[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

STEROIDS. XXXVI.[1] DESULFURIZATION EXPERIMENTS IN THE 7-KETOPREGNANE SERIES

J. ROMO, G. ROSENKRANZ, AND CARL DJERASSI[2]

Received April 29, 1952

7,11-Diketones of the steroid series represent important intermediates in several syntheses of 11-oxygenated steroids from ring-C unsubstituted precursors and the removal of the 7-keto group is usually the penultimate step. In a number of instances (1–3) this is accomplished by formation of the cycloethylene mercaptol followed by Raney nickel desulfurization according to the procedure first introduced into the steroid series by Hauptmann (4). At the present time, the C-11 oxygen introduction methods have been applied only to ring-C unsubstituted steroids with the *allo* configuration at C-5 (α). Since the corresponding saturated "normal" (5 β) and Δ^4-unsaturated 11-oxygenated derivatives are of very considerable importance and might possibly be obtainable from the intermediate 7,11-diketones of the *allo* series, there were carried out certain model experiments with Δ^5-pregnene-3β,20β-diol-7-one diacetate (I) in order to study feasible approaches to this problem.

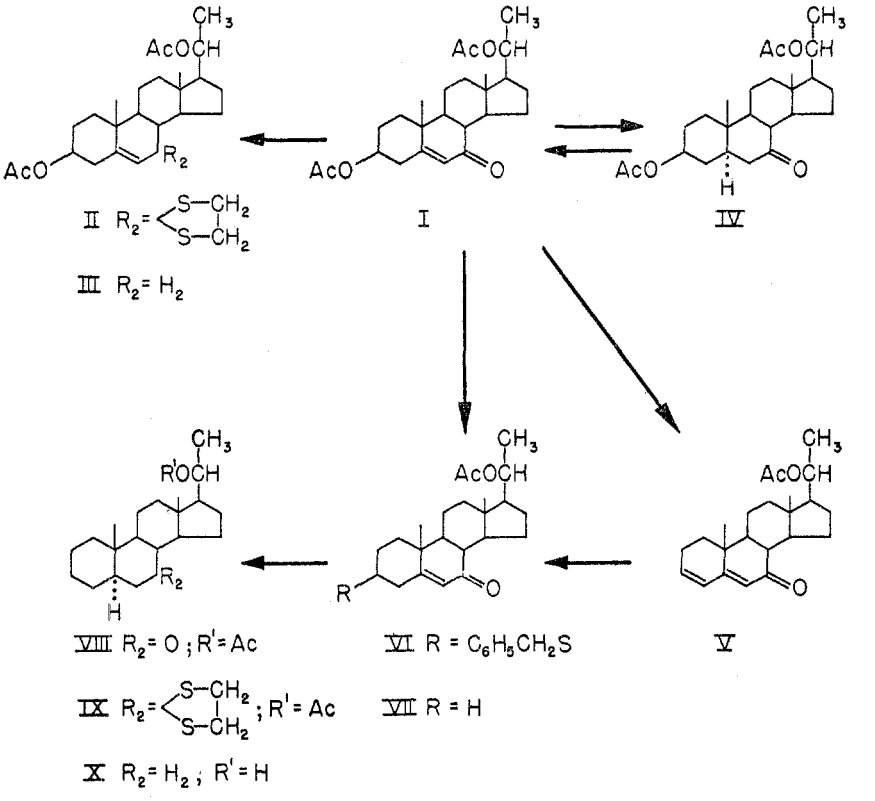
Since Oppenauer oxidation of steroidal Δ^5-3β-ols invariably produces the corresponding Δ^4-3-ketone (5) and the latter is reducible in a number of instances to saturated 5β-derivatives, it appeared important to develop a satisfactory route from 7-ketoallosteroids to the corresponding Δ^5-7-desoxy analogs which could then be applied to 7,11-diketones. The bromination of cholestan-3β-ol-7-one acetate under certain conditions has been reported (6) to afford a 6-bromo derivative which could be dehydrobrominated with pyridine in unspecified yield to 7-ketocholesteryl acetate. The latter has been converted (7) by means of cycloethylene mercaptol formation and Raney nickel desulfurization in 16% yield to cholesterol (isolated as the dibromo acetate), thus demonstrating the feasibility of transforming a 7-ketoallosteroid into the corresponding Δ^5-unsaturated 7-desoxy compound, albeit in extremely low yield. A reinvestigation of this approach with suitable experimental modifications employing Δ^5-pregnene-3β,20β-diol-7-one diacetate (I) as a model has resulted in much higher yields. Catalytic hydrogenation of I afforded the desired saturated allo-7-ketone IV, which upon bromination followed by dehydrobromination with collidine produced *ca.* 70% of the Δ^5-7-ketone I. Conversion of I to the cycloethylene mercaptol II was accomplished in 83% yield with ethanedithiol and anhydrous zinc chloride (rather than hydrogen chloride as in ref. 7), while the desulfurization to Δ^5-pregnene-3β,20β-diol diacetate proceeded in 85% yield when carried out in acetone solution for 1.5 hours (rather than dioxane for 8 hours as in ref. 7). The yields realized by the presently described experimental conditions with the

