Des-A-pregnanes. Degradation of 11α-Hydroxyprogesterone

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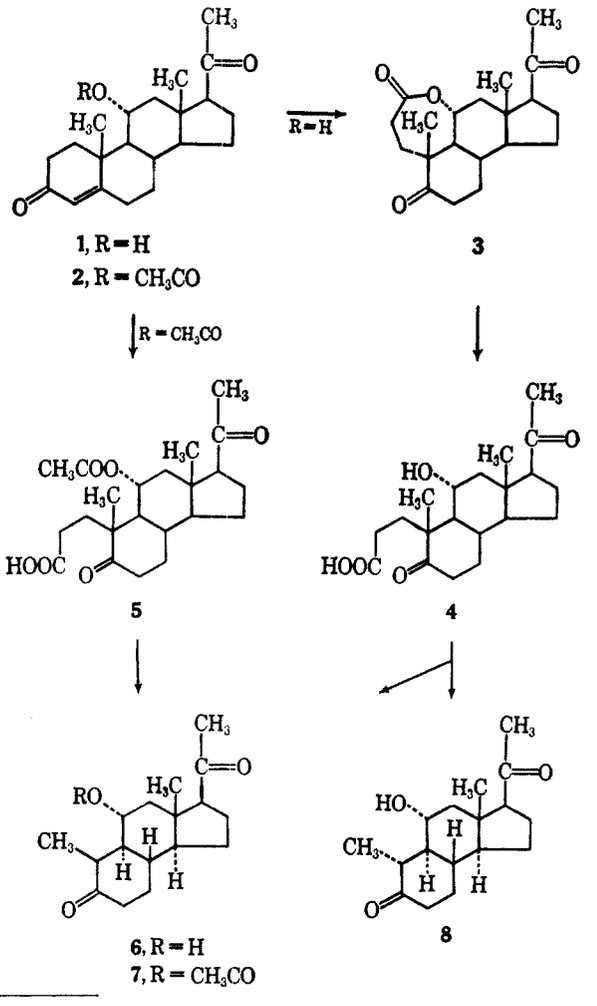
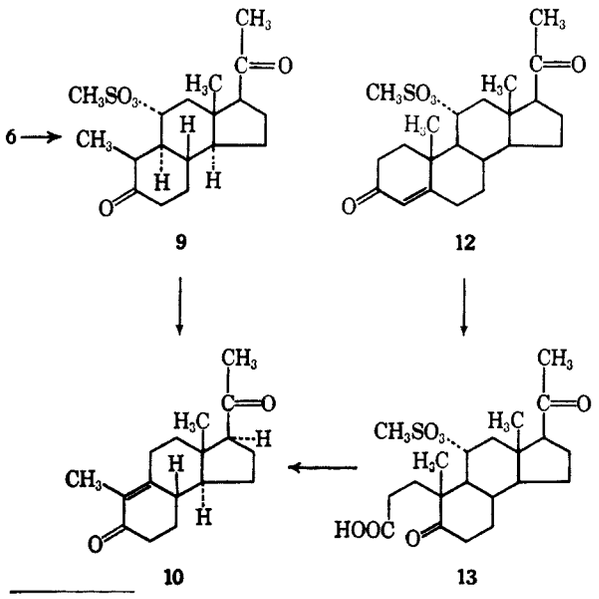
Degradation of 11α-hydroxyprogesterone to des-A-pregnanes is described. The substituent effect of the des-A-9-en-5-one grouping on the chemical shift of the C_{18} protons was deduced from the nmr spectra of des-A-9-en-5-one steroids with various substituents in position 17. This substituent effect was used in the determination of the configuration in position 20 of the epimeric 20-hydroxy- and 20-acetoxy-des-A-pregn-9-en-5-ones.

In an earlier communication[1] we described des-A-pregn-9-ene-5,20-dione (**10**) as an intermediate in the synthesis of 10α- and 9β,10α-progesterone. In this paper a full description of two different methods for the synthesis of **10**, and of its reduction to 20-hydroxy analogs is presented.

