Synthesis of Some Pregnane 16-Thioesters

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1,4-Addition of thioacids to 16-dehydropregnane 20-ketones affords 16-acylthio 20-ketones with steric results dependent on the steroid and the thioacid involved. Both 16α- and 16β-thioesters result. The structures of the thioester products have been assigned on the basis of proton nuclear magnetic resonance and optical rotatory dispersion spectra.

For studies relating mineralocorticoid activity to substitution at the C-16 position in the pregnane nucleus, we desired to have certain analogs of 16α-oxygenated steroids. Of particular interest were the 16α-thio analogs of 16α-hydroxycortexone (16α,21-dihydroxypregn-4-ene-3,20-dione) and the sodium excreting factor (3β,16α-dihydroxy-5α-pregnan-20-one) of Neher, *et al.*[1]

For their synthesis the well-known 1,4-addition of substituted thiols to 16-dehydropregnane 20-ketones was chosen.[2] Specifically, addition of thioacids and of hydrogen sulfide to select 16-dehydropregnane 20-ketones resulted in the formation of 16-thioester and 16-mercapto derivatives of the type sought.

The reaction between steroid and neat thioacid began immediately after solution was effected, mild heat evolution occurred, and the reaction was complete within minutes. Only very small amounts of starting material could be detected by thin layer chromatography or by ultraviolet light absorption spectra in the reaction mixture after this time. The reaction also occurred in methylene chloride solutions of steroid and thioacid.

The resultant thioester derivatives II, III, VII, VIII, IXa, XI, XII, and XIII thus prepared were assigned the 16-acylthio 20-ketone structure on the basis of elemental analysis and ultraviolet and infrared absorption spectra. The thioesters VII, VIII, IXa, XI, XII, and XIII exhibit selective ultraviolet absorption typical of such derivatives[3] and infrared carbonyl and C–S stretching bands characteristic of thioacetates.[4] The thiopropionates IIIa, IIIc, and VIIIb absorb near 10.7 μ.[4b]

The stereoselectivity with which thioacids add to the 16-dehydro 20-ketone system depends on both the structure of the steroid and the thioacid. Since the addition of thioacids to the Δ^1- and Δ^6-double bonds of $\Delta^{1,4}$- and $\Delta^{4,6}$-3-ketone systems is known to give both possible epimeric 1- and 7-thioester products[5] and addition of thioacetic acid to 3β-acetoxypregna-5,16-dien-20-one affords three of the four possible isomeric 16-thioesters,[2f] it was anticipated that 16,17-isomeric products would be encountered in the present study. Indeed, two crystalline thioesters VIIa and VIIIa, readily differentiated from one another by their melting point behavior and infrared and nuclear magnetic resonance spectra but not separable on thin layer chromatograms, were isolated from the reaction of thioacetic acid and 3β-hydroxy-5β-pregn-16-en-20-one (IVa). Two of the three known isomeric 16-thioesters derived from 3β-acetoxypregna-5,16-dien-20-one and thioacetic acid[2f] were obtained (XI and XII). Thioester XI isomerizes to the more stable 16α-acetylthio-17β-pregnan-20-one XII,[2f] and we have isomerized with concomitant acetylation the thioester VIIIa with sodium acetate and acetic acid to the 16α-thioester VIIb.

In other cases we were unable to obtain more than one crystalline thioester from the reaction mixtures, although low yields, difficultly purified products, and nuclear magnetic resonance spectra indicated that isomeric thioesters had been formed. The apparent isomer composition of the thioester reaction products is presented in Table I.

The several thioesters prepared in this study can be grouped into two sets depending on their proton nuclear magnetic resonance spectra. The first group consists of thioesters II, VII, IXa, XII, and XIII, and is characterized by the proton resonances: C-18 methyl at 0.60–0.76 p.p.m.,[6] C-21 methyl at 2.12–2.17 p.p.m., 16-thioacetate methyl at 2.25–2.28 p.p.m., 17-proton doublet at 2.59–2.67 p.p.m., and 16-proton at 4.25–4.28 p.p.m. Except for the 16-proton and thioacetate methyl resonances, these spectra are typical of those obtained with 16α-hydroxy and acetoxy-substituted 17β-pregnane-20-ketones.[7]

(1) (a) R. Neher, P. Desaulles, E. Vischer, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1667 (1958); (b) R. Neher, C. Meystre, and A. Wettstein, *ibid.*, **42**, 132 (1959).

(2) (a) R. Bourdon and G. Rosseels, *Prod. Pharm.*, **16**, 425, 471 (1961); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951); (c) J. Romo, G. Rosenkranz, and C. Djerassi, *ibid.*, **73**, 4961 (1951); (d) J. Romo and G. Contreras, *Bol. Inst. Quim. Univ. Nal. Auton. Mex.*, **4**, 101 (1952); (e) G. Rosenkranz, C. Djerassi, and J. Romo, U. S. Patent 2,697,108 (Dec. 14, 1954); (f) R. M. Dodson and P. B. Sollman, U. S. Patent 2,912,443 (Nov. 10, 1959); (g) H. Reimann and E. L. Shapiro, U. S. Patent 2,988,557 (June 13, 1961); (h) A. S. Hoffman, H. M. Kissman, and M. J. Weiss, *J. Med. Pharm. Chem.*, **5**, 962 (1962).

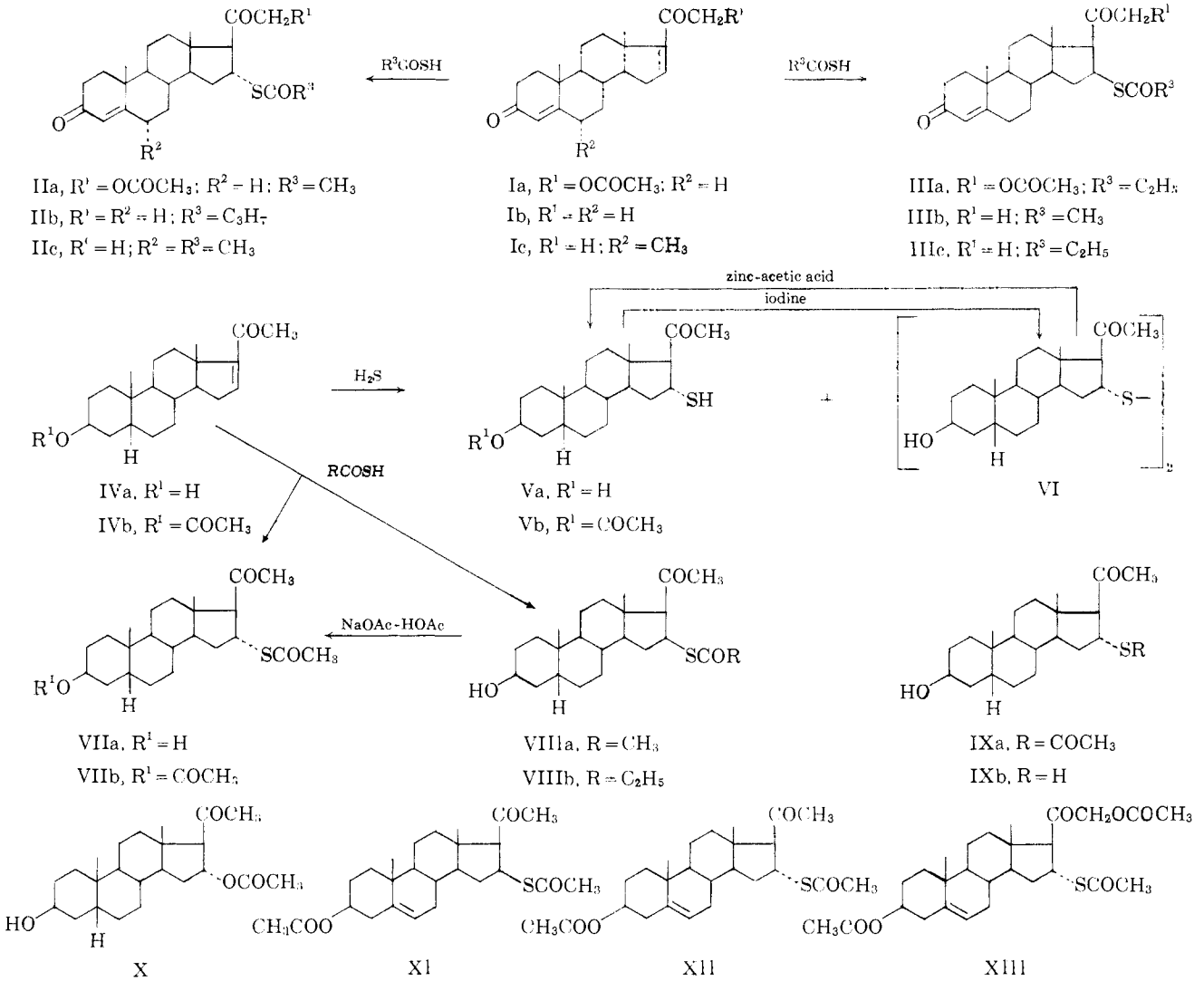
(3) Steroid thioacetates absorb in the region 230–237 mμ (ε 3500–6000); see (a) S. Bernstein and K. J. Sax, *J. Org. Chem.*, **16**, 685 (1951); (b) C. Djerassi and A. L. Nussbaum, *J. Am. Chem. Soc.*, **75**, 3700 (1953); (c) T. Komeno, *Chem. Pharm. Bull.* (Tokyo), **8**, 668, 672, 680 (1960); (d) T. Komeno, U. S. Patent 3,016,386 (Jan. 9, 1962); (e) K. Takeda and T. Komeno, *Chem. Ind.* (London), 1793 (1962).

