Recrystallization from hexane–acetone gave 240 mg. of IV, m.p. 160–161°, λ^{KBr} 5.80, and 5.88 μ, $[\alpha]^{25}D$ −6° (c 1, $CHCl_3$). Mass spectrum showed a strong *m/e* 342 peak.

Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.59; H, 9.96.

4,4,6,16α-Tetramethyl-5-androstene-17β-ol-3-one (V).—4,4,-6,16α-Tetramethyl-5-androstene-3,17-dione (IV) (175 mg.) was dissolved in 30 ml. of absolute methanol and the system was flushed with nitrogen gas for 3 min. Sodium borohydride (40 mg.) was then added and the mixture stirred for 30 min. at room temperature. A few drops of acetic acid were added and the mixture diluted with water. The resulting crystals were collected by filtration, washed well with water, and dried to give 174 mg. of crystals, m.p. 96–99°. Recrystallization from aqueous methanol furnished pure 4,4,6,16α-tetramethyl-5-androstene-17β-ol-3-one (V), 162 mg. of crystals, m.p. 101–102°, λ^{KBr} 2.90, and 5.85 μ, $[\alpha]D$ −42° (c 1, $CHCl_3$). V exhibited no significant ultraviolet absorption.

Anal. Calcd. for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.12; H, 10.47.

4,4,6,16α-Tetramethyl-5-androstene-3β,17β-diol (VI).—A solution of 4,4,6,16α-tetramethyl-5-androstene-3,17-dione (IV) (235 mg.) in 30 ml. of anhydrous ether was added at ambient temperature during a period of 15 min. to a stirred solution of lithium aluminum hydride (300 mg.) in 30 ml. of anhydrous ether. The mixture was then refluxed for 30 min., cooled to 0°, and excess lithium aluminum hydride decomposed with water. The mixture was further diluted with water and extracted with ethyl acetate. The organic layer was washed well with water, dried over magnesium sulfate, filtered, and concentrated to give 228 mg. of crystals, m.p. 105–118°, which was put on a 5 g. Florisil column. Elutions with hexane gave crude crystals (164 mg.) m.p. 199–121°. Recrystallization of 156 mg. of crude product from hexane–acetone gave a first crop of 62 mg. of crystals, m.p. 120–121°, λ^{KBr} 3.00, no carbonyl absorption, 9.45, and 9.88 μ. There was no significant ultraviolet absorption. The mass spectrum showed a parent peak corresponding to molecular weight of 346, and M − CH_3, M − H_2O, M − (CH_3 + H_2O) and strong M − 83 peaks have been observed.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 79.68; H, 11.03.

16α-Fluorinated Steroids from the Reaction of Perchloryl Fluoride with Enamides[1]

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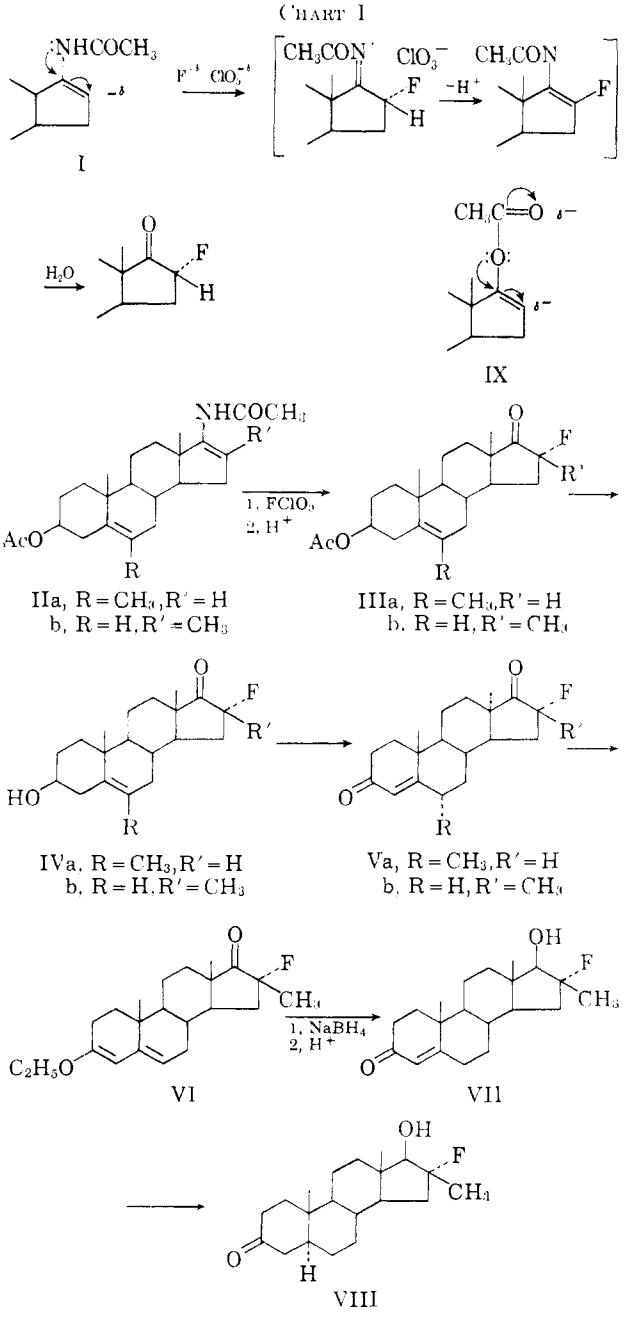
Received July 12, 1963

The reaction of perchloryl fluoride with enamines,[2,3] enol ether,[4] and enol ester[5] derivatives of saturated and 4,5-unsaturated 3-ketosteroids provides a convenient method for the introduction of a fluorine substituent adjacent or vinylogous to the carbonyl group. Application of these reactions to 17-ketosteroids has been limited by the reluctance of the 17-ketone to form enol ethers[1] or enamines.[1,6,7]

We have found that acetylated 17-amino-Δ^{16}-steroids (enamides), conveniently prepared[8] by the Beckmann rearrangement of the oxime of 20-keto-Δ^{16}-steroids, react smoothly and stereospecifically with perchloryl fluoride to furnish the corresponding 16α-fluoro-17-ketosteroids in high yield.[1]

Presumably, the reaction proceeds by electrophilic attack of the fluorine at the negative center at position C-16 (I) followed by loss of a proton to produce a

CHART I



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