First, ozonization of 11α-hydroxyprogesterone (**1**) at −70° followed by spontaneous cyclization of the resulting keto acid **4** gave nicely crystalline 11α-hydroxy-5,20-dioxo-3,5-seco-A-norpregnan-3-oic acid 3,11-lactone (**3**). The assignment of the structure for this compound rests on microanalysis, and infrared data: the lactone carbonyl absorbs at 1730 cm^{-1} and the C–O–C vibration at 1285 and 1150 cm^{-1}. Treatment of lactone **3** with methanolic sodium hydroxide gave the sodium salt of the acid **4** which, on pyrolysis in molten sodium phenylacetate, was transformed to a mixture of 11α-hydroxy-10β-desA-pregnane-5,20-dione (**6**) and 11α-hydroxy-10α-des-A-pregnane-5,20-dione (**8**). The latter compound was obtained only as an amorphous solid even after chromatography and might not be completely pure. The 10β isomer **6** could also be made *via* pyrolysis of the 11α-acetoxy keto acid **5**, which in turn was available from 11α-acetoxyprogesterone (**2**). The structure of **6** and **8** were evident from nmr data. We observed previously that the equatorial 10α-methyl group of 17α-methyl- and 17α-ethyl-17β-hydroxy-10α-des-A-androstan-5-ones,[2] appears at δ 1.01, whereas the axial 10β-methyl group of 17α-methyl- and 17α-ethyl-17β-hydroxy-10β-des-A-androstan-5-ones[2] is shown at δ 1.12. It is also known[3] that in the normal steroids the *syn*-axial 11β-hydroxyl group exerts a larger (0.25 ppm) deshielding effect than the 11α-hydroxyl group (0.10 ppm) on the C_{19} protons. In the case of compound **6** (with the relationship of the hydroxyl and methyl groups the same as in an 11α-hydroxy steroid) by adding to the reference value of δ 1.12 for the 10β-axial group the 0.10-ppm deshielding effect of the 11α-hydroxyl group, one would expect the 10-methyl protons to show at δ 1.22. This is in good agreement with the experimental value of 1.18 found for compound **6**. Further, in the case of compound **8** (with the relationship as in an 11β-hydroxy steroid), by adding to the reference value of δ 1.01 for the 10α-equatorial group the 0.25-ppm deshielding effect of the *syn*-axial 11α-hydroxyl group, one would expect the 10-methyl protons to show at δ 1.26. This is in good agreement with the experimental value of δ 1.28 found for compound **8**.

Conversion of the 10β isomer **6** into des-A-pregn-9-ene-5,20-dione (**10**) was accomplished by mesylation





(1) M. Uskoković, J. Iacobelli, R. Philion, and T. Williams, *J. Am. Chem. Soc.*, **88**, 4538 (1966).

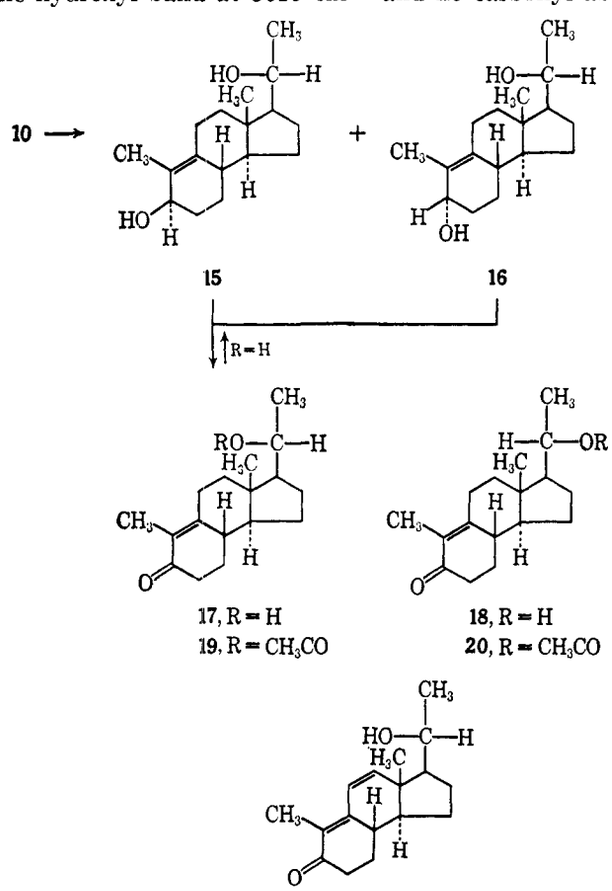
(2) Belgian Patent 663,197 (Oct 1965).

(3) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

which gave **9**, followed by elimination of methanesulfonic acid with concomitant shift of the newly formed double bond into conjugation with the 5-carbonyl group.