(4) Steroidal thioacetates absorb in the region 5.87–6.04 and 8.77–9.1 μ; see (a) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959); (b) R. Bourdon and S. Ranisteano, *Bull. soc. chim. France*, 1982 (1960); (c) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223, 3915 (1961); (d) ref. 10a–10d; (e) F. C. Uhle, *J. Org. Chem.*, **27**, 2797 (1962).

(5) (a) R. C. Tweit, *ibid.*, **27**, 2693 (1962); (b) R. C. Tweit, F. B. Colton, N. L. McNiven, and W. Klyne, *ibid.*, **27**, 3325 (1962).

(6) Proton nuclear magnetic resonance spectra were obtained on 10–15% solutions of steroids in deuteriochloroform with tetramethylsilane as an internal reference, using a Varian Associates Model A-60 spectrometer (60 Mc.). The resonance lines are measured from the internal reference in a downfield direction.

(7) Several 16α-hydroxy-17β-pregnane 20-ketones have C-18 methyl resonances at 0.62–0.65 p.p.m., C-21 methyl at 2.13–2.18 p.p.m., 17α-proton at 2.51–2.66 p.p.m. (doublet, J = 6–7 c.p.s.), 16β-proton at 4.73–5.00 p.p.m. (multiplet). Unsubstituted 17β-pregnane 20-ketones have C-18 methyl resonances at 0.60–0.71 p.p.m., C-21 methyl at 2.11–2.15 p.p.m., 17α-proton at 2.46–2.47 p.p.m. (doublet, J = 8–9 c.p.s.).



IIa, $R^1 = OCOCH_3$; $R^2 = H$; $R^3 = CH_3$
IIb, $R^1 = R^2 = H$; $R^3 = C_3H_7$
IIc, $R^1 = H$; $R^2 = R^3 = CH_3$

Ia, $R^1 = OCOCH_3$; $R^2 = H$
Ib, $R^1 = R^2 = H$
Ic, $R^1 = H$; $R^2 = CH_3$

IIIa, $R^1 = OCOCH_3$; $R^3 = C_2H_5$
IIIb, $R^1 = H$; $R^3 = CH_3$
IIIc, $R^1 = H$; $R^3 = C_2H_5$

IVa, $R^1 = H$
IVb, $R^1 = COCH_3$

Va, $R^1 = H$
Vb, $R^1 = COCH_3$

VI

VIIa, $R^1 = H$
VIIb, $R^1 = COCH_3$

VIIIa, $R = CH_3$
VIIIb, $R = C_2H_5$

IXa, $R = COCH_3$
IXb, $R = H$

X XI XII XIII

The second set of thioesters consists of III, VIII, and XI, and is characterized by the proton resonances: C-18 methyl at 0.87–0.96 p.p.m.; C-21 methyl at 2.05–2.07 p.p.m.; 16-thioacetate methyl at 2.29–2.32 p.p.m., 17-proton doublet at 2.83–2.86 p.p.m., and 16-proton at 4.23–4.37 p.p.m.

The structures of members of the first group follow from the aforementioned similarities in nuclear magnetic resonance spectra with 16α-oxygenated 17β-pregnane 20-ketones and from optical rotatory dispersion data. The thioesters VIIa, VIIb, IXa, and XII are characterized by strong, positive Cotton effects typical of 17β-pregnane 20-ketones.[8] In Fig. 1 the dispersion spectra of VIIa and IXa are compared with data of the known 16α-acetoxy-3β-hydroxy-5β,17β-pregnan-20-one (X).[9]

Molecular rotational differences, $\Delta M_D^{16\text{-thioester}}$, for VIIa, VIIb, IXa, XII, and XIII range between -231 and -288, which range is well within the limits found for 16α-acetoxy-17β-pregnan-20-one analogs.[10] These arguments together with the preferred stability of the 16,17-*trans* system in general support in detail the assigned 16α-acylthio-17β-pregnan-20-one structure for these thioesters. The Δ^4-3-ketone thioesters II have more negative ΔM_D values of -321 to -467 which overlap the limits found in 16α-acyloxy analogs and are also assigned the 16α-acylthio-17β-pregnan-20-one structure.

The thioesters III, VIII, and XI necessarily must be 16ξ-acylthio-17α-pregnan-20-one or 16β-acylthio-17β-pregnan-20-one derivatives. The 17α-pregnan-20-one structure for VIIIa and XI is ruled out on the basis of the positive Cotton effects in the optical rotatory dispersion spectra (Fig. 1). All 16-substituted 17α-pregnan-20-one derivatives which have been examined have negative Cotton effects.[8] Although the Cotton effects for VIIIa and XI are much weaker than are those for their respective isomers VIIa and XII, the definitely positive character of the Cotton effect supports in detail the 17β-pregnan-20-one structure. The structure of VIIIa must therefore be that of 16β-

(8) (a) C. Djerassi, *Bull. soc. chim. France*, 741 (1957); (b) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 51-52; (c) W. A. Struck and R. L. Houtman, *J. Org. Chem.*, **26**, 3883 (1961); (d) P. F. Beal and J. E. Pike, *ibid.*, **26**, 3887 (1961); (e) P. Crabbé and J. Romo, *Chem. Ind.* (London), 408 (1962); (f) P. Crabbé, M. Pérez, and G. Vera, *Can. J. Chem.*, **41**, 156 (1963); (g) P. Crabbé, *Tetrahedron*, **19**, 51 (1963); (h) M. B. Rubin, *Steroids*, **2**, 561 (1963).

(9) H. Hirschmann and M. A. Dana, *J. Org. Chem.*, **24**, 1114 (1959); we present a new synthesis of X by selective acetylation of 3β,16α-dihydroxy-5β-pregnan-20-one with acetic anhydride and dinepyri.