[1] Paper XXXV, Mancera, Romo, Sondheimer, Rosenkranz, and Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

[2] Present address: Department of Chemistry, Wayne University, Detroit, Mich.

model 7-monoketone indicate that the sequence — bromination, dehydrobromination, cycloethylene mercaptol formation, and desulfurization — might be of utility in the important 7,11-diketo series.

As an alternate approach, there was studied the formation of a benzylthioenol ether of Δ^5-pregnene-3β,20β-diol-7-one diacetate (I) according to the conditions utilized so successfully with Δ^4-3-ketosteroids (8). This aim was not accomplished but a number of interesting transformations were realized which are described briefly below. Thus treatment of the unsaturated ketone I (ultraviolet absorption maximum at 236 mμ) with benzyl mercaptan in the presence of *p*-toluenesulfonic



acid led to a substance $C_{30}H_{40}O_3S$ (loss of one acetyl group) with an ultraviolet absorption maximum at 236 mμ and infrared carbonyl bands corresponding to acetate and α,β-unsaturated carbonyl moieties. These results strongly indicated that the product was Δ^5-3-benzylthiopregnen-7-one-20β-ol acetate (VI) and had arisen from initial dehydration to the $\Delta^{3,5}$-dien-7-one (V) followed by 1,6-addition of benzyl mercaptan in a manner analogous to that reported by Ralls, Dodson, and Riegel (7) in the reaction of 7-ketocholesteryl acetate with ethyl mercaptan in the presence of hydrochloric acid. The correctness of structure VI was established in the following manner:

Dehydration of Δ^5-pregnene-3β,20β-diol-7-one diacetate (I) with ethanolic

hydrochloric acid in the usual manner (9) yielded $\Delta^{3,5}$-pregnadien-7-one-20β-ol acetate (V) (ultraviolet absorption maximum at 278 mμ) which in the presence of *p*-toluenesulfonic acid underwent 1,6-addition of benzyl mercaptan to give Δ^5-3-benzylthiopregnen-7-one-20β-ol acetate (VI), identical with the product obtained directly from I. Raney nickel desulfurization of VI in acetone solution smoothly removed the thiobenzyl group without affecting the unsaturated keto moiety[3] and catalytic hydrogenation of the resulting Δ^5-pregnen-7-one-20β-ol acetate (VII) led to allopregnan-7-one-20β-ol acetate (VIII), identical with a specimen prepared by hydrogenation of the $\Delta^{3,5}$-dien-7-one (V). This sequence of reactions (I $\rightarrow$ V $\rightarrow$ VIII) establishes the position of the keto group in the unsaturated ketones VI and VII at C-7. Conversion of allopregnan-7-one-20β-ol acetate (VIII) to allopregnan-20β-ol (X) (15) was accomplished by reductive desulfurization of the mercaptol IX followed by saponification and the identity of X was established by oxidation to allopregnan-20-one and comparison with an authentic sample (10).

EXPERIMENTAL[4]

Δ^5-Pregnene-3β,20β-diol-7-one diacetate (I). This substance was prepared in approximately 30% yield by means of the conventional chromium trioxide–acetic acid oxidation of steroidal Δ^5-3-ol acetates (11, 13) of Δ^5-pregnene-3β,20β-diol diacetate (III); m.p. 192–193° (capillary), 198–200° (Kofler), $[\alpha]_D^{20}$ −87°, $\lambda_{max.}^{EtOH}$ 236 mμ, log ϵ 4.24.

Anal. Calc'd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71.
Found: C, 72.15; H, 8.70.

Allopregnane-3β,20β-diol-7-one diacetate (IV) was prepared in 85% yield by catalytic hydrogenation (5% palladized charcoal, ethyl acetate solution, 1.5 hours) of I; after recrystallization from methanol, m.p. 154–156°, $[\alpha]_D^{20}$ −15°, no selective absorption in the ultraviolet.