The multistep nature of the synthesis described above and the low yield in the pyrolysis step (**4** → **6** + **8**, ~25%) prompted us to investigate a more direct route to **10**. Ozonization of 11α-mesyloxyprogesterone (**12**) gave the 11α-mesyloxy keto acid (**13**). Heating of the sodium salt of this acid in triethanolamine at 200° resulted in a mixture of two α,β-unsaturated ketones (λ_{max} 248 mμ) in a ratio of 4:1 as estimated by gas chromatography. The major component of the mixture corresponded to des-A-pregn-9-ene-5,20-dione (**10**). This compound was separated and purified in the form of its bissemicarbazone **14**, from which it was regenerated by hydrolysis with pyruvic acid. The yield of **10** from **13** was 40%. Attempts to isolate the minor product in pure form failed.[4]

Reduction of the conjugated ketone **10** with excess sodium borohydride yielded a mixture of 5,20-diols, under conditions which are expected to transform stereoselectively a 20-keto to a 20β-hydroxyl group.[5,6] Two of the four possible stereoisomers, which could arise by introduction of two new asymmetric centers at C_5 and C_{20}, were characterized. The major product was des-A-pregn-9-ene-5β,20β-diol (**15**), which shows the hydroxyl band at 3610 cm^{-1} and no carbonyl absorption in the infrared spectrum. A broad multiplet at δ 4.05 in the nmr spectrum indicates that the C_5 methine proton is pseudo-axial; *i.e.*; the newly formed hydroxyl group at C_5 is pseudo-equatorial. Des-A-pregn-9-ene-5α,20β-diol (**16**), the C_5 epimer of **15**, was formed as a minor product in 5% yield. A narrow peak at δ 3.88 indicates that the C_5 methine proton is pseudo-equatorial; *i.e.*, the newly formed hydroxyl group at C_5 was pseudo-axial.



That the reduction of **10** also gave some 20α-hydroxyl product was recognized after the whole reduction product was oxidized with manganese dioxide. The major product, 20β-hydroxy-des-A-pregn-9-en-5-one (**17**), was then obtained in 79% over-all yield from **10**. The minor product (5%) was the 20α-hydroxy analog **18**, an oil which was converted into a crystalline acetate **20**. When a somewhat more active form of manganese dioxide was used, 20β-hydroxy-des-A-pregna-9,11-dien-5-one (**21**) was formed as the product of over oxidation. The diols **15** and **16**, epimeric at C_5, were shown to possess the same configuration at C_{20}, since sodium borohydride reduction of **17** yielded both of these diols.

Assignment of configuration at C_{20} was supported by molecular rotation ([M]D) data. The difference (Δ[M]D) in molecular rotation of C_{20} epimeric acetates (**20** → **19**) was found to be +149°, in good agreement with a value of +178°,[7] for the C_{20} epimeric pair of 20-hydroxy-pregn-4-en-3-one acetates (20α → 20β). Further confirmation of the structures **17**, **18**, **19**, and **20**, was provided by chemical shift data of the C_{18} protons. Using the base value of δ 0.69 known[8,9] for the C_{18} signal of androstanes, and the substituent effect values (Table I, column 2) known[8,9] for the groups listed in column 1, the calculated shifts for 17-substituted androstanes were obtained.

TABLE I

(1) 17 substituent	(2) Substituent effect	Chemical shifts of C_{18} protons (3) Androstanes (calcd)	(4) Des-A-androst-9-en-5-ones (found)	(5)
17β-Hydroxy-17α-methyl	+0.150	0.84	1.03	0.19
17β-Hydroxy	+0.033	0.72	0.92	0.20
17β-Acetoxy	+0.083	0.77	0.96	0.19
17β-Acetyl	−0.083	0.61	0.80	0.19

Subtraction of these calculated values (Table I, column 3) for androstanes from the experimental values (column 4) of corresponding des-A-androst-9-en-5-ones[2] showed a constant value of +0.19 ppm (column 5), which is therefore the substituent effect of a des-A-9-en-5-one grouping.

In Table II, column 2 are the known[8,9] 17β-(α-hydroxyethyl) substituent effects on the C_{18} proton shift in androstanes. In column 3 are the calculated values for the same shift in des-A-androst-9-en-5-ones: the sum of base value δ 0.69,[8,9] substituent effect (Table II, column 2), and increment +0.19 (Table I, column 5).

(4) Nmr spectra show the signal for the 13-methyl group of **10** at δ 0.80, and for that of the minor component at δ 1.10. See M. B. Rubin, *Steroids*, **2**, 561 (1963). We thank Dr. R. Micheli of these laboratories, who suggested on this basis that the minor component probably corresponds to the 17α analog of **10**.

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 568.

