EXPERIMENTAL[9]

To 12.6 g. (0.1 mole) of 2-acetylthiophene in 10 ml. of acetic acid at 90–100°, 13 ml. of 69% nitric acid (*d*, 1.42) in 10 ml. of glacial acetic acid was added in one portion with stirring. Immediately a small amount of sodium nitrate was added. Stirring was continued for several minutes until the exothermic reaction subsided. Dilution with 200 ml. of water caused separation of a yellow oil which solidified. The solid was washed with aqueous sodium carbonate and dried in a vacuum desiccator, wt. 12.3 g. (0.04 mole, 80%). The solid was recrystallized from methanol, m.p. 114–115°. Infrared absorption ($cm.^{-1}$) for di(2-thenoyl)furoxan was obtained from a potassium bromide pellet, 1635S, 1605S 1510M, 1475M, 1410S, 1335M, 1250M, 1050M, 1020W, 890W, 835M, 775M, 755M, 675M. Ultraviolet absorption in ethanol was 282 mμ.

Anal. Calcd. for $C_{12}H_6N_2O_4S_2$ (mol. wt. 306): C, 47.05; H, 1.96; N, 9.15; S, 20.91. Found: C, 47.15; H, 2.24; N, 8.87; S, 21.23; Mol. wt., 319.

Alkaline hydrolysis. A suspension of 0.5 g. (0.0016 mole) of di(2-thenoyl)furoxan in 10 ml. of 10% sodium hydroxide was heated to boiling for 10 min. and then allowed to cool. On acidification with acid and extraction with ether, 0.4 g. (0.0031 mole, 96% based on 1 mole of furoxan to 2 moles of acid) of 2-thiophenecarboxylic acid, m.p. 128°, was obtained.

Anal. Calcd. for $C_5H_4SO_2$: C, 46.87; H, 3.12; S, 25.00. Found: C, 47.15; H, 3.31; S, 25.22.

Reaction of di(2-thenoyl)furoxan with phenylhydrazine. One gram (0.0209 mole) of the furoxan was suspended in 5 ml. of phenylhydrazine in a small flask and shaken until an exothermic reaction began. This was noted by the evolution of a gas. The flask was allowed to cool slowly to room temperature. The reaction mixture was then poured into a large volume of water. After decanting the water layer, the residue was fractionally crystallized from ethanol to yield two fractions, 0.50 g. (0.001 mole, 81%) which melted at 175–176° and 0.3 g. (0.0013 mole, 62%) which melted at 180–181°.

The material melting at 175–176° was yellow and appeared to be 3-(β-phenylhydrazino-4-nitroso-5-thienylisoxazole (III) which would be analogous to the product obtained by Quist[7] from the reaction of dibenzoylfuroxan with phenylhydrazine.

Anal. Calcd. for $C_{13}H_{10}N_4O_2S$: C, 54.54; H, 3.49; N, 19.58; S, 11.18. Found: C, 54.78; H, 3.09; N, 19.29; S, 11.19.

The material melting at 180–181° was white and appeared to be 1-thenoyl-2-phenylhydrazine (II) which would be analogous to a second product Quist[7] isolated from the reaction of dibenzoylfuroxan with phenylhydrazine.

Anal. Calcd. for $C_{11}H_{10}N_2OS$: C, 60.55; H, 4.58; N, 12.84; S, 14.67. Found: C, 60.65; H, 4.58; N, 12.76.

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(9) Melting points are uncorrected.

Nucleophilic Substitution of 9α-Bromo-11-ketoprogesterone

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The recent publication by Cox[1] on the nucleophilic substitution of 9α-bromo-11-keto steroids in the 5α- and 5β-pregnane series prompts us to report our results with a similar reaction on 9α-bromo-11-ketoprogesterone[2] (I). Reaction of I with sodium methoxide in methanol under the conditions of the Favorskii rearrangement[3] furnished a product II in 30% yield which was bromine-free, gave correct analyses for $C_{22}H_{30}O_4$ and contained one methoxyl group. In order to differentiate between the expected Favorskii rearrangement product—*i.e.*, a 9α- or 11α-carbomethoxylated C-nor compound and an unrearranged methoxy derivative formed by displacement of bromine by methoxyl II was reduced with lithium aluminum hydride. Acetylation of the product afforded a crystalline product III which gave an analysis corresponding to $C_{26}H_{40}O_6$, and which had retained the methoxyl group. Thus, displacement of the bromine by methoxyl must have occurred. From the results of Cox[1] it would seem likely that the methoxyl occupied the 12α-position. Indeed, comparison of the proton magnetic resonance spectra[4] of I and 11-ketoprogesterone provided convincing support for this assumption. The peaks which are ascribed[5] to the two protons at position 12 in 11-ketoprogesterone (τ = 7.41 and 7.45) had disappeared in the spectrum of I and been replaced by two new bands, one (area three protons) at 6.65 τ corresponding to the three protons of the methoxyl group and one (area one proton) at 6.56 τ representing the 12β-proton, which had been shifted to lower field because of its attachment to C-12 carrying a methoxyl, as well as being α to the C-11 carbonyl.