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15.
Found: C, 71.93; H, 9.26.

Lithium aluminum hydride reduction of IV in ether solution followed by recrystallization from acetone-methanol produced *allopregnane-3β,7,20β-triol* with m.p. 218–220°, $[\alpha]_D^{20}$ +22° (ethanol).

Anal. Calc'd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78.
Found: C, 74.94; H, 10.70.

Chromium trioxide oxidation of the triol led to *allopregnane-3,7,20-trione*, m.p. 207–209°, $[\alpha]_D^{20}$ +25°; reported (13) m.p. 206–208°, $[\alpha]_D$ +22.5°.

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15.
Found: C, 76.67; H, 9.39.

Conversion of allopregnane-3β,20β-diol-7-one diacetate (IV) *to Δ^5-pregnene-3β,20β-diol-7-one diacetate* (I). A solution of 1.6 g. of the saturated ketone IV in 50 cc. of glacial acetic acid containing two drops of 4 *N* hydrogen bromide in acetic acid was brominated with a 5% solution of 1.05 moles of bromine in glacial acetic acid. After one-half hour, the solution was filtered and the quantitatively precipitated product was collected. Recrystallization

[3] Ralls, Dodson, and Riegel (ref. 7) carried out the desulfurization of Δ^5-3-ethylthiocholesten-7-one in dioxane solution at 120° for 24 hours and isolated cholestan-7-ol.

[4] Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque and staff for these measurements and to Srta. Amparo Barba for the microanalyses.

of a sample from methylene chloride—hexane yielded the analytical sample of 6-bromo-allopregnane-3β,20β-diol-7-one diacetate with m.p. 197–198°, $[\alpha]_D^{20}$ +19°.

Anal. Calc'd for $C_{25}H_{37}BrO_5$: C, 60.34; H, 7.49.

Found: C, 60.23; H, 7.30.

The above crude bromo derivative was refluxed for one hour with 10 cc. of collidine, the collidine hydrobromide was filtered, and the product was extracted with ether, washed until neutral, dried, and evaporated. Trituration with hexane gave 1.18 g. of colorless crystals with m.p. 185–188°. One recrystallization from methanol—methylene chloride raised the m.p. to 192–193°, $[\alpha]_D^{20}$ −89°, $\lambda_{max.}^{EtOH}$ 236 mμ, log ϵ 4.22. The infrared spectrum was identical with that of the above described specimen of I obtained from Δ^5-pregnene-3β,20β-diol diacetate (III).

The *semicarbazone* showed m.p. 227–228°, $[\alpha]_D^{20}$ −272°, $\lambda_{max.}^{CHCl_3}$ 276 mμ, log ϵ 4.28.

Anal. Calc'd for $C_{26}H_{39}N_3O_6$: C, 65.93; H, 8.30; N, 8.86.

Found: C, 66.37; H, 8.59; N, 9.17.

Δ^5-Pregnene-3β,20β-diol diacetate 7-cycloethylene mercaptol (II). A solution of 1.5 g. of the diacetate I in 20 cc. of dioxane was treated with 10 g. of anhydrous sodium sulfate, 10 g. of freshly fused zinc chloride, and 1.5 cc. of ethanedithiol and the mixture was allowed to stand overnight. Dilution with water, filtration, and recrystallization from methylene chloride—hexane furnished 1.45 g. (83%) of the mercaptol with m.p. 215–217°. The analytical sample was obtained from the same solvent and possessed m.p. 216–217°, $[\alpha]_D^{20}$ −71° (dioxane), no selective absorption in the ultraviolet.

Anal. Calc'd for $C_{27}H_{40}O_4S_2$: C, 65.82; H, 8.18; S, 12.99.

Found: C, 65.83; H, 8.16; S, 13.20.

Δ^5-Pregnene-3β,20β-diol diacetate (III). The above mercaptol (0.8 g.) was desulfurized by refluxing for 1.5 hours with 10 g. of W-2 Raney nickel catalyst in 300 cc. of acetone. Filtration of the catalyst, evaporation to dryness, and recrystallization from methanol yielded 0.56 g. (85%) of colorless crystals with m.p. 126–127°, undepressed on admixture with an authentic specimen (12), $[\alpha]_D^{20}$ −38°; the infrared spectra were identical.