(6) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(7) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(8) R. F. Zürcher, *ibid.*, **46**, 2054 (1963).

(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden Day, Inc., San Francisco, Calif., 1964 Chapter 2.

TABLE II

(1) 17 substituent	(2) Substituent effect[a]	—Chemical shift of C_{18} protons— (3) Calcd	(4) Found	(5) Compd
17β-CH[OH(β)]CH_3	+0.041	0.92	0.91	**17**
17β-CH[OH(α)]CH_3	−0.050	0.83	0.83	**18**
17β-CH[OAc(β)]CH_3	−0.082	0.80	0.80	**19**
17β-CH[OAc(α)]CH_3	−0.033	0.85	0.85	**20**

[a] See ref 8 and 9.

A comparison of the calculated with experimental values (Table II, compare column 3 with column 4) shows very good agreement, thus giving strong support for the correctness of the structure assignment of the compounds **17–20**.

After we had completed our investigations, we became aware of the paper by Robinson and Hofer,[10] which is relevant to the determination of the stereochemistry at C_{20}. These authors showed that the shift of the C_{21}-methyl protons for the 20α-hydroxy epimer is downfield relative to that for the 20β epimer. Our experimental data are in agreement with their findings.

Experimental Section[11]

11α-Hydroxy-5,20-dioxo-3,5-seco-A-nor-pregnan-3-oic Acid 3,11-Lactone (3) from 11α-Hydroxyprogesterone (1).—A solution of 6.4 g of 11α-hydroxyprogesterone (1) in 100 ml of ethyl acetate and 50 ml of methylene chloride was ozonized at −70° until the solution turned blue. After oxygen was passed through, the solution was evaporated at room temperature *in vacuo*. The sirupy residue was dissolved in 100 ml of glacial acetic acid and, after the addition of 5 ml of 30% hydrogen peroxide, stood at 2° for 24 hr. The solution was then evaporated *in vacuo* and the residue triturated with ether to induce crystallization. After recrystallization from acetone, 4.6 g of **3** was obtained: mp 253–256°; $[\alpha]^{25}D$ +193.3° (*c* 1, in $CHCl_3$); infrared spectrum (in $CHCl_3$), 1730 and 1705 (carbonyl groups), 1285 and 1155 cm^{-1} (C–O–C).

Anal. Calcd for $C_{20}H_{28}O_4$ (332.44): C, 72.26; H, 8.49. Found: C, 71.95; H, 8.65.

11α-Hydroxy-10α-des-A-pregnane-5,20-dione (8) and 11α-Hydroxy-10β-des-A-pregnane-5,20-dione (6) from 3.—A methanolic solution of 7.5 g of **3** was treated with 1 equiv of 10 *N* sodium hydroxide solution and upon evaporation to dryness the sodium salt of the acid **4** was obtained (an intense carboxylate ion absorption at 1600 cm^{-1} in the ir spectrum of a KBr pellet). After it was mixed with 26 g of sodium phenylacetate, the mixture was pyrolyzed at 225° for 2 hr *in vacuo*. The crude sublimate (3.42 g) was chromatographed on a silica gel column and eluted with 10% ethyl acetate in benzene. The amorphous substance first eluted was 11α-hydroxy-10α-des-A-pregnane-5,20-dione (**8**). The infrared spectrum (in $CHCl_3$) showed 3620 and 3600 (OH), 1706 cm^{-1} (carbonyl group); the nmr spectrum (in $CDCl_3$) gave 10α-CH_3 doublet (J = 7 cps) at δ 1.28 and 13-CH_3 and 17β-$COCH_3$ singlets at 0.71 and 2.51, respectively.

The crystalline 11α-hydroxy-10β-des-A-pregnane-5,20-dione (**6**) eluted later from the column, was recrystallized from methylene chloride–petroleum ether (30–60°): mp 150–152°; $[\alpha]^{25}D$ +84.0° (*c* 0.5 in absolute C_2H_5OH); infrared spectrum (in $CHCl_3$), 3620 and 3600 (–OH), 1706 cm^{-1} (carbonyl group); nmr spectrum (in $CDCl_3$), 10β-CH_3 doublet (J = 7 cps) at δ 1.18 and 13-CH_3 and 17β-$COCH_3$ singlet at 0.71 and 2.16, respectively; ORD (in methanol), $[\alpha]_{400}$ +300°, $[\alpha]_{350}$ +720°, $[\alpha]^{max}_{310}$ +2390°, $[\alpha]_{300}$ +2010°.