(10) ΔM_D values associated with 16α-acetoxy substitution range from -113.2 to -333; with 16β-acetoxy substitution from -49 to $+108$. See (a) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950); (b) D. K. Fukushima and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951); (c) J. A. Moore, *Helv. Chim. Acta*, **37**, 659 (1954); (d) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

TABLE I

STEREOSELECTIVITY OF ADDITION OF THIOACIDS

16-Dehydro 20-ketone	Thioacid	Method[a]	Isomer isolated[b]	Yield, %	Isomer ratio[c]
Pregna-4,16-diene-3,20-dione (Ib)	Thioacetic	A	16β (IIIb)	34	9:1
	Thiopropionic	A	16β (IIIc)	52	4:1
	Thiobutyric	A	16α (IIb)	62	0:1
21-Acetoxypregna-4,16-diene-3,20-dione (Ia)	Thioacetic	B	16α (IIa)	72	1:7
	Thiopropionic	B	16β (IIIa)	39	...
3β-Hydroxy-5β-pregn-16-en-20-one (IVa)	Thioacetic	B	16α (VIIa)[e]	37–49	1:1
	Thioacetic	A	16α (VIIa)	60	...
	Thiopropionic	B	16β (VIIIb)	52	7:1
3β-Hydroxy-5α-pregn-16-en-20-one	Thioacetic	B	16α (IXa)	60	1:8
3β-Acetoxypregna-5,16-dien-20-one	Thioacetic	A	16β (XI)[d]	60	13:1

[a] A, neat thioacid warmed 5–30 min. on a steam bath; B, methylene chloride solution plus thioacid, 0.5–3 hr. at room temperature. [b] Only one isomer was readily isolated pure from a given reaction mixture. [c] In certain experiments the 16β-isomer was isolated in 53–64% yields, isomer ratio *ca.* 1:1. [d] In one experiment a low yield of the 16α-isomer was obtained. [e] The isomer ratio, defined as the ratio of the 16β-isomer content to the 16α-isomer content, was determined by nuclear magnetic resonance analysis of total reaction products, mother liquor fractions, etc., on the assumption that spurious lines in the C-18 methyl region (0.60–0.96 p.p.m.) not present in spectra of the pure isolated isomer were due to the presence of 16-isomeric products.

acetylthio-3β-hydroxy-5β,17β-pregnan-20-one, and XI must be 3β-acetoxy-16β-acetylthio-17β-pregn-5-en-20-one.

By analogy other members of the group are assigned the 16β-acylthio-17β-pregnan-20-one structure. Although the ΔM_D values for the 16-thioester functional group in these cases are negative and of the same order (−195 to −409) found for the 16α-thioester group, the molecular rotational differences $\Delta M_D^{16\beta\text{-}16\alpha}$ for the isomeric pairs VIIa–VIIIa and XII–XI are +51 and +90, respectively, which is in accord with

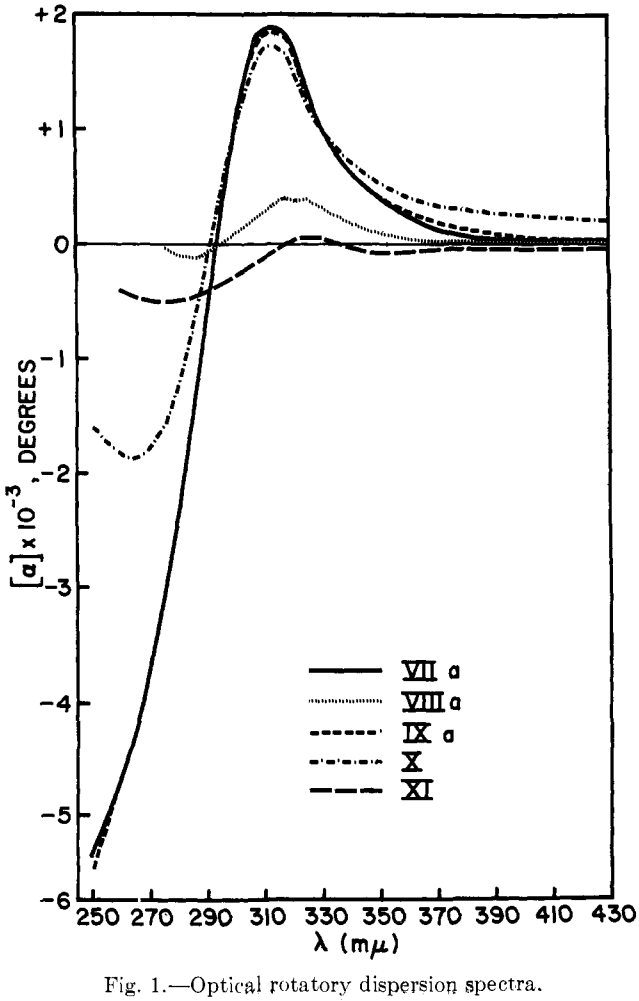


Fig. 1.—Optical rotatory dispersion spectra.

other 16α- and 16β-acetoxy-17β-pregnane 20-ketone pairs.[11]

Analysis of the proton nuclear magnetic resonance spectra of these thioesters also supports the 16β-acylthio-17β-pregnan-20-one structure. Whereas the downfield shifts of the C-18 methyl group protons to 0.87–0.96 p.p.m. (relative to 0.60–0.71 p.p.m. for simple 17β-pregnane 20-ketones and 0.60–0.76 p.p.m. for the several 16α-thioesters) is characteristic of 17α-pregnane 20-ketones,[8h,12] other aspects of the spectra are not in accord with a 17α-pregnane formulation.

Thus the C-21 methyl protons in III, VIII, and XI are found upfield from their position in simple 17α-pregnan-20-one derivatives,[8h,12] in 17β-pregnan-20-one derivatives, and in the 16α-thioesters. This increased shielding of the C-21 methyl protons thus cannot readily be associated with isomerization of the C-17 side chain. Furthermore the 17-proton doublet in this set of thioesters at 2.83–2.86 p.p.m. is unshielded in comparison with the 17α-proton of the 16α-thioesters and of 16α-hydroxy-17β-pregnan-20-one derivatives (2.51–2.66 p.p.m.).[13]

The downfield shift of the C-18 methyl protons in the 16β-thioesters is also characteristic of 1,3-diaxial interactions between the C-18 protons and 8β-, 11β-, and 15β-hydroxyl groups and between C-18 protons and 11β- and 15β-acetoxyl groups.[14] Although the 16β-acylthio feature cannot be considered axial, its 1,3-pseudo-axial relation to the C-18 methyl group should lead to a deshielding influence.[15]

The three effects of increased shielding of the C-21 methyl protons, of decreased shielding of the 17-proton, and of decreased shielding of the C-18 methyl protons

(11) ΔM_D (16β-acetoxyl–16α-acetoxyl) values range from +67 to +410.[8i]

(12) C-18 methyl protons in simple 17α-pregnane 20-ketones have been reported at 0.85–1.02 p.p.m.; see (a) W. J. Wechter and H. C. Murray, *J. Org. Chem.*, **28**, 755 (1963); (b) P. Crabbé and J. Romo, *Bull. soc. chim. Belges*, **72**, 208 (1963); (c) J. E. Pike, G. Slomp, and F. A. MacKellar, *J. Org. Chem.*, **28**, 2502 (1963).

(13) It must be noted, however, that the 17β-proton in some 17α-pregnane 20-ketones has been found as a doublet at 2.92–3.19 p.p.m. with J = 7.5 c.p.s.[12d]

(14) (a) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962); (b) K. Tori and E. Kondo, *Tetrahedron Letters*, **No. 10**, 645 (1963).

(15) The 16β-acetoxyl group of two pregnane 20-ketones show a deshielding effect on the C-18 methyl protons; see compounds no. 132 and 134 in R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

are best reconciled with the 16β-acylthio-17β-pregnan-20-one structure.[15a]

The 16-proton signals in both types of thioester spectra were poorly resolved multiplets, but at high gain it was possible to differentiate the two proton types into triplet and quartet character. The 16β-proton signal of 16α-thioesters appeared as a triplet of doublets, the 16α-proton signal of 16β-thioesters as a quartet suggestive of higher multiplicity. First-order analysis of the 16-proton signals of the epimeric pair VIIa and VIIIa and of the homologous 16-epimeric pair IIc and IIIb gave the coupling constants 2.6, 9, and 9 c.p.s. for coupling between the 16β-proton and the 15α-, 15β-, and 17α-protons, respectively, and 7, 9, and 10 c.p.s. for coupling between the 16α-proton and the same 15α-, 15β-, and 17α-protons.[16] It is of interest to note that both the 16α- and 16β-protons coupled with the 15β- and 17α-protons to about the same extent.[18]

Addition of hydrogen sulfide to 3β-hydroxy-5β-pregn-16-en-20-one (IVa) gave 16α-thiol Va plus disulfide VI. Thiol Va was oxidized by iodine to disulfide VI, which in turn could be reduced by zinc and acetic acid to thiol Va. Some 3β-acetylation occurred during the reduction, as some 3β-acetate Vb was also isolated. Similarly, hydrogen sulfide addition to 3β-hydroxy-5α-pregn-16-en-20-one gave the 5α-pregnane-16α-thiol IXb.