$\Delta^{3,5}$-Pregnadien-7-one-20β-ol acetate (V). Deacetylation was accomplished by refluxing 6.0 g. of the 7-keto diacetate (I) with 500 cc. of methanol and 72 cc. of conc'd hydrochloric acid for 3 hours. Dilution with water, filtration, and acetylation with acetic anhydride–pyridine furnished 2.7 g. of the diene V with m.p. 171–172°, $[\alpha]_D^{20}$ −287°, $\lambda_{max.}^{EtOH}$ 278 mμ, log ϵ 4.48, $\lambda_{max.}^{Nujol}$ 1724 and 1656 cm.$^{-1}$.

Anal. Calc'd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05.

Found: C, 77.54; H, 8.76.

The dark red *2,4-dinitrophenylhydrazone* was prepared in acetic acid solution and after recrystallization from chloroform–methanol had m.p. 254–257°.

Anal. Calc'd for $C_{29}H_{36}N_4O_6$: C, 64.91; H, 6.76; N, 10.43.

Found: C, 64.89; H, 6.90; N, 10.75.

3-Benzylthio-Δ^5-pregnen-7-one-20β-ol acetate (VI). (*a*) *From Δ^5-pregnene-3β,20β-diol-7-one diacetate* (I). A solution of 4.0 g. of the diacetoxy ketone I in 100 cc. of benzene was dried by distilling 20 cc.; 0.4 g. of *p*-toluenesulfonic acid and 5 cc. of benzyl mercaptan were added and the mixture was refluxed for five hours, whereupon it assumed a dark red color. After dilution with water, extraction with ether, washing until neutral, drying, and evaporating, the residue was recrystallized three times from methanol giving 2.1 g. of colorless needles with m.p. 219–221°, $[\alpha]_D^{20}$ −87° (dioxane), $\lambda_{max.}^{EtOH}$ 236 mμ, log ϵ 4.29, $\lambda_{max.}^{Nujol}$ 1724 cm.$^{-1}$ (acetate) and 1674 cm.$^{-1}$ (α,β-unsaturated ketone).

Anal. Calc'd for $C_{30}H_{40}O_3S$: C, 74.96; H, 8.38.

Found: C, 74.92; H, 8.08.

(*b*) *From $\Delta^{3,5}$-pregnadien-7-one-20β-ol acetate* (V). The diene V (1 g.) was treated in benzene solution with benzyl mercaptan and *p*-toluenesulfonic acid as described under (*a*) except that the reflux time was reduced to 2 hours; yield, 0.6 g., m.p. 219–221°, $[\alpha]_D^{20}$ −91° (dioxane), no depression in m.p. on admixture of a sample prepared according to (*a*).

Δ^5-Pregnen-7-one-20β-ol acetate (VII). The desulfurization of 0.5 g. of the thiobenzyl

derivative VI was carried out by refluxing for one hour with 10 g. of W-2 Raney nickel catalyst in 300 cc. of acetone. The usual work-up followed by recrystallization from hexane–acetone led to 0.280 g. of VII with m.p. 145–147°, $[\alpha]_D^{20}$ −134°, $\lambda_{max.}^{EtOH}$ 236 mμ, log ε 4.24.

Anal. Calc'd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56.
Found: C, 76.68; H, 9.41.

The *2,4-dinitrophenylhydrazone* had m.p. 278–280°, $\lambda_{max.}^{CHCl_3}$ 387 mμ, log ε 4.59.

Anal. Calc'd for $C_{29}H_{38}N_4O_6$: C, 64.66; H, 7.11; N, 10.39.
Found: C, 64.65; H, 6.82; N, 10.47.

Allopregnan-7-one-20β-ol acetate (VIII). This substance was isolated in 76% yield upon hydrogenation of the above Δ^5-7-one (VII) for two hours in ethyl acetate solution with 5% palladized charcoal. The analytical sample was recrystallized from acetone-methanol and showed m.p. 202–203°, $[\alpha]_D^{20}$ −33°, $\lambda_{max.}^{EtOH}$ 286 mμ, log ε 1.60. The same product was obtained on catalytic hydrogenation of the $\Delta^{3,5}$-dien-7-one (V).

Anal. Calc'd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07.
Found: C, 76.68; H, 10.14.

The yellow *2,4-dinitrophenylhydrazone* had m.p. 231–233°, $[\alpha]_D^{20}$ −398°, $\lambda_{max.}^{CHCl_3}$ 370 mμ, log ε 4.48; the position of the absorption maximum coincides with that of saturated 3-keto steroidal dinitrophenylhydrazones (14).

