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21-Derivatives of Compound S, Cortisone and Hydrocortisone

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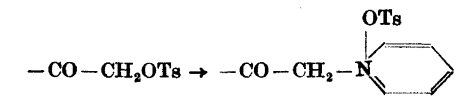
Treatment of compound S, cortisone and hydrocortisone with tosyl chloride and pyridine at low temperature (+ 2° and − 18°) affords the corresponding 21-tosylates. By means of tosyl anhydride and pyridine the 21-tosylate of compound S and cortisone have been prepared at higher temperature (*e. g.* room temperature). Cortisone tosylate has been prepared at room temperature by treatment with tosyl chloride and NaOH-solution. By reaction with salts of halide acids (NaI, NaBr, $CaCl_2$ and NH_4Cl) the corresponding halogen compounds have been prepared from the 21-tosylates. Treatment of the 21-iodo compounds with KCN affords the 21-cyano compounds. From the 21-tosylates and the 21-iodo compounds the 21-thiocyanates and the 21-thiolacetates have been prepared by reaction with KSCN and potassium thiolacetate, respectively.

For the purpose of investigating the biological effect of steroids of the cortisone (II) and hydrocortisone (III) type in which the primary hydroxyl group in the 21-position has been replaced by other groups, in particular groups containing S or N atoms, it would be desirable from II or III to prepare the corresponding steroids in which a halogen atom has been substituted for the hydroxyl group in the 21-position.

One of the generally known methods of substituting a halogen atom for a primary OH group is to prepare the *p*-toluenesulphonic acid ester (the tosylate) and subsequently treat the tosylate with a salt of a halide acid [1].

The attempts hitherto made to obtain the tosylate in the 21-position in pure condition and in good yield by treating steroids with the side chain —CO—CH_2OH with tosyl chloride in the presence of pyridine have not succeeded.

Reichstein and Schindler [2] recommend the preparation of such tosylates from the corresponding diazo-ketone, —$COCHN_2$, by treatment with anhydrous *p*-toluenesulphonic acid, as the tosylate formed primarily through the interaction of the 21-OH group with tosyl chloride in pyridine will readily react with pyridine to form the pyridinium salt:



Reichstein and Fuchs[3] have treated desoxycorticosterone and corticosterone in pyridine/chloroform solution with tosyl chloride at room temperature and have obtained a mixture of tosylate and 21-chloro compound and a small amount of pyridinium compound. A considerable excess of pyridine was avoided so that only a small amount of pyridinium compound was formed, but the tosylate formed primarily will react to some extent with pyridine hydrochloride to form the 21-chloro compound:

$$—CO—CH_2OTs \rightarrow —CO—CH_2Cl$$

Djerassi and Nussbaum[4] have treated compound S (I) and cortisone, respectively, in pyridine/chloroform solution at 0° C with tosyl chloride allowing the solution to stand at room temperature for 14 and 17 hours. From compound S a yield of 45 % of a substance which consists chiefly of the 21-chloro compound is obtained. From cortisone a yield of 65 % is obtained of a substance which probably contains pyridinium salt, 21-chloro compound, and tosylate.

Leanza and coworkers[5] have treated cortisone in pure pyridine solution with tosyl chloride heating gently for a few minutes and then allowing the solution to stand overnight at room temperature. In one case they have obtained 78.5 % 21-pyridinium chloride and in another 56 % 21-pyridinium tosylate. In a third case the cortisone solution was cooled to 15° C, tosyl chloride was added, the mixture was kept at a temperature of 10—15° C for one hour and allowed to stand overnight at room temperature. This resulted in a yield of 46 % of 21-chloro compound.

If the side reactions are taken to be the result of reactions between the tosylate formed primarily and the other components in the solution, tosylation must be assumed to be a reaction which takes place very readily. None of the authors mentioned apply temperatures below 0° C, and the possibility therefore existed that at very low temperatures tosylation would occur while the side reactions would take place less readily.