Anal. Calcd for $C_{17}H_{26}O_3$ (278.39): C, 73.34; H, 9.41. Found: C, 73.11; H, 9.30.

11α-Hydroxy-10β-des-A-pregnane-5,20-dione Acetate (7) from 6.—Compound **6** (70 mg) was acetylated with 1 ml of acetic anhydride in 1 ml of pyridine. This gave 58 mg of **7**: mp 130–131° (from aqueous methanol); $[\alpha]^{25}D$ +61.0 (*c* 0.5 in C_2H_5OH); infrared spectrum (in $CHCl_3$), 1730 (acetate), 1706 cm^{-1} (ketone); nmr spectrum (in $CDCl_3$), 10β-CH_3 doublet (J = 7 cps) at δ 1.10 and 13-CH_3 and 17β-$COCH_3$ singlets at 0.77 and 2.13, respectively; ORD (in methanol) shows a positive Cotton effect ($[\alpha]_{400}$ +258°, $[\alpha]^{max}_{307}$ +1830°, $[\alpha]_{300}$ +1580°).

Anal. Calcd for $C_{19}H_{28}O_4$ (320.43): C, 71.22; H, 8.81. Found: C, 71.23; H, 8.82.

11α-Hydroxy-5,20-dioxo-3,5-seco-A-nor-pregnan-3-oic Acid Acetate (5) from 11α-Acetoxyprogesterone (2).—A solution of 6.4 g of **2** in 100 ml of ethyl acetate and 50 ml of methylene chloride was ozonized at −70° until the solution became blue. After oxygen was passed through, the solution was evaporated at room temperature *in vacuo*. The sirupy residue was dissolved in 100 ml of glacial acetic acid and, after addition of 5 ml of 30% hydrogen peroxide, it was allowed to stand 2° for 24 hr. The reaction mixture was then evaporated to dryness, the residue dissolved in 1 l. of ether, and the ether solution extracted ten times with 50-ml portions of 2 *N* sodium carbonate solution. The carbonate extracts were acidified with concentrated hydrochloric acid and the noncrystalline precipitate was extracted with methylene chloride. The extract was dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The residue (5.8 g) was purified by chromatography on a "Florisil" column. The elution with ethyl acetate gave the crystalline acid **5**, which after several recrystallizations from methylene chloride–hexane, had mp 171–172°, $[\alpha]^{25}D$ +64.6° (*c* 1, in $CHCl_3$).

Anal. Calcd for $C_{22}H_{32}O_6$ (392.48): C, 67.32; H, 8.22. Found: C, 67.05; H, 8.34.

11α-Hydroxy-10β-des-A-pregnane-5,20-dione (6) from 5.—A solution of 4.5 g of **5** in 1 equiv of aqueous sodium carbonate solution was evaporated to dryness *in vacuo*. The residual sodium salt was mixed well with 15 g of sodium phenylacetate and the mixture pyrolyzed at 290° *in vacuo* (0.02 mm) for 2.5 hr. The crude sublimate (2.63 g) was chromatographed on a silica gel column and elution with petroleum ether–ether (3:7) gave a fraction (302 mg) which was recrystallized from acetone–petroleum ether. This gave 11α-hydroxy-10β-des-A-pregnane-5,20-dione (**6**), which was identified by mixture melting point and by comparison of optical rotation with that of a sample of the same compound prepared in the experiment described above.

11α-Hydroxy-10β-des-A-pregnane-5,20-dione Methanesulfonate (9) from 6.—To a solution of 100 mg of methanesulfonyl chloride in 0.7 ml of pyridine was added 100 mg of **6**. The mixture was allowed to stand overnight in a refrigerator, then was diluted with 100 ml of water, and extracted three times with 150-ml portions of chloroform and once with 100 ml of methylene chloride. The combined extracts were washed with water, 1 *N* hydrochloric acid, again with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crystalline residue was recrystallized from ether to give a quantitative yield of **9**: mp 139–140°; $[\alpha]^{25}D$ +46° (*c* 0.5, in absolute C_2H_5OH); infrared spectrum (in $CHCl_3$), 1706 cm^{-1} (carbonyls); nmr spectrum (in $CDCl_3$), 10β-CH_3 doublet (J = 7 cps) at δ 1.23 and 13-CH_3, 17β-$COCH_3$, and 11α-OSO_2CH_3 singlets at 0.77, 2.16, and 3.08, respectively.

Anal. Calcd for $C_{18}H_{28}O_5S$ (356.48): C, 60.65; H, 7.92. Found: C, 60.90; H, 8.16.