The 17β-pregnan-20-one structures assigned thiols Va and IXb and disulfide VI are based on their nuclear magnetic resonance spectra (C-18 methyl at 0.60–0.61 p.p.m., C-21 methyl at 2.12–2.18 p.p.m.) and on conversion of thiol Va with acetic anhydride and pyridine to the 3β,16α-diacetate VIIIb.

The thioesters could not be hydrolyzed satisfactorily to their respective 16-thiols by a variety of acid and base conditions. Treatment with base led to elimination of sulfur with formation of the parent 16-dehydro 20-ketone or to very complex mixtures as indicated by thin layer chromatography.[21] Elimination of the 16-thioester functional group is more facile than elimination of the 16α-acetoxyl group, for hydrolysis of 16α-acetoxy 20-ketones can be accomplished although some elimination does result.[1,9] 16β-Acetoxy 20-ketones are not stable to such conditions, however.

Table II

Chromatographic Behavior of 16β-Thioesters and 16α-Thiols

Derivative of pregnan-20-one	Mobility, R_f[a] I	I	III
16α-Acetylthio-3β-hydroxy-5β- (VIIa)	0.71	0.10	0.44
16α-Acetoxy-3β-hydroxy-5β- (X)	0.61	0.07	0.35
3β-Acetoxy-16α-acetylthio-5β- (VIIb)	0.92	0.41	0.75
3β,16α-Diacetoxy-5β-	0.85	0.21	0.64
3β-Hydroxy-16α-mercapto-5β- (Va)	0.78	0.18	0.51
3β,16α-Dihydroxy-5β-	0.00	0.01	0.08
3β-Acetoxy-16α-mercapto-5β- (Vb)	0.99	0.59	0.81
3β-Acetoxy-16α-hydroxy-5β-	0.20	0.04	0.19
3β,16α-Dihydroxy-5α-	0.00	0.01	0.06
3β-Acetoxy-16α-hydroxy-5α-	0.26	0.05	0.24

[a] Systems I, II, and III as defined in the Experimental part.

Hydrolysis with bovine albumin,[22] rat intestine preparation,[23] or malt diastase[24] did not occur.

The 16-thiols and 16-thioesters Va, Vb, VIIa, and VIIb are more mobile on paper and thin layer chromatograms than their respective oxygen analogs (Table II). This behavior is in agreement with similar behavior of 21-thiols and 21-thioesters.[25] However, 16α-thiols Va and Vb are much more mobile than anticipated, more so than their respective 16α-thioacetates VIIa and VIIb.

Whereas the 16α-thioester analog IXa of Neher's sodium excreting factor (3β,16α-dihydroxy-5α-pregnan-20-one)[1] was devoid of mineralocorticoid activity, the 5β,16α-thioester analog VIIa and its 5β,16β-thioester epimer VIIIa antagonized the action of cortexone acetate in adrenalectomized rats (Kagawa test).[26] A dose of 5–6 mg. per rat of either VIIa or VIIIa reduced the mineralocorticoid effects of 10–12 μg. of cortexone acetate by 50%. Neither 3β-acetate VIIb or any other thioester, nor the 16α-acetoxy analog X of VIIa blocked the action of cortexone acetate in the Kagawa test.

Experimental[27]

21-Acetoxy-16α-acetylthiopregn-4-ene-3,20-dione (IIa).—A solution of 2 g. of 21-acetoxypregna-4,16-diene-3,20-dione (Ia) in 100 ml. of methylene chloride and 20 ml. of technical thioacetic acid was stirred at room temperature for 3 hr., after which time

(15a) Note Added in Proof. In a recent paper, A. D. Cross and P. Crabbé [*J. Am. Chem. Soc.*, **86**, 1221 (1964)] report proton spectra for four possible 16,17-isomeric pregnanes. Their data support our assignments in that they find large coupling constants (7.0–8.9 c.p.s.) between the 16- and 17-protons in the 16α,17β- and 16β,17β- isomeric pairs *vs.* small coupling constants (1–3 c.p.s.) between the same protons in the 16α,17α- and 16β,17α- isomeric pairs. Also the C-18 methyl protons are shifted 0.2 p.p.m. downfield in the 16β,17β- isomer. They did find, however, that the 17α-protons in both 16α,17β- and 16β,17β- isomers are found at the same frequency, some 0.3 p.p.m. to higher fields than the 17β-proton signals of the 16,17α- isomers.

(16) A few coupling patterns for 16β-protons have been reported: an octuplet for cyclobuxine and its 16α-acetate, with J = 3, 7, and 9.5 c.p.s.,[5a] and a triplet for dihydroelatericin B.[5b] We observed an octuplet for the 16α-acetoxy derivative X with approximate J values of 3, 6, and 10 c.p.s.

(17) (a) K. S. Brown and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590 (1962); (b) D. Lavie, Y. Shvo, O. R. Gottlieb, and E. Glotter, *J. Org. Chem.*, **28**, 1790 (1963).

(18) The triplet and quartet character of the 16-proton signals may be reconciled with the assigned configurations by an extension of the Karplus correlation[19] to the five-membered ring system.[20] More complex spectra are predicted for the 16β-thioester, with quartet character being likely with poor resolution, whereas triplet character appears more likely for 16α-thioesters; *see* ref. 17b.

(19) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(20) The validity of the Karplus correlation in other five-membered ring systems has been discussed; see F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 513 (1962); R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962); see ref. 17b.

(21) A 16-thiol has recently been obtained by hydrolysis of 21-acetoxy-16-acetylthio-9α-fluoropregn-4-ene-3,20-dione with sodium methoxide in methanol; see ref. 2b.

(22) E. L. Rongone, R. C. Rocklage, D. R. Strength, and E. A. Doisy, *J. Biol. Chem.*, **225**, 969 (1957).

(23) E. T. Janssen, H. P. Schedl, and J. A. Clifton, *Arch. Biochem. Biophys.*, **98** 516 (1962).

(24) S. Noguchi, *J. Pharm. Soc. Japan*, **81**, 369, 373, 377, 385 (1961).

(25) L. L. Smith, *J. Chromatog.*, **8**, 17 (1962).

(26) C. M. Kagawa, *Proc. Soc. Exptl. Biol. Med.*, **99**, 705 (1958).

(27) Optical rotations are reported for chloroform solutions of 0.5–1% concentrations; optical rotatory dispersion spectra were obtained on dioxane solutions. Ultraviolet absorption spectra were obtained on solutions in 95% ethanol, infrared spectra on pressed potassium bromide disks. Corrected melting points were obtained using capillary tubes except where noted "Kofler" in which case a calibrated Kofler hot stage under microscopic magnification was used. Each preparation was examined for homogeneity by paper and/or thin layer chromatography. Mobility data are reported for the systems: I, hexane–methanol–water (10:7:3) with Whatman No. 1 paper at 30°; Ia, the same system run at room temperature; II, hexane–ethyl acetate (5:2) run on neutral silica gel thin layer chromatoplates bound with rice starch[28]; III, hexane–ethyl acetate (1:1) on neutral chromatoplates; IIIa, hexane–ethyl acetate (1:1) in acidic chromatoplates. Detection in all cases was with a 10% ethanolic solution of phosphomolybdic acid.

(28) L. L. Smith and T. Foell, *J. Chromatog.*, **9**, 339 (1962).

the solvents were removed under vacuum. The gummy residue was crystallized and recrystallized from ethanol three times, yielding 1.0 g. of product, m.p. 161–162°. Chromatography on silica gel (elution with 10% ether in benzene) afforded the analytical sample, m.p. 162–164°; $[\alpha]_D$ +94.8°[29]; λ_{max} 238 mμ (ε 19,400); λ_{max}^{KBr} 5.74, 5.79, 5.95, 6.03, 6.22, 8.17, 9.01, and 10.61 μ, etc.; R_f 0.34 in system Ia, 0.23 in system IIIa.