It proved possible to prepare the 21-tosylates of compound S (IV), cortisone (V), and hydrocortisone (VI) in pure condition and in good yields (in the case of cortisone tosylate (V) the yield was, *e. g.*, 73 %) by dissolving the steroid in pure, dry pyridine, cooling the solution in dry ice-acetone, adding tosyl chloride dissolved in dry methylene chloride and cooled to such an extent that the tosyl chloride just remained in solution, allowing the mixture to stand in dry ice-acetone for about two hours while occasionally shaking the flask, and finally setting aside the solution for 16—17 hours at +2° C and —18° C, respectively.

The preparation of cortisone tosylate (V) requires cooling to a lower temperature than does the preparation of compound S tosylate (IV). If the same temperature is used as in the preparation of compound S tosylate (IV), a substance is formed which has a melting point of 230—232° C and contains 7.1 % chlorine. As the Lassaigne test for N is negative (*i. e.* it is not a pyridinium compound), the substance must be assumed to consist of about 75 % 21-chloro compound (the theoretical content of chlorine in the 21-chloro compound is 9.36 %).

To eliminate this formation of 21-chloro compound completely it was tried to use *p*-toluenesulphonic acid anhydride (tosyl anhydride) [6] instead of tosyl chloride. Compound S tosylate (IV) was prepared by means of tosyl anhydride in pyridine and methylene chloride at low temperature, room temperature and with refluxing. The yields obtained at low temperature and at room temperature were the same, although somewhat lower than those obtained by the tosyl chloride method. When refluxing, the yields obtained were very low, as the formation of pyridinium salt is of course facilitated in this case, but in spite of this it is possible to isolate the tosylate in pure condition. As regards the preparation of cortisone tosylate (V) the same conditions apply when using tosyl anhydride as when using tosyl chloride. Already at room temperature the yield is low, the formation of side products occurring more readily than in the case of the compound S tosylate (IV) preparation.

To eliminate the formation of pyridinium salts and 21-chloro compound an attempt was made to replace pyridine with aqueous NaOH solution; cortisone tosylate (V) was obtained in good yield at a temperature of 25° C when using dioxan as the solvent, adding tosyl chloride and adding NaOH solution dropwise.

The tosylates tend to crystallize with 1 mole methanol, benzene, or ethanol which cannot be removed readily by drying. In case of cortisone tosylate (V) the benzene does not disappear when subjected to vacuum drying (about 10^{-1} mm) at room temperature for 20 hours. For this reason the melting points are often somewhat indefinite, and the melting is accompanied by vesiculation.

By means of NaI in acetone the corresponding 21-iodo compounds Δ^4-21-iodopregnene-3,20-dione-17α-ol (VII), Δ^4-21-iodopregnene-3,11,20-trione-17α-ol (VIII), and Δ^4-21-iodopregnene-3,20-dione-11β,17α-diol (IX) were prepared from compound S tosylate (IV), cortisone tosylate (V), and hydrocortisone tosylate (VI). These iodo compounds are white crystalline substances, which are fairly stable. After storage for about one month without exposure to light they tend to turn dark.