In order to confirm that I was 12α-methoxy-11-ketoprogesterone, 11β,12β-oxidoprogesterone[6] (IV) was treated with methanol and perchloric acid[7] to give 12α-methoxy-11β-hydroxyprogesterone[8] (V), which was oxidized with chromic acid[9] to give

(1) J. S. G. Cox, *J. Chem. Soc.*, 4508 (1960).

(2) J. Fried, J. E. Herz, E. F. Sabo, A. Borman, F. Singer, and P. Numerof, *J. Am. Chem. Soc.*, **77**, 1068 (1955).

(3) For a general review of the Favorskii rearrangement see A. S. Kende, *Org. Reactions*, Vol. XI, 216–316 (1960).

(4) The proton magnetic resonance spectra were taken in deuterochloroform with tetramethylsilane as an internal standard using a Varian Model A-60 instrument.

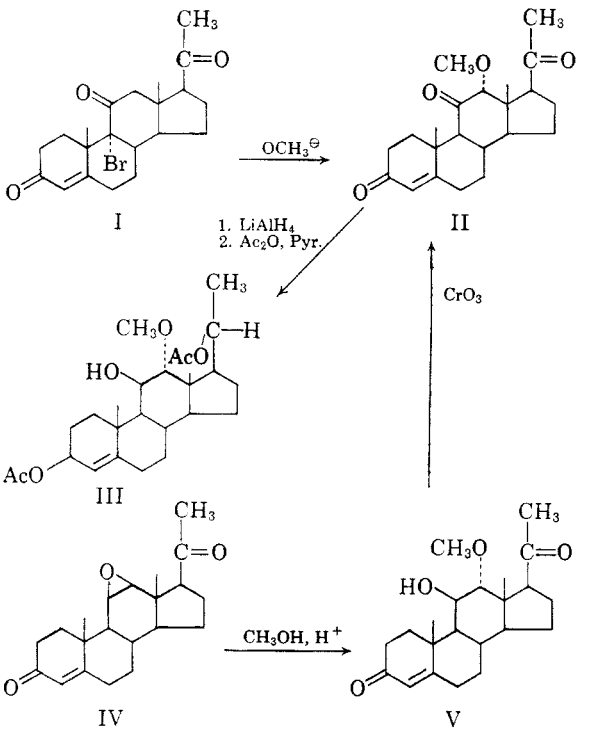
(5) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958). The NMR spectra of 11-ketoprogesterone cited in this reference were obtained using the 40 megacycles/sec. Varian Associates V-4300-B instrument and shows one peak at 152 cps. for the 12-protons. Using the 60 megacycles/sec. Varian Associates A-60 model however, this band has been split into two distinct bands showing the unequivalence of the 12α-proton (axial) and 12β-proton (equatorial).

(6) J. E. Herz, J. Fried, and E. F. Sabo, *J. Am. Chem. Soc.*, **78**, 2017 (1956).

(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(8) The opening of 11β,12β-oxides by nucleophilic reagents of the type HX has been shown to lead to the *trans* diaxial (11β-OH, 12α-X) configuration, cf. J. Schmidlin and A. Wettstein, *Helv. Chim. Acta.*, **36**, 1241 (1953); J. W. Cornforth, J. M. Osbond, and G. H. Phillips, *J. Chem. Soc.*, 907 (1954) and D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **79**, 452 (1957).

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39**, (1946).



12α-methoxy-11-ketoprogesterone identical with the product of the reaction of I with methoxyl ion. The lithium aluminum reduction product III must then be 12α-methoxy-Δ⁴-pregnene-3β,11β,20β-triol 3,20-diacetate.[10]

EXPERIMENTAL[11]