Des-A-pregn-9-ene-5,20-dione (10) from 9.—A solution of 200 mg of **9** in 50 ml of dimethylformamide was refluxed for 8 hr and evaporated to dryness *in vacuo*. The residue was chromatographed on a Florisil column. The elution with benzene gave des-A-pregn-9-ene-5,20-dione (**10**) in the form of colorless needles, mp 111–113°. It was proven by mixture melting point to be identical with the analytical sample of the same compound prepared in a later experiment.

11α-Mesyloxyprogesterone (12) from 1.—To a solution of 20 g of **1** in 150 ml of pyridine cooled at 0°, was added 6 ml of methanesulfonyl chloride, and the reaction mixture was allowed to stand overnight at 0°. It was then diluted with a large excess of water and extracted with chloroform. The extracts were washed with 2 *N* hydrochloric acid and with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The solid residue was recrystallized from methanol to give 24 g of **12**: mp 159.5–160°; $[\alpha]^{25}D$ +145.6 (*c* 1, in $CHCl_3$); infrared spectrum (in $CHCl_3$), 1700 (saturated ketone), 1665 and 1610 (conjugated ketone), 1347, 1330, and 1165 cm^{-1} (mesyloxyl group).

Anal. Calcd for $C_{22}H_{32}O_5S$ (408.56): C, 64.52; H, 8.12. Found: C, 64.39; H, 8.11.

11α-Mesyloxy-5,20-dioxo-3,5-seco-A-nor-pregnan-3-oic Acid (13) from 12.—Oxygen was bubbled through a solution of 12 g

(10) C. H. Robinson and P. Hofer, *Chem. Ind.* (London), 377 (1966).

(11) Melting points are corrected. The nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as internal reference.

of **12** in 300 ml of (2:1) methylene chloride–ethyl acetate for 5 min and then ozonized oxygen was bubbled through for 45 min (color of solution changed from pale yellow to green to blue). The excess ozone was removed by bubbling oxygen through the solution for 5 min. The solution was placed in a 2-l. round-bottom flask, concentrated to 100 ml, and diluted with 100 ml of ethyl acetate. After the addition of 12 ml of 30% aqueous hydrogen peroxide, the mixture was allowed to stand in the refrigerator overnight. Removal of solvents under reduced pressure at 35° gave a viscous oil to which was added 125 ml of benzene. The ozonization was repeated three times; the products were combined and extracted four times with 600 ml of 2 *N* sodium carbonate. The carbonate layers were acidified with 500 ml of concentrated hydrochloric acid and extracted four times with 800-ml portions of methylene chloride. The organic layers were dried over anhydrous sodium sulfate and filtered. Removal of solvents under reduced pressure at room temperature gave 46 g of crude product as a viscous oil, which crystallized from ether to give **13**. The mother liquors were taken down to dryness and thin layer chromatograms indicated that they contained predominantly the desired acid **13**. Recrystallization from acetone–petroleum ether gave an analytical sample: mp 152–153°; $[\alpha]^{25}D$ +47.9° (*c* 1, in $CHCl_3$); infrared spectrum (in $CHCl_3$), 1708 (carbonyl), 1335 and 1170 cm^{-1} (mesyloxyl group).

Anal. Calcd for $C_{21}H_{32}O_7S$ (428.55): C, 58.86; H, 7.53. Found: C, 58.95; H, 7.82.

Des-A-pregn-9-ene-5,20-dione (10) and Des-A-17α-pregn-9-ene-5,20-dione (11)[4] from 13.—A solution of 1.5 g of **13** in 45 ml of methanol mixed with 0.385 g of sodium carbonate in 15 ml of water was evaporated to dryness. The last traces of water were removed by adding benzene and evaporating to dryness again. To the residual salt was added 50 ml of freshly distilled triethanolamine, and the reaction mixture was heated for 3 hr in a metal bath of 215–220° under nitrogen. The temperature of the reaction solution varied between 190 and 205°. After cooling, it was diluted with 1 l. of water, and extracted ten times with 150-ml portions of ether. The ethereal extract was washed with water, 1 *N* hydrochloric acid, and with water again, dried, and evaporated. The crystalline residue, 561 mg, absorbed at λ_{max} 248 mμ (ε 14,700), and by gas chromatographic analysis contained **10** and **11** in a ratio of 78:22. The same experiment was repeated several times with similar results. The solution of 2.418 g of crude product (λ_{max} 248 mμ, ε 14,500) and 1.4 g of semicarbazide in 60 ml of 95% ethanol and 9 ml of glacial acetic acid was stirred and refluxed for 2 hr. After cooling in ice, the precipitate was filtered and washed with ethanol, yield 2.223 g. Evaporation of the mother liquors and crystallization from 10 ml of 95% ethanol gave an additional 320 mg of product. Both crops were combined, suspended in 100 ml of 95% ethanol, refluxed for 1 hr, concentrated to a volume of 50 ml, cooled in an ice bath, and filtered to give 2.4 g of des-A-pregn-9-ene-5,20-dione disemicarbazone (**14**), which did not melt below 340°, but showed slight decomposition above 270°. The ultraviolet spectrum (in 95% ethanol + 5% dimethyl sulfoxide) showed λ_{max} 271 mμ (ε 29,350).