Anal. Calcd. for $C_{25}H_{34}O_5S$: C, 67.23; H, 7.67; S, 7.18. Found: C, 67.35; H, 7.39; S, 6.84.

Nuclear magnetic resonance spectra: C-18 methyl at 0.76 p.p.m.; C-19 methyl at 1.18 p.p.m.; C-21 acetoxyl methyl at 2.17 p.p.m.; 16α-thioacetate methyl at 2.28 p.p.m.; 17α-proton at 2.61 p.p.m. (doublet, J = 9 c.p.s.); 16β-proton at 4.28 p.p.m. (triplet of doublets); C-21 methylene at 4.63 p.p.m. (quartet, J = 17 c.p.s.); 4-proton at 5.75 p.p.m.

16α-Butyrylthiopregn-4-ene-3,20-dione (IIb).—16-Dehydroprogesterone (Ib) (2 g.) dissolved in 5 ml. of technical thiobutyric acid was warmed on a steam bath for 15 min., after which time the thioacid was removed under vacuum. The yellow gum obtained was crystallized from ether–methanol, 920 mg., m.p. 150–152°. A second and third crop, 420 mg., m.p. 148–150°, and 300 mg., m.p. 134–139°, was taken. Recrystallization from ethanol and from acetone gave the pure product, m.p. 152–153.5°; $[\alpha]_D$ +40.5°; λ_{max} 239 mμ (ε 20,200); λ_{max}^{KBr} 5.84, 5.95, 6.01, and 6.18 μ, etc.

Anal. Calcd. for $C_{25}H_{36}O_3S$: C, 72.07; H, 8.71; S, 7.70. Found: C, 72.17; H, 8.67; S, 7.68.

Nuclear magnetic resonance spectra: C-18 methyl at 0.71 p.p.m.; 16α-thiobutyrate methyl at 0.93 p.p.m. (triplet, J = 7 c.p.s.); C-19 methyl at 1.20 p.p.m.; C-21 methyl at 2.17 p.p.m.; 17α-proton at 2.62 p.p.m. (doublet, J = 9 c.p.s.); 16β-proton at 4.26 p.p.m. (triplet of doublets); 4-proton at 5.73 p.p.m.

16α-Acetylthio-6α-methylpregn-4-ene-3,20-dione (IIc).—6α-Methylpregna-4,16-diene-3,20-dione (Ic) (4 g.) was treated by the procedure used for IIa. The resultant oil was crystallized from 2-propanol, yielding 3.2 g. of product, m.p. 158–160°. Several recrystallizations from 2-propanol afforded the pure product, m.p. 160–161°; $[\alpha]_D$ +31.5°; λ_{max} 238 mμ (ε 19,700); λ_{max}^{KBr} 5.87, 5.93, 6.01, 6.23, 7.37, 8.87, and 10.45 μ, etc.; R_f 0.81 in system Ia, 0.42 in system IIIa.

Anal. Calcd. for $C_{24}H_{34}O_3S$: C, 71.60; H, 8.51; S, 7.96. Found: C, 71.79; H, 8.32; S, 7.80.

Nuclear magnetic resonance spectra: C-18 methyl at 0.72 p.p.m.; 6α-methyl at 1.06 p.p.m. (doublet, J = 6.5 c.p.s.); C-19 methyl at 1.18 p.p.m.; C-21 methyl at 2.16 p.p.m.; 16α-thioacetate methyl at 2.27 p.p.m.; 17α-proton at 2.63 p.p.m. (doublet, J = 9 c.p.s.); 16β-proton at 4.28 p.p.m. (triplet of doublets); 4-proton at 5.80 p.p.m.

21-Acetoxy-16β-propionylthiopregn-4-ene-3,20-dione (IIIa).—Using the procedure for IIa, except that technical thiopropionic acid was substituted for thioacetic acid, 3.0 g. of 21-acetoxypregna-4,16-diene-3,20-dione (Ia) was converted to 1.5 g. of crude 16β-thiopropionate, m.p. 118–121°. After chromatography on silica gel (elution with 5% ether in benzene) the pure thiopropionate was obtained, m.p. 129–131°; $[\alpha]_D$ +61.5°; λ_{max} 238 mμ (ε 18,500); λ_{max}^{KBr} 5.72, 5.78, 5.95, 6.02, 6.20, 8.15, 9.49, and 10.65 μ, etc.; R_f 0.36 in system IIa.

Anal. Calcd. for $C_{26}H_{36}O_5S$: C, 67.79; H, 7.88; S, 6.96. Found: C, 67.81; H, 7.86; S, 6.88.

Nuclear magnetic resonance spectra: C-18 methyl at 0.87 p.p.m.; 16β-thiopropionate methyl at 1.15 p.p.m. (triplet, J = 7.5 c.p.s.); C-19 methyl at 1.18 p.p.m.; C-21 acetoxyl methyl at 2.20 p.p.m.; 16β-thiopropionate methylene at 2.53 p.p.m. (quartet, J = 8 c.p.s.); 16α-proton at 4.28 p.p.m. (multiplet); C-21 methylene centered at 4.63 p.p.m. (quartet, J = 17 c.p.s.); 4-proton at 5.75 p.p.m.

16β-Acetylthiopregn-4-ene-3,20-dione (IIIb).—A solution of 4.0 g. of 16-dehydroprogesterone (Ib) in 4.0 ml. of technical thioacetic acid was warmed on a steam bath for 20 min. The thioacetic acid was removed under vacuum, and the gummy residue was washed with water and crystallized from ethanol, yielding 1.66 g. of product, m.p. 172.5–176.5°. After several recrystallizations from ethanol the pure product was obtained, m.p. 184–185°; $[\alpha]_D$ +81°; λ_{max} 239 mμ (ε 20,000); λ_{max}^{KBr} 5.85, 5.93, 6.01, 6.20, and 8.90 μ, etc.; $\lambda_{max}^{H_2SO_4}$ ($E_{1\,cm}^{1\%}$) after 2 hr. 290 (543), 400 mμ (30); R_f 0.59 in system Ia (R_f of Ib is 0.74), 0.84 in propylene glycol–toluene.

Anal. Calcd. for $C_{23}H_{32}O_3S$: C, 71.09; H, 8.30; S, 8.25. Found: C, 71.15; H, 8.23; S, 8.30.

Nuclear magnetic resonance spectra: C-18 methyl at 0.96 p.p.m.; C-19 methyl at 1.20 p.p.m.; C-21 methyl at 2.07 p.p.m.; 16β-thioacetate methyl at 2.32 p.p.m.; 17α-proton at 2.86 p.p.m. (doublet, J = 10 c.p.s.); 16α-proton at 4.28 p.p.m. (quartet); 4-proton at 5.75 p.p.m.

16β-Propionylthiopregn-4-ene-3,20-dione (IIIc).—Two grams of 16-dehydroprogesterone (Ib) was dissolved in 30 ml. of technical thiopropionic acid and after 5 min. on the steam bath the thioacid was removed under vacuum. The gum obtained was crystallized from ethanol, yielding 990 mg. of material, m.p. 156–159°, λ_{max} 239 mμ (ε 19,000), from which an analytical sample was prepared, m.p. 163.5–164.5°; $[\alpha]_D$ +71.4°; λ_{max} 239 mμ (ε 21,400); λ_{max}^{KBr} 5.89, 5.93, 6.02, 6.21, 9.22, and 10.7 μ, etc.[30]

Anal. Calcd. for $C_{24}H_{34}O_3S$: C, 71.60; H, 8.51; S, 7.96. Found: C, 71.68; H, 8.63; S, 7.50.

Nuclear magnetic resonances spectra: C-18 methyl at 0.96 p.p.m.; C-19 methyl at 1.18 p.p.m.; 16β-thiopropionate methyl at 1.16 p.p.m. (triplet, J = 8 c.p.s.); C-21 methyl at 2.06 p.p.m.; 16β-thiopropionate methylene at 2.53 p.p.m. (quartet, J = 8 c.p.s.); 16α-proton at 4.30 p.p.m. (multiplet); 4-proton at 5.75 p.p.m.