12α-Methoxy-11-ketoprogesterone (II). (a) *Via 9α-bromo-11 ketoprogesterone* (I). To a stirred suspension of 10 g. of 9α-bromo-11-ketoprogesterone in 300 ml. of methanol which had been flushed with nitrogen, 25 ml. of 2*N* sodium methoxide in methanol was added, and the mixture stirred under nitrogen at room temperature for 2.5 hr. during which time the steroid dissolved. The solution was then neutralized with 10% acetic acid, diluted with 500 ml. of water and extracted three times with 200-ml. portions of chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. The residue (9.4 g.) was dissolved in 60 ml. of benzene diluted with 120 ml. of hexane and adsorbed onto 200 g. of Woelm neutral alumina. Elution with benzene-hexane (3:1) or benzene gave a residue on evaporation of the solvent which on crystallization from acetone-hexane gave 3.2 g. of 12α-methoxy-11-ketoprogesterone having a m.p. of 121–122°; $[\alpha]_D^{23}$ +281° (chloroform); λ_{max}^{alc} 235 mμ (ε 19,200); λ_{max}^{Nujol} 2.99, 5.82, 6.02, 6.18, and 6.26 μ.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3, 8.65. Found: C, 73.40; H, 8.30; OCH_3, 8.76.

(b) *Via 12α-methoxy-11β-hydroxyprogesterone* (V). To a solution of 100 mg. of 12α-methoxy-11β-hydroxyprogesterone in 4 ml. of reagent grade acetone, 0.13 ml. of an aqueous solution containing 20.0 g. of chromic anhydride and 32.0 g. sulfuric acid per 100 ml. was added dropwise. After stirring at room temperature for 15 min. the excess chromic acid was decomposed by adding a few drops of methanol. The mixture was filtered and washed with acetone. The filtrate was then diluted with 10 ml. of water and extracted with three 5-ml. portions of chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Crystallization from acetone-hexane gave 70 mg. of 12α-methoxy-11-ketoprogesterone (II).

12α-methoxy-Δ⁴-pregnene-3β,11β,20α-triol 3,20-diacetate (III). To a solution of 200 mg. of 12α-methoxy-11-ketoprogesterone in 10 ml. of dry tetrahydrofuran 104 mg. of lithium aluminum hydride was added and the mixture stirred at room temperature for 3 hr. The excess lithium aluminum hydride was decomposed by adding a few drops of ethyl acetate; then 20 ml. each of water and chloroform was added and the mixture acidified with dilute hydrochloric acid. The chloroform was separated, washed with water until neutral and evaporated to dryness *in vacuo*. The residue was dissolved in 3 ml. of dry pyridine and 1 ml. of acetic anhydride was added. After 16 hr. at room temperature ice water was added and the mixture was extracted with chloroform. The chloroform was washed successively with 2*N* hydrochloric acid, 5% sodium bicarbonate, and water and then evaporated to dryness, *in vacuo*. Crystallization of the residue from acetone-hexane gave 100 mg. of 12α-methoxy-Δ⁴-pregnene-3β,-11β,20α-triol 3,20-diacetate having a m.p. of 200–202°; λ_{max}^{Nujol} 2.83, 5.79, 5.86, 6.03 μ.

Anal. Calcd. for $C_{26}H_{40}O_6$ (448.58): C, 69.61; H, 8.99; OCH_3, 6.92. Found: C, 69.16; H, 8.70; OCH_3, 7.32.

12α-Methoxy-11β-hydroxyprogesterone (V). To a suspension of 200 mg. of 11β,12β-oxidoprogesterone in 5 ml. of methanol, 0.1 ml. of 70% perchloric acid was added and the mixture stirred at room temperature for 5 hr. during which time the steroid dissolved. After neutralization with 5% sodium bicarbonate and slow addition of 5 ml. of water, crystals separated. These were filtered, washed with water, and dried to give 172 mg. of 12α-methoxy-11β-hydroxyprogesterone (IV) having a m.p. of 164–165°; $[\alpha]_D^{23}$ + 210° (chloroform); λ_{max}^{alc} 242 mμ (ε 16400); λ_{max}^{Nujol} 2.74, 2.92, 5.88, 6.04, 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; OCH_3, 8.60. Found: C, 73.30; H, 8.88; OCH_3, 8.92.

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(10) The assignment of the 20β-configuration to compound III is based on analogy with the work of others [E. P. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 6111 (1954); **76**, 6113 (1954), E. P. Oliveto and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 488 (1953); O. Mancera, H. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953)] who observed that reduction of 20-ketones by lithium borohydride or sodium borohydride led predominantly to the 20β-isomer.

(11) All melting points were taken in an open capillary and are uncorrected. Ultraviolet spectra were obtained in absolute ethanol.

Sulfur Substitution Compounds of Amino Sugars. IV.[1] Derivatives of 6-Thio-D-glucosamine

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Since completion of our syntheses in the 1-thio-D-glucosamine series,[2,3] we have attempted

(1) Part III, W. Meyer zu Reckendorf and W. A. Bonner, *Proc. Chem. Soc. (London), in press.*