Anal. Calc'd for $C_{29}H_{40}N_4O_6$: C, 64.42; H, 7.46; N, 10.35.
Found: C, 64.98; H, 7.89; N, 10.71.

Allopregnan-7-one-20β-ol acetate 7-cycloethylene mercaptol (IX). A mixture of 500 mg. of the above ketone VIII, 10 cc. of glacial acetic acid, 0.5 cc. of ethanedithiol, and 10 drops of 4 *N* hydrogen bromide in acetic acid was allowed to stand at room temperature over night and then diluted with water. The precipitate was collected and recrystallized from chloroform-methanol giving 480 mg. of colorless needles with m.p. 165–167°, $[\alpha]_D^{20}$ +19° (dioxane).

Anal. Calc'd for $C_{25}H_{40}O_2S_2$: C, 68.77; H, 9.23; S, 14.65.
Found: C, 68.90; H, 9.05; S, 14.18.

Allopregnan-20-one. The desulfurization of IX was carried out in the manner indicated above except that ethanol rather than acetone was used. The crude product was saponified with 5% alcoholic potassium hydroxide and recrystallized from methanol yielding 72% of allopregnan-20β-ol (X) with m.p. 139–141°, $[\alpha]_D^{20}$ +4°; reported (15): m.p. 140°.

Anal. Calc'd for $C_{21}H_{36}O$: C, 82.83; H, 11.92.
Found: C, 82.64; H, 11.67.

Chromium trioxide oxidation of X in 90% acetic acid solution (3 hours) produced allopregnan-20-one, m.p. 134–136°, identified by a mixture melting point determination and infrared comparison with an authentic sample (10).

SUMMARY

As a model experiment for certain cortical hormone syntheses, there was studied the conversion of allopregnane-3β,20β-diol-7-one diacetate to Δ^5-pregnene-3β,20β-diol by monobromination at C-6, dehydrobromination, and reductive removal of the 7-keto group *via* its cycloethylene mercaptol. Treatment of Δ^5-pregnene-3β,20β-diol-7-one diacetate with benzyl mercaptan in the presence of *p*-toluenesulfonic acid furnishes 3-benzylthio-Δ^5-pregnen-7-one-20β-ol acetate, also produced by 1,6-addition of benzyl mercaptan to $\Delta^{3,5}$-pregnadien-7-one-20β-ol acetate. The addition product was transformed by desulfurization, hydrogenation, reductive removal of the 7-cycloethylene mercaptol, and oxidation to allopregnan-20-one.

LAGUNA MAYRAN 413
MEXICO CITY 17, D.F., MEXICO

REFERENCES

(1) FIESER, BABCOCK, HERZ, HUANG, AND SCHNEIDER, *J. Am. Chem. Soc.*, **73**, 4053 (1951)
(2) HEUSSER, *et al.*, *Helv. Chim. Acta*, **34**, 2106 (1951); **35**, 295 (1952).
(3) ROMO, STORK, ROSENKRANZ, AND DJERASSI, *J. Am. Chem. Soc.*, **74**, 2918 (1952).
(4) HAUPTMANN, *J. Am. Chem. Soc.*, **69**, 562 (1947).
(5) DJERASSI, *Org. Reactions*, **6**, Chapter V (1951).
(6) BARR, HEILBRON, JONES, AND SPRING, *J. Chem. Soc.*, 334 (1938).
(7) RALLS, DODSON, AND RIEGEL, *J. Am. Chem. Soc.*, **71**, 3320 (1949).
(8) ROMO, ROMERO, DJERASSI, AND ROSENKRANZ, *J. Am. Chem. Soc.*, **73**, 1528 (1951).
(9) *Cf.* BUTENANDT, HAUSMANN, AND PALAND, *Ber.*, **71**, 1316 (1938).
(10) MANCERA, ROSENKRANZ, AND DJERASSI, *J. Org. Chem.*, **16**, 192 (1951).
(11) *Cf.* FIESER, FIESER, AND CHAKRAVARTI, *J. Am. Chem. Soc.*, **71**, 2226 (1949).
(12) KLYNE AND MILLER, *J. Chem. Soc.*, 1972 (1950).
(13) KLYNE, *J. Chem. Soc.*, 3449 (1951).
(14) DJERASSI AND RYAN, *J. Am. Chem. Soc.*, **71**, 1000 (1949).
(15) MARKER AND LAWSON, *J. Am. Chem. Soc.*, **61**, 852 (1939).