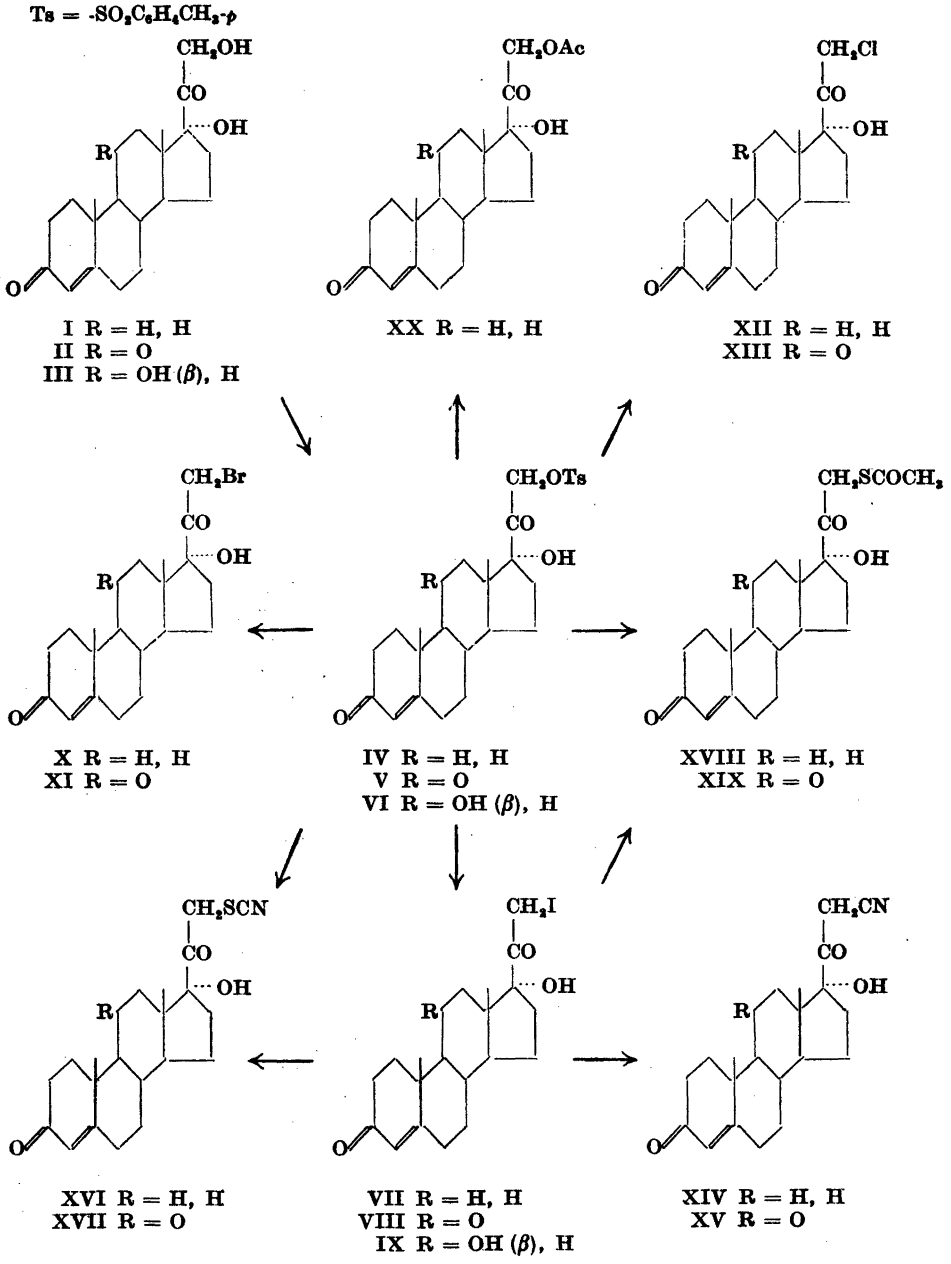
By the action of NaBr in methanol the 21-bromo compounds Δ^4-21-bromopregnene-3,20-dione-17α-ol (X) and Δ^4-21-bromopregnene-3,11,20-trione-17α-ol (XI) were prepared from IV and V.

According to Reichstein and Schindler [2] NaCl cannot be used for the preparation of 21-chloro compounds from tosylates on account of too low solubility in acetone and methanol, for which reason these authors use tetramethylammonium chloride.

Since $CaCl_2$ and NH_4Cl are soluble in ethanol, these substances were used for the preparation of the 21-chloro compounds Δ^4-21-chloropregnene-3,20-dione-17α-ol (XII) and Δ^4-21-chloropregnene-3,11,20-trione-17α-ol (XIII) from compound S tosylate (IV) and cortisone tosylate (V).

From the 21-iodo compounds (VII) and (VIII) the 21-cyano compounds, Δ^4-21-cyanopregnene-3,20-dione-17α-ol (XIV) and Δ^4-21-cyanopregnene-3,11,20-trione-17α-ol (XV), were prepared by means of KCN in methanol. By means of KSCN in acetone the 21-thiocyano compounds, Δ^4-21-thiocyanopregnene-3,20-dione-17α-ol (XVI) and Δ^4-21-thiocyanopregnene-3,11,20-trione-17α-ol (XVII), were prepared. XVII was also prepared from cortisone tosylate (V) by reaction with KSCN in acetone.