16α-Acetylthio-3β-hydroxy-5β-pregnan-20-one (VIIa).—To a solution of 1 g. of IVa in 50 ml. of methylene chloride was added 10 ml. of technical thioacetic acid. After 3 hr. at room temperature the solvents were removed under vacuum and the residue crystallized from cyclohexane–petroleum ether yielding 300 mg., m.p. 127–129°; $[\alpha]_D$ +8.9°; λ_{max} 233 mμ (ε 4720); λ_{max}^{KBr} 5.84, 5.99, 6.91, 7.39, 8.92, 9.69, and 10.45 μ, etc.; $\lambda_{max}^{H_2SO_4}$ ($E_{1\,cm}^{1\%}$) after 2 hr. 286 (42), 347 (33), 382 (31), and 456 mμ (26); R_f 0.32 in system IIIa, 0.54 in system Ia.

Anal. Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.52; H, 9.40; S, 7.70.

Nuclear magnetic resonance spectra: C-18 methyl at 0.66 p.p.m.; C-19 methyl at 0.95 p.p.m.; C-21 methyl at 2.12 p.p.m.; 16α-thioacetate methyl at 2.26 p.p.m.; 17α-proton at 2.62 p.p.m. (doublet, J = 8.5 c.p.s.); 16β-proton at 4.26 p.p.m. (triplet of doublets); 3α-proton at 4.13 p.p.m. (broad).

Optical rotatory dispersion: $[\alpha]_{450}$ +20°, $[\alpha]_{311}$ +1950°, and $[\alpha]_{250}$ −5450°.

Reaction of 1.0 g. of IVa in 2.0 ml. of neat technical thioacetic acid with warming for 5 min. afforded 740 mg. (60%) of crude thioester VIIa, m.p. 124.5–125.5°; λ_{max} 233 mμ (ε 4700).

3β-Acetoxy-16α-acetylthio-5β-pregnan-20-one (VIIb). A. By Thioacetic Acid Addition.—A solution of 3 g. of 3β-acetoxy-5β-pregn-16-en-20-one (IVb) in 75 ml. of methylene chloride and 30 ml. of technical thioacetic acid was held at room temperature for 30 min. and the product was isolated in the usual manner. After chromatography on silica gel (elution with 2% ethyl acetate in benzene) the pure product was obtained, 540 mg., m.p. 140–158°; $[\alpha]_D$ +18.3°; λ_{max} 232 mμ (ε 4500); λ_{max}^{KBr} 5.78, 5.85, 5.93, 6.92, 8.00, 8.03, 8.10, and 8.83 μ, etc.; R_f 0.92 in system Ia, 0.80 in system IIIa.

Anal. Calcd. for $C_{25}H_{38}O_4S$: C, 69.08; H, 8.81; S, 7.38. Found: C, 69.47; H, 9.02; S, 7.36.

Nuclear magnetic resonance spectra: C-18 methyl at 0.65 p.p.m.; C-19 methyl at 0.98 p.p.m.; 3β-acetoxyl methyl at 2.05 p.p.m.; C-21 methyl at 2.14 p.p.m.; 16α-thioacetate methyl at 2.26 p.p.m.; 17α-proton at 2.62 p.p.m. (doublet, J = 8 c.p.s.); 16β-proton at 4.25 p.p.m. (triplet); 3α-proton at 5.11 p.p.m. (broad).

Optical rotatory dispersion of VIIb: $[\alpha]_{425}$ +47°, $[\alpha]_{310}$ +1530°, and $[\alpha]_{250}$ −5270°.

B. By Isomerization.—16β-Acetylthio-3β-hydroxy-5β-pregnan-20-one (VIIIa) (200 mg.) dissolved in 3 ml. of glacial acetic acid containing 200 mg. of anhydrous sodium acetate was refluxed. After 15 min. a sample was taken, diluted with water, and extracted with chloroform; the extracts were dried and evaporated. After 3 hr. a second sample was taken and treated in the same way. Nuclear magnetic resonance spectra of the first sample indicated a ratio of VIIIa to VIIa of 3:1. The second sample was identified as pure VIIb by nuclear magnetic resonance and by thin layer chromatography.

(29) Hoffman, *et al.*,[2h] report m.p. 153–155° and $[\alpha]_D$ +71° for IIa. The M_D and ΔM_D values calculated by these investigators are in error and should read M_D +317, ΔM_D −375.

(30) Dodson and Sollman report a 16-propionylthioprogesterone, m.p. 134–135°; see ref. 2f.

16β-Acetylthio-3β-hydroxy-5β-pregnan-20-one (VIIIa).—A mixture of 5 g. of IVa and 10 ml. of technical thioacetic acid was warmed for 3 min. to dissolve. The thioacetic acid then was removed under vacuum, the yellow gum obtained dissolved in methylene chloride, and the solution was washed well with water. The solution was dried over anhydrous magnesium sulfate and the solvent was removed under vacuum, yielding a gummy residue which was chromatographed on silica gel. Bad-smelling gums were eluted with petroleum ether, and diethyl ether eluted the thioester. The colorless gum was crystallized from ether-hexane, yielding 600 mg. of VIIIa. From the mother liquor there was obtained after slow (4 days) crystallization 3.0 g. of mixed isomers VIIIa and VIIIa. Further fractionation of this mixture from ether gave 1.31 g. of crude VIIIa, m.p. 140–168°. After several recrystallizations from ethyl acetate–hexane there was obtained the pure isomer, m.p. 176–178° (Kofler); $[\alpha]_D$ +21.6°; λ_{max} 235 mμ (ε 5250); λ_{max}^{KBr} 2.83, 5.85, 5.95, 8.85, 9.07, 10.38, 10.63, and 11.38 μ, etc.

The isomers VIIIa and VIIIa could not be separated on the several paper and thin layer chromatographic systems used in this study.

Anal. Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.66; H, 9.08; S, 8.00.

Nuclear magnetic resonance spectra: C-18 methyl at 0.87 p.p.m.; C-19 methyl at 0.96 p.p.m.; C-21 methyl at 2.06 p.p.m.; 16β-thioacetate methyl at 2.30 p.p.m.; 17α-proton at 2.85 p.p.m. (doublet, J = 9.5 c.p.s.); 3α-proton at 4.10 p.p.m. (broad); 16α-proton at 4.37 p.p.m. (quartet).

Optical rotatory dispersion: $[\alpha]_{436}$ +8.6°, $[\alpha]_{365}$ +378°, $[\alpha]_{325}$ +368°, $[\alpha]_{305}$ +380°, $[\alpha]_{275}$ −116°, and $[\alpha]_{250}$ −94.5°.

3β-Hydroxy-16β-propionylthio-5β-pregnan-20-one (VIIIb).—A solution of 3 g. of IVa in 75 ml. of methylene chloride was treated with 10 ml. of technical thiopropionic acid. After 3 hr. at room temperature the solvents were removed under vacuum and the resultant gum was crystallized from ethanol, then recrystallized from carbon tetrachloride and twice from cyclohexane yielding 700 mg. of product, m.p. 154–156°; $[\alpha]_D$ +17.7°; λ_{max} 234 mμ (ε 4770); λ_{max}^{KBr} 5.84, 5.97, 6.91, 8.88, 9.68, 9.94, and 10.88 μ, etc.; R_f 0.71 in system Ia, 0.52 in system IIIa.

Anal. Calcd. for $C_{24}H_{38}O_3S$: C, 70.89; H, 9.42; S, 7.89. Found: C, 70.81; H, 9.46; S, 7.70.

Nuclear magnetic resonance spectra: C-18 methyl at 0.88 p.p.m.; C-19 methyl at 0.95 p.p.m.; 16β-thiopropionate methyl at 1.15 p.p.m. (triplet, J = 8 c.p.s.); C-21 methyl at 2.05 p.p.m.; 16β-thiopropionate methylene at 2.55 p.p.m. (quartet, J = 8 c.p.s.); 17α-proton at 2.83 p.p.m. (doublet, J = 10 c.p.s.); 3α-proton at 4.11 p.p.m. (broad); 16α-proton at 4.23 p.p.m. (multiplet).