Anal. Calcd: N, 22.44; Found: N, 22.18.

A solution of 1.87 g of the disemicarbazone in 75 ml of acetic acid, 25 ml of water, and 6.5 ml of 1.66 *N* pyruvic acid was warmed for 2 min at 40°, then left overnight at room temperature. It was then diluted with 1.5 l. of ether, washed with water, aqueous 2 *N* sodium carbonate, and again with water, dried, and evaporated. The crystalline residue (1.34 g) was dissolved almost completely in 50 ml of hot heptane and filtered, and the filtrate was evaporated; 1.3 g of a colorless crystalline **10** was obtained, mp 110–114° (softened 100°), λ_{max} 248 mμ (ε 15,500). After recrystallization from ether, it melted at 113–113.5°, $[\alpha]^{25}D$ +54.1° (*c* 1, in $CHCl_3$). The infrared spectrum (in $CHCl_3$) showed bands at 1704 (20-carbonyl), 1660 and 1605 cm^{-1} (conjugated ketone); th euv spectrum (in 95% C_2H_5OH) had a band at λ_{max} 248 mμ (ε 15,950). The nmr spectrum (in $CDCl_3$) showed 10-CH_3 at δ 1.81, 18-CH_3 at 0.80, and 17β-$COCH_3$ at 2.15.

Anal. Calcd for $C_{17}H_{24}O_2$ (260.36): C, 78.42; H, 9.29. Found: C, 78.66; H, 9.19.

20β-Hydroxy-des-A-pregn-9-en-5-one (17) from 10. Isolation of a By-product as 20α-Hydroxy-des-A-9-en-5-one Acetate (20). A.—To a solution of 1.2 g of **10** in 20 ml of methanol cooled to 0° was added slowly a cooled solution of 1.2 g of sodium borohydride in 22 ml of methanol; the mixture was left for 72 hr at 0°. It was then diluted with 100 ml of water and extracted with four 100-ml portions of chloroform. The extract was dried over anhydrous sodium sulfate and evaporated *in vacuo*, giving 1.2 g of a colorless oily product. To the solution of this product in 250 ml of chloroform was added 6 g of manganese dioxide. The reaction mixture was stirred for 72 hr at room temperature and then filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on a silica gel column, and the eluates with 5% ethyl acetate in benzene after concentration gave 780 mg of crystalline **17**. Recrystallization from methylene chloride–petroleum ether gave **17** as colorless needles: mp 122–123°; $[\alpha]^{25}D$ −33° (*c* 0.5, in C_2H_5OH); infrared spectrum (in $CHCl_3$), 3610 (–OH), 1655 and 1605 cm^{-1} (conjugated ketone); uv spectrum (in 95% C_2H_5OH), λ_{max} 249 mμ (ε 16,300); nmr spectrum (in $CDCl_3$), 10-CH_3 band at δ 1.80, 13-CH_3 singlet at 0.91, and 17β-CH(β-OH)CH_3 methyl doublet (*J* = 6 cps) at 1.17; ORD curve (in methanol) shows a negative Cotton effect ($[\alpha]_{400}$ −104°; $[\alpha]_{360}^{min}$ −266°; $[\alpha]_{340}$ 0°; $[\alpha]_{321}$ +316°).

Anal. Calcd for $C_{17}H_{26}O_2$ (262.40): C, 77.82; H, 9.99. Found: C, 77.62; H, 10.18.