For the identification of the 21-halogen compounds and the 21-tosylates, the thiolacetates, compound S-thiolacetate (Δ^4-pregnene-3,20-dione-17α-ol-21-thiol-21-acetate, XVIII) and cortisone thiolacetate (Δ^4-pregnene-3,11,20-



trione-17α-ol-21-thiol-21-acetate, XIX) were prepared by reaction with potassium thiolacetate in acetone from the corresponding iodides and tosylates. The substances proved to be identical with the substances prepared by Djerassi and Nussbaum [4]. Finally compound S acetate (XX) was obtained from compound S tosylate (IV) by reaction with potassium acetate in acetone.

EXPERIMENTAL

Microanalyses by G. Cornali. All melting points are uncorrected.

Δ^4-pregnene-3,20-dione-17α,21-diol-21-tosylate (IV)

A. *With tosyl chloride and pyridine at low temperature.* A solution of 1.0 g (0.00289 mole) of compound S (I) in 10 ml of dry pyridine was placed in a bath of dry ice and acetone. 600 mg (0.00315 mole) of tosyl chloride (which had been dried by solution in a little benzene and subsequent evaporation of the benzene) was dissolved in 6 ml of dry methylene chloride, and the solution was cooled to such an extent that the tosyl chloride just remained in solution. This solution was poured rapidly into the solidified solution of I. By removing the flask at intervals from the bath and rotating the flask a clear solution was obtained. This solution was allowed to stand in the bath for 2 hours and subsequently at +2° C for 18 hours. The solution was now diluted with ether and washed twice with water, three times with dilute hydrochloric acid, four times with dilute sodium carbonate solution and twice with water. After drying over sodium sulphate the solution was evaporated to dryness. The residue was dissolved in 5 ml of methanol. This solution was filtered and allowed to stand. The crystals which separated were collected and air-dried to yield 1.0 g (69.2 %) with m. p. 159–160° C. (Found: C 66.95; H 7.34; S 6.34. Calc. for $C_{28}H_{36}O_6S$: C 67.17; H 7.25; S 6.40.) In some cases the m. p. was found to be 97–98° C with vesiculation. (Found: C 65.42; H 7.50; S 6.30. Calc. for $C_{28}H_{36}O_6S$, 1 mole CH_3OH: C 65.38; H 7.57; S 6.02.) Following recrystallization from 96 % ethanol the substance with m. p. 159–160° C melted at 160–161° C. (Found: C 65.20; H 7.72; S 5.81. Calc. for $C_{28}H_{36}O_6S$, 1 mole C_2H_5OH: C 65.90; H 7.75; S 5.86.)

B. *With tosyl anhydride and pyridine at low temperature.* Compound S (1 g) was treated as described under A with the exception that a cooled suspension of 1.1 g (0.00337 mole) of tosyl anhydride in 30 ml of dry methylene chloride was added. The solution was allowed to stand for 18 hours at +2° C and subsequently treated as described under A. The yield was 600 mg (41.5 %) of IV.

C. *With tosyl anhydride and pyridine at room temperature.* To a solution of 1 g of compound S in 10 ml of dry pyridine was added a suspension of 1.1 g of tosyl anhydride in dry methylene chloride. The resulting clear solution was allowed to stand at room temperature for 18 hours and subsequently treated as described under A. The yield was 600 mg (41.5 %) of IV.

D. *With tosyl anhydride and pyridine under reflux.* To a solution of 1 g of compound S in 10 ml of dry pyridine was added a suspension of 1.1 g of tosyl anhydride in 30 ml of dry methylene chloride. The solution was refluxed for 2.5 hours and cooled to room temperature, ether was added, and the treatment proceeded as described under A. The yield was 250 mg (17.3 %) of IV.

Δ^4-pregnene-3,11,20-trione-17α,21-diol-21-tosylate (V)

A. *With tosyl chloride and pyridine at low temperature.* Cortisone (II) (1 g; 0.00277 mole) was treated as described in the case of IV A with the exception that the mixture was allowed to stand for 18 hours at a temperature of −18° C. When the ether had been evaporated, the residue was dissolved in 5 ml of benzene and set aside for a short time. The crystals which formed were collected and air-dried to yield 1.2 g (73.0 %). M. p. 108–109° C with vesiculation. (Found: C 68.87; H 6.89; S 5.37. Calc. for $C_{28}H_{34}O_7S$, 1 mole C_6H_6: C 68.89; H 6.80; S 5.41.) A small sample was dissolved in methanol, the solution was filtered and set aside for a short time. The crystals which formed were collected. M. p. 141–143° C (sinters at about 100° C). (Found: C 64.27; H 7.00; S 5.86. Calc. for $C_{28}H_{34}O_7S$, 1 mole CH_3OH: C 63.71; H 7.01; S 5.86.)