16α-Acetylthio-3β-hydroxy-5α-pregnan-20-one (IXa).—To a solution of 0.6 g. of 3β-hydroxy-5α-pregn-16-en-20-one in 25 ml. of methylene chloride was added 5 ml. of technical thioacetic acid. After 30 min. the solvents were removed under vacuum and the residue was crystallized from carbon tetrachloride, yielding 450 mg. of product, m.p. 164–168°. Recrystallization raised the melting point to 168–171°; $[\alpha]_D$ +11.8°; λ_{max} 233 mμ (ε 4630); λ_{max}^{KBr} 5.86, 5.91, 7.39, 8.87, 9.65, and 10.52 μ, etc.; R_f 0.43 in system Ia, 0.37 in system IIIa.

Anal. Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.66; H, 9.21; S, 8.20.

Nuclear magnetic resonance spectra: C-18 methyl at 0.64 p.p.m.; C-19 methyl at 0.80 p.p.m.; C-21 methyl at 2.13 p.p.m.; 16α-thioacetate methyl at 2.25 p.p.m.; 17α-proton at 2.67 p.p.m. (doublet, J = 9 c.p.s.); 16β-proton at 4.25 p.p.m. (triplet of doublets, J = 3, 8.5, 9 c.p.s.); 3α-proton at 3.65 p.p.m. (multiplet).

Optical rotatory dispersion: $[\alpha]_{425}$ +34°, $[\alpha]_{312}$ +1930°, and $[\alpha]_{250}$ −5480°.

3β-Acetoxy-16β-acetylthiopregn-5-en-20-one (XI).—Five grams of 3β-acetoxypregna-5,16-dien-20-one was mixed with 5.0 ml. of technical thioacetic acid and shaken until dissolved. The solution was poured into water and the precipitated gum was dissolved in hot ethanol. On slow cooling there precipitated 1.5 g. of crude crystalline XI which was chromatographed on silica gel and recrystallized from ethanol, thus affording the pure thioester, m.p. 166.5–167.0° (Kofler[30]); $[\alpha]_D$ −32.7°; λ_{max} 234 mμ (ε 5250); λ_{max}^{KBr} 5.75, 5.87, 5.97, 8.08, 8.87, 9.68, 10.45, and 10.60 μ, etc.

Anal. Calcd. for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.54. Found: C, 69.18; H, 8.15; S, 7.28.

Nuclear magnetic resonance spectra: C-18 methyl at 0.90 p.p.m.; C-19 methyl at 1.05 p.p.m.; 3β-acetoxyl methyl at 2.02 p.p.m.; C-21 methyl at 2.06 p.p.m.; 16β-thioacetate methyl at 2.29 p.p.m.; 17α-proton at 2.85 p.p.m. (doublet, J = 10 c.p.s.); 3α-proton at 4.4–4.9 p.p.m. (multiplet); 16α-proton at 4.25 p.p.m. (multiplet); C-6 proton at 5.36 p.p.m. (broad).

Optical rotatory dispersion: $[\alpha]_{589}$ −40°, $[\alpha]_{365}$ −43°, $[\alpha]_{350}$ −88°, $[\alpha]_{325}$ +38°, $[\alpha]_{295}$ −498°, $[\alpha]_{272}$ −470°, $[\alpha]_{265}$ −470°, and $[\alpha]_{250}$ −450°.

3β-Acetoxy-16α-acetylthiopregn-5-en-20-one (XII).—The mother liquor from which the 16β-isomer XI had crystallized was concentrated and 1.5 g. of product containing the second isomer XII was obtained. Fractional crystallization from ether followed by several recrystallizations from ether gave the pure thioester, m.p. 183–185° (Kofler)[32]; λ_{max} 234 mμ (ε 5400); λ_{max}^{KBr} 5.75, 5.87, 5.97, 8.05, 8.83, 8.98, 9.67, and 10.55 μ, etc.

Anal. Calcd. for $C_{25}H_{36}O_4S$: C, 69.41; H, 8.39; S, 7.54. Found: C, 70.02; H, 8.31; S, 7.50.

Nuclear magnetic resonance spectra: C-18 methyl at 0.68 p.p.m.; C-19 methyl at 1.02 p.p.m.; 3β-acetoxyl methyl at 2.03 p.p.m.; C-21 methyl at 2.15 p.p.m.; 16α-thioacetate methyl at 2.27 p.p.m.; 17α-proton at 2.60 p.p.m. (doublet, J = 8.5 c.p.s.); 3α-proton at 4.4–4.9 p.p.m. (multiplet); 16β-proton at 4.28 p.p.m. (triplet); 6-proton at 5.37 p.p.m. (broad).

Optical rotatory dispersion: $[\alpha]_{436}$ −28.4°, $[\alpha]_{300}$ +1300°, and $[\alpha]_{250}$ −5503°.

3β,21-Diacetoxy-16α-acetylthiopregn-5-en-20-one (XIII).—To a solution of 4.0 g. of 3β,21-diacetoxypregna-5,16-dien-20-one in 200 ml. of methylene chloride was added 40 ml. of technical thioacetic acid. After 3 hr. at room temperature the solvents were removed under vacuum, and the residue was crystallized from 2-propanol, yielding 2.1 g., m.p. 196–198°. Two recrystallizations from 2-propanol afforded the pure thioester, m.p. 198–199°; $[\alpha]_D$ −29°; λ_{max} 232 mμ (ε 4700); λ_{max}^{KBr} 5.67, 5.79, 5.95, 7.30, 8.15, 8.87, and 9.65 μ, etc.; R_f 0.85 in system IIIa.

Anal. Calcd. for $C_{27}H_{38}O_5S$: C, 66.09; H, 7.81; S, 6.53. Found: C, 66.22; H, 7.70; S, 6.54.

Nuclear magnetic resonance spectra: C-18 methyl at 0.71 p.p.m.; C-19 methyl at 0.99 p.p.m.; 3β-acetoxyl methyl at 2.01 p.p.m.; 21-acetoxyl methyl at 2.15 p.p.m.; 16α-thioacetate methyl at 2.25 p.p.m.; 17α-proton at 2.59 p.p.m. (doublet, J = 8.5 c.p.s.); 16β-proton at 4.25 p.p.m. (triplet); C-21 methylene at 4.60 p.p.m. (quartet, J = 17 c.p.s.); 6-proton at 5.36 p.p.m. (doublet, J = 2 c.p.s.).

3β-Acetoxy-16α-mercapto-5β-pregnan-20-one (Vb) and 3β-Hydroxy-16α-mercapto-5β-pregnan-20-one (Va).—Hydrogen sulfide was bubbled through a solution of 3.0 g. of IVa in 75 ml. of pyridine and 0.25 ml. of piperidine held at room temperature for 22 hr. The solvents were removed under vacuum and the residue was crystallized from acetone-cyclohexane, yielding 3.35 g. of material analyzing as an approximately equal mixture of thiol Va and disulfide VI by thin layer chromatography. Chromatography on a silica gel column afforded thiol Va, eluted with 5% ethyl acetate in benzene, and disulfide VI, eluted with 10% ethyl acetate in benzene. Both Va and VI isolated from the column were identical with the completely characterized preparations obtained by oxidation and reduction of the thiol–disulfide mixture below.

The thiol–disulfide mixture was recrystallized from cyclohexane–5% acetone, 1.2 g. of the recrystallized product was dissolved in 300 ml. of refluxing glacial acetic acid, and 600 mg. of zinc dust was added in portions (under nitrogen atmosphere). After 4 hr. of reflux the mixture was cooled and filtered, and the filtrate was evaporated under vacuum. The residue was dissolved in benzene, washed with water, and dried over anhydrous magnesium sulfate. After evaporation of the benzene the residue was chromatographed on silica gel. Elution with 5% ether in benzene gave 166 mg. of thiol 3β-acetate Vb, m.p. 128–130°; λ_{max}^{KBr} 5.78, 5.87, 8.02, 8.13, and 9.79 μ, etc.; R_f 0.91 in system Ia, 0.36 in system IIIa.

Anal. Calcd. for $C_{23}H_{36}O_3S$: C, 70.36; H, 9.24; S, 8.17. Found: C, 70.16; H, 8.96; S, 8.40.