In all calculations in which this substance occurs the molecular weight of cortisone tosylate has been taken to be 592.72 corresponding to $C_{28}H_{34}O_7S$, 1 mole C_6H_6.

B. *With tosyl anhydride and pyridine at room temperature.* Cortisone (1 g) was treated as described in the case of IV C. The residue obtained following the removal of the ether was dissolved in benzene, the crystals formed were collected and air-dried to yield 250 mg (15.2 %) of V.

C. *With tosyl chloride and NaOH solution (Schotten-Baumann).* To a solution of 1 g (0.00277 mole) of cortisone in 30 ml of dioxan was added 300 mg (0.00158 mole) of tosyl chloride. 10 ml (0.00158 mole) of aqueous NaOH solution (6.3 g—1 000 ml) was then added dropwise while stirring in the course of 30 min. Another 300 mg of tosyl chloride was now added followed by 10 ml of the abovementioned NaOH solution in the course of 3/4 hour. Ether was added, and the mixture was washed four times with dilute sodium carbonate solution and three times with water. After drying over sodium sulphate and filtration the solution was evaporated to dryness. The residue was dissolved in a little benzene and set aside for a short time. The crystals which formed were collected and air-dried to yield 800 mg (48.6 %) of V.

Δ^4-pregnene-3,20-dione-11β,17α,21-triol-21-tosylate (VI)

Compound F (III) (1 g; 0.00276 mole) was treated as described in the case of V A. The residue obtained after the evaporation of the ether crystallized by the addition of methanol. The solid was collected, washed with methanol and air-dried to yield 800 mg (52.8 %). M. p. 119—121° C with vesiculation. (Found: C 63.37; H 7.20; S 5.67. Calc. for $C_{28}H_{36}O_7S$, 1 mole CH_3OH: C 63.48; H 7.35; S 5.84.)

Δ^4-21-iodopregnene-3,20-dione-17α-ol (VII)

To a solution of 1 g (0.0020 mole) of IV in 5 ml of acetone was added a solution of 1 g (0.0067 mole) of sodium iodide in 7 ml of acetone. In the course of a few minutes separation of sodium tosylate started. The mixture was refluxed for 7—8 minutes, most of the acetone was distilled off, and the solution was cooled to room temperature. On the addition of dilute sodium thiosulphate solution and water a white precipitate was formed. This precipitate was collected, washed thoroughly with water and air-dried to yield 870 mg (95.4 %) of analytically pure VII. M. p. 135—136° C dec. (the substance turns dark at about 125° C). (Found: C 55.06; H 6.59; I 27.70. Calc. for $C_{21}H_{29}IO_3$: C 55.26; H 6.41; I 27.81.)

Δ^4-21-iodopregnene-3,11,20-trione-17α-ol (VIII)

Cortisone tosylate (V) (1 g; 0.0017 mole) was treated as described in the case of VII. The substance obtained was dried to yield 780 mg (98.3 %) of VIII, decomposition of which starts at about 140° C. Following recrystallization from dioxan of a small sample, it was found to have m. p. 155—156° C dec. (Found: C 53.71; H 5.99; I 26.79. Calc. for $C_{21}H_{27}IO_4$: C 53.62; H 5.79; I 26.98.)

Δ^4-21-iodopregnene-3,20-dione-11β,17α-diol (IX)

Compound F tosylate (VI) (1 g; 0.0018 mole) was treated as described in the case of VII. The substance obtained was dried to yield 750 mg (87.1 %) of IX. M. p. 148—149° C dec. (Found: C 53.57; H 6.30; I 26.60. Calc. for $C_{21}H_{29}IO_4$: C 53.39; H 6.19; I 26.87.)