Nuclear magnetic resonance spectra: C-18 methyl at 0.60 p.p.m.; C-19 methyl at 0.96 p.p.m.; 3β-acetoxyl methyl at 2.05 p.p.m.; C-21 methyl at 2.15 p.p.m.; 17α-proton at 2.62 p.p.m.

(31) Dodson and Sollman report m.p. 168–169°, $[\alpha]_D$ −32°; see ref. 21.

(32) Dodson and Sollman report m.p. 186–187°, $[\alpha]_D$ −53.5°; see ref. 21.

(doublet, J = 9 c.p.s.); 16β-proton at 3.76 p.p.m. (multiplet); 3α-proton at 5.10 p.p.m.

Further elution of the column with 5% ether in benzene gave 120 mg. of the thiol Va, crystallized from hexane, m.p. 168–171°; λ_{max}^{KBr} 5.86, 6.91, 7.40, and 9.70 μ, etc.; R_f 0.73 in system Ia, 0.70 in system IIIa.

Anal. Calcd. for $C_{21}H_{34}O_2S$: C, 71.95; H, 9.66; S, 9.15. Found: C, 71.83; H, 9.60; S, 8.80.

Both thiols Va and Vb gave a violet-red color with sodium nitroprusside solution and decolorized a carbon tetrachloride solution of iodine.

Acetylation of Va with excess acetic anhydride in pyridine in the usual manner gave the acetoxy thioester VIIb, m.p. 154–157°, identical in infrared and chromatographic properties with VIIb prepared from IVb.

16α,16α'-Dithiobis(3β-hydroxy-5β-pregnan-20-one) (VI).—A solution of 400 mg. of the thiol–disulfide mixture (Va and VI) dissolved in 100 ml. of benzene and 50 ml. of water was treated with a solution of iodine in benzene until a slight excess of iodine was present. Aqueous sodium thiosulfate was added to destroy the excess of iodine and the organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded a gum which was crystallized from benzene–hexane, yielding 140 mg. of disulfide, m.p. 171–178°; λ_{max}^{KBr} 5.90, 6.92, 7.40, 8.12, and 9.71 μ, etc.; R_f 0.70 in system Ia, 0.18 in system IIIa.

Anal. Calcd. for $C_{42}H_{66}O_4S_2$: C, 72.16; H, 9.52; S, 9.17. Found: C, 72.27; H, 9.28; S, 9.20.

Nuclear magnetic resonance spectra: C-18 methyl at 0.60 p.p.m.; C-19 methyl at 0.95 p.p.m.; C-21 methyl at 2.18 p.p.m.; 17α-proton at 2.71 p.p.m. (doublet, J = 8 c.p.s.); 16β-proton at 3.88 p.p.m. (multiplet); 3α-proton at 4.13 p.p.m. (broad).

3β-Hydroxy-16α-mercapto-5α-pregnan-20-one (IXb).—A solution of 1.0 g. of 3β-hydroxy-5α-pregn-16-en-20-one in 25 ml. of pyridine and 0.09 ml. of piperidine was alternately flushed with nitrogen and evacuated four times. Hydrogen sulfide was bubbled through the solution at room temperature for 2.5 hr. (efficient stirring). The solvents were removed under vacuum, the solid residue was extracted with hot ethyl acetate, and the solids remaining crystallized from 2-propanol, yielding 150 mg. of pure IXb, m.p. 175–180 and 251–256° (Kofler); $[\alpha]_D$ +81.5°; λ_{max}^{KBr} 2.95 and 5.85 μ, etc.; R 0.44 in system III.

Anal. Calcd. for $C_{21}H_{34}O_2S$: C, 71.96; H, 9.66; S, 9.15. Found: C, 71.78; H, 9.92; S, 8.80.

Nuclear magnetic resonance spectra: C-18 methyl at 0.61 p.p.m.; C-19 methyl at 0.80 p.p.m.; C-21 methyl at 2.13 p.p.m.; 17α-proton at 2.58 p.p.m. (doublet, J = 9 c.p.s.); 3α- and 16β-protons at 3.6–3.9 p.p.m. (multiplets).

16α-Acetoxy-3β-hydroxy-5β-pregnan-20-one (X).—A solution of 350 mg. of 3β,16α-dihydroxy-5β-pregnan-20-one in 0.5 ml. of dry pyridine and 0.5 ml. of dry benzene was treated with 100 μl. of acetic anhydride. After standing overnight methanol was added, and the solvents were removed under vacuum. The residue obtained was crystallized from ethyl acetate–hexane, yielding 200 mg. of 16α-monoacetate X containing traces of the 3β,16α-diol by thin layer chromatography. Several recrystallizations from ethyl acetate–hexane and from hexane gave the pure sample, m.p. 86.5–92.0°, resolidifying and remelting 129.5–130.5° (Kofler); λ_{max}^{KBr} 2.93, 5.78, 5.84, 8.04, and 9.68 μ, etc.[33]; R_f 0.48 in system Ia, 0.26 in system IIIa; see also Table II.[34]

Nuclear magnetic resonance spectra: C-18 methyl at 0.65 p.p.m.; C-19 methyl at 0.97 p.p.m.; 16α-acetoxyl methyl at 2.00 p.p.m.; C-21 methyl at 2.18 p.p.m.; 17α-proton at 2.66 p.p.m. (doublet, J = 6 c.p.s.); 3α-proton at 4.15 p.p.m. (multiplet); 16β-proton at 5.50 p.p.m. (octuplet).

Optical rotatory dispersion: $[\alpha]_{600}$ +67°, $[\alpha]_{589}$ +70°, $[\alpha]_{410}$ +1720°, $[\alpha]_{264}$ −1890°, and $[\alpha]_{250}$ −1590°.

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(33) Hirschmann and Daus (see ref. 9) report m.p. 134–135.5° and a double melting point 89 and 137° for X, with $\lambda_{max}^{CS_2}$ 2.77, 5.74, 5.84, 8.06, and 9.70 μ, etc. Recrystallization of our sample showing the double melting point from ethyl acetate–cyclohexane using a seed crystal of 16α-acetoxy-3β-hydroxy-5β-pregnan-20-one, m.p. 132.5–135.0° (Kofler), kindly supplied by Dr. Hirschmann gave the second crystalline form, m.p. 130.0–131.5°, with infrared spectra identical with that of the Hirschmann sample, λ_{max}^{KBr} 2.88, 5.82, 7.94, 8.13, and 9.68 μ, etc. Chromatographic identity of the two samples was also established.

(34) The greater mobility of the 16α-monoacetate X relative to the 3β-monoacetate (3β-acetoxy-16α-hydroxy-5β-pregnan-20-one) in several solvent systems is the reverse of the order found in the 5α-series, where 16α-acetoxy-5β-hydroxy-5α-pregnan-20-one is less mobile than 5β-acetoxy-16α-hydroxy-pregnan-20-one in the Bush A and B-3 systems.[18]

Some 20-Substituted 21-Norprogesterone Derivatives

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Several new analogs of progesterone have been prepared in which the acetyl side chain has been replaced by benzoyl, *o*-anisoyl, and propiolyl groups. They were prepared by allowing the appropriate aryl- or ethinyllithium or Grignard reagent to react with corticosterone or deoxycorticosterone and subsequently cleaving the 20,21-diol with periodic acid to give the corresponding 20-ketone. The 20-(*p*-anisyl)-20,21-diol underwent a facile pinacol rearrangement under mildly acidic conditions to give a 20-(*p*-anisyl)-21-aldehyde derivative.

The lengthening of the acetyl side chain of 20-ketopregnane steroids has been accomplished by the synthesis of several types of derivatives. Among these are the 21-alkyl,[1] 21-methylene,[2] 21-cyano,[3] 21-acyl,[4] 21-benzilidene,[5] and 21-ethoxyoxalyl[6] derivatives. Two groups of investigators have introduced a 20-(α-pyridyl) group[7,8] which in one case[8] afforded a 17β-picolinoylandrostane derivative by oxidative removal of the 21-methyl group. However, there have been no reports in the literature of 20-phenyl-21-nor-20-ketopregnanes (17β-benzoylandrostanes), and it seemed

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