Δ^4-21-bromopregnene-3,20-dione-17α-ol (X)

A solution of 0.5 g (0.0010 mole) of IV in 5 ml of dry methanol was prepared by heating on a steam bath, and a solution of 350 mg (0.0034 mole) of NaBr in 10 ml of dry methanol was added. The resulting solution was refluxed for 3 hours. Half of the methanol added was distilled off and the residue cooled in running water. The precipitate which formed was collected, washed thoroughly with water and dried to yield 300 mg (73.4 %) of X. M. p. 223—224° C dec. (Found: C 61.73; H 7.25; Br 19.55. Calc. for $C_{21}H_{29}BrO_3$: C 61.61; H 7.14; Br 19.52.)

Δ^4-21-bromopregnene-3,11,20-trione-17α-ol (XI)

Cortisone tosylate (V) (0.5 g; 0.0008 mole) was treated as described in the case of X. The 21-bromo compound started to crystallize during the boiling. After refluxing for three hours and cooling in running water, the solid was collected, washed thoroughly with water and dried to yield 300 mg (85.0 %) of XI with m. p. 249—250° dec.*. (Found: C 59.54; H 6.58; Br 18.75. Calc. for $C_{21}H_{27}BrO_4$: C 59.57; H 6.43; Br 18.88.)

Δ^4-21-chloropregnene-3,20-dione-17α-ol (XII)

To a solution of 0.5 g (0.0010 mole) of IV in 25 ml of dry ethanol was added a filtered solution of 1 g (0.0090 mole) of dried $CaCl_2$ in 25 ml of dry ethanol. The solution was refluxed for 5 hours. Most of the ethanol was distilled off and water was added. The precipitate was collected, washed with water and dried to yield 350 mg (96.0 %) of XII. M. p. 234—235° C dec. (Found: C 68.90; H 7.88; Cl 9.59. Calc. for $C_{21}H_{29}ClO_3$: C 69.12; H 8.01; Cl 9.72.)

Δ^4-21-chloropregnene-3,11,20-trione-17α-ol (XIII)

Cortisone tosylate (V) (0.5 g; 0.0008 mole) was treated as described in the case of XII. The precipitate was collected, washed with water and air-dried to yield 300 mg (93.9 %) of analytically pure XIII. M. p. 282—284° C dec.**. (Found: C 66.48; H 7.45; Cl 9.40. Calc. for $C_{21}H_{27}ClO_4$: C 66.57; H 7.18; Cl 9.36.)

To a solution of 0.5 g (0.0093 mole) of NH_4Cl in 150 ml of dry ethanol prepared by heating was added 0.5 g of V and the solution was refluxed for 5 hours. Most of the ethanol was distilled off and water was added. The precipitate was collected, washed with water, dried and recrystallized from 99 % C_2H_5OH to yield 275 mg (86.0 %) of XIII. M. p. 282—284° C dec. Identity with a sample prepared with $CaCl_2$ was established by a mixed melting point.

Δ^4-21-cyanopregnene-3,20-dione-17α-ol (XIV)

To a solution of 0.5 g (0.0011 mole) of VII in 70 ml of methanol was added 0.5 g (0.0077 mole) of KCN. The solution was refluxed for 10 min. and most of the methanol was then distilled off in vacuum. Water was added and the precipitate collected, washed with water and dried to yield 300 mg of a crude product, m. p. 210—225° C. After recrystallization from methanol the yield was 150 mg (38.5 %), m. p. 249—251° C. (Found: C 74.13; H 8.45; N 3.90. Calc. for $C_{22}H_{29}NO_3$: C 74.33; H 8.22; N 3.94.)

Δ^4-21-cyanopregnene-3,11,20-trione-17α-ol (XV)

To a solution of 0.5 g (0.0011 mole) of VIII in 80 ml of methanol was added 200 mg (0.0031 mole) of KCN dissolved in 4 ml of water. The solution was refluxed for 10 min. Most of the methanol was then distilled off in vacuum and a solution of sodium chloride was added. The precipitate was collected, washed with water and dried to yield 175 mg of a crude product with m. p. 210—220° C. Recrystallization from 96 % C_2H_5OH yielded 75 mg (19.1 %) with m. p. 236—237° C. (Found: C 71.53; H 7.63; N 3.82. Calc. for $C_{22}H_{27}NO_4$: C 71.52; H 7.37; N 3.79.)

Δ^4-21-thiocyanopregnene-3,20-dione-17α-ol (XVI)

To a solution of 0.5 g (0.0011 mole) of VII in 40 ml of dry acetone was added 0.5 g (0.0052 mole) of dried KSCN (benzene was poured over KSCN and then distilled off). The solution was refluxed for 3.5 hours and most of the acetone subsequently distilled off. Water was added, and the precipitate collected, washed with water and dried to yield 400 mg (94.2 %) of XVI with m. p. 188—189° C. Recrystallization from methanol did not raise the melting point. (Found: C 68.14; H 8.00; S 8.17; N 3.55. Calc. for $C_{22}H_{29}NO_3S$: C 68.18; H 7.54; S 8.27; N 3.62.)

* Velluz, L., Warnandt, J., Nominé, G., Joly, R. and Petit, A. *(Bull. soc. chim. France* (5) **20** (1953) 906) found m. p. 297—300° C.

** J. Leanza and coworkers [5] found m. p. 243—245° C dec.

Δ^4-21-thiocyanopregnene-3,11,20-trione-17α-ol (XVII)

The 21-iodo compound (VIII) (0.5 g; 0.0011 mole) was treated as described in the case of XVI. The yield obtained was 420 mg (98.4 %) of XVII with m. p. 193—194° C. Recrystallization from benzene did not raise the melting point. (Found: C 66.05; H 6.86; N 3.46; S 7.98. Calc. for $C_{23}H_{27}NO_4S$: C 65.81; H 6.78; N 3.49; S 7.98.)

To a solution of 0.5 g (0.0008 mole) of V in 40 ml of dry acetone was added 0.5 g of dried KSCN. The solution was refluxed for 3.5 hours and most of the acetone was subsequently distilled off. Water was added and the precipitate collected, washed with water and dried to yield 300 mg (88.6 %) of XVII with m. p. 192—193° C. The melting point was not depressed on admixture with the substance prepared from VIII.

Δ^4-pregnene-3,20-dione-17α-ol-21-thiol-21-acetate (XVIII)

To a solution of 1 g (0.0022 mole) of VII in 50 ml of dry acetone was added 650 mg (0.0057 mole) of potassium thiolacetate, and the mixture was refluxed for 2.5 hours and most of the acetone was subsequently distilled off. Water was added and the precipitate collected, washed with water and dried to yield 750 mg (84.6 %) of XVIII with m. p. 214—217° C. Recrystallization from 99% ethanol raised the m. p. to 219—222° C. (Found: C 68.22; H 7.88; S 7.72. Calc. for $C_{23}H_{32}O_4S$: C 68.28; H 7.97; S 7.93.)

Δ^4-pregnene-3,11,20-trione-17α-ol-21-thiol-21-acetate (XIX)

To a solution of 1 g (0.0021 mole) of VIII in 50 ml of dry acetone was added 650 mg of potassium thiolacetate, and the mixture was refluxed for 2.5 hours. Most of the acetone was then distilled off, and after addition of water the precipitate was collected, washed with water and dried to yield 650 mg (73.0 %) analytically pure XIX with m. p. 224—226° C. Recrystallization from methanol did not raise the melting point. (Found: C 65.83; H 7.30; S 7.36. Calc. for $C_{23}H_{30}O_5S$: C 66.00; H 7.23; S 7.66.)

To a solution of 1 g (0.0017 mole) of V in 50 ml of dry acetone was added 600 mg of potassium thiolacetate, and the mixture was refluxed for 2.5 hours. Most of the acetone was then distilled off, and after addition of water the precipitate was collected, washed with water and dried to yield 500 mg (70.8 %) of XIX with m. p. 224—226° C. Identity with a sample prepared from VIII was established by a mixed melting point.

Δ^4-pregnene-3,20-dione-17α,21-diol-21-acetate (XX)

To a solution of 0.5 g (0.0010 mole) of IV in 50 ml of dry acetone was added 250 mg (0.0025 mole) fused potassium acetate, and the mixture was refluxed for 4.5 hours. Most of the acetone was then distilled off, water was added and the precipitate was collected, washed with water and air-dried to yield 300 mg (77.3 %) of XX with m. p. 228—231° C. Identity with a sample of compound S acetate was established by a mixed melting point.

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