Semicarbazone.—Ketone **17** was allowed to react with semicarbazide in a 10:1 (v/v) ethanol–acetic acid solution to give 20β-hydroxy-des-A-9-en-5-one semicarbazone as colorless needles: mp 196–198° (ethyl acetate); $[\alpha]^{25}D$ +110° (*c* 0.5, ethanol); infrared spectrum (in $CHCl_3$), 3620 (–OH), 3400 (NH), 1690, 1560, 1450 cm^{-1} (semicarbazone of conjugated ketone); uv spectrum (in 95% C_2H_5OH), λ_{max} 271 mμ (ε 30,000); nmr spectrum (in DMF-d_7), 10-CH_3 band at δ 1.90, 13-CH_3 singlet at 0.86, and 17β-CH(β-OH)CH_3 methyl doublet (*J* = 6 cps) at 1.10.

Anal. Calcd for $C_{18}H_{29}N_3O_2$ (319.46): C, 67.67; H, 9.15; N, 13.16. Found: C, 67.80; H, 9.21; N, 13.47.

B.—A solution of 524 mg of **10**, in absolute methanol (65 ml), was stirred at 5°. Over a period of 40 min, 0.5 g of sodium borohydride was added in portions. The total reaction time allowed was 1 hr. This was followed by the addition of cold glacial acetic acid until the pH was about 7.5 and concentration of the solution to dryness *in vacuo*. The residue was dissolved in 150 ml of chloroform, and the resulting solution was washed with water until it was neutral, dried with sodium sulfate, and evaporated to dryness to give 569 mg of a clear oil. A solution of 552 mg of this oil in 50 ml of chloroform was stirred with 10 g of precipitated manganese dioxide (Code No. 37, General Metallic Oxides) for 19 hr. The suspension was filtered through a sintered-glass funnel coated with Celite, and evaporated to dryness *in vacuo* to give 550 mg of colorless oil (λ_{max} 249 mμ, ε 13,200). Crystallization of 520 mg of this oil gave 321 mg (67%) of 20β-hydroxy-des-A-pregn-9-en-5-one (**17**) as colorless needles, mp 116–122°. A further 64 mg (12%) of this compound (mp 114–120°) was isolated from thin layer chromatograms. At the same time, a second band which was fluorescent under ultraviolet light was eluted to give the by-product, 20α-hydroxy-des-A-pregn-9-en-5-one (**18**). Yield of **18** was 5%, based on isolation as the crystalline acetate **20** as colorless needles: mp 87–89° (ether–petroleum ether); $[\alpha]^{25}D$ −37° (*c* 0.312, in C_2H_5OH); infrared spectrum (in $CHCl_3$), 1660 and 1610 (conjugated ketone), 1725 cm^{-1} (acetate); uv spectrum (in 95% C_2H_5OH), λ_{max} 248 mμ (ε 15,500); nmr spectrum (in $CDCl_3$), 10-CH_3 band at δ 1.78, 13-CH_3 singlet at 0.85, and 17β-CH(α-OAc)CH_3 methyl doublet (*J* = 6 cps) at 1.24.

Anal. Calcd for $C_{19}H_{28}O_3$ (304.43): C, 74.96; H, 9.27. Found: C, 75.14; H, 9.47.

Des-A-pregn-9-ene-5β,20β-diol (15) and Des-A-pregn-9-ene-5α,20β-diol (16) from 10 and 17. 20β-Hydroxy-des-A-pregna-9,11-dien-5-one (21) from 15. A.—To a solution of 5 g of **10** in 100 ml of ethanol at 5° was added 5 g of sodium borohydride, and the reaction mixture stirred for 1.5 hr at this temperature. Glacial acetic acid was added dropwise to the cold solution until the pH was 7 and, after evaporation to dryness *in vacuo*, the residue was dissolved in chloroform (500 ml). The solution was washed with dilute sodium hydroxide and water, dried over sodium sulfate, and evaporated to dryness to give 5.2 g of oil, which crystallized from methanol–water; 2.5 g of des-A-pregn-9-ene-5β,20β-diol (**15**), mp 155–164°, was obtained. An analytical sample was prepared by two recrystallizations from methanol–water. It melted at 167–169°, $[\alpha]^{25}D$ +2° (*c* 0.5, in C_2H_5OH). The infrared spectrum (in $CHCl_3$) had a band at 3620 cm^{-1} (OH); the nmr spectrum (in $CDCl_3$) showed a 10-CH_3 band at δ 1.76, 13-CH_3 singlet at 0.86, 17β-CH(β-OH)CH_3 methyl doublet (*J* = 6 cps) at 1.15, and 5α-H and 20α-H broad methine absorptions at 4.05 and 3.75.

Anal. Calcd for $C_{17}H_{28}O_2$ (264.41): C, 77.22; H, 10.67. Found: C, 77.03; H, 10.92.

Des-A-pregn-9-ene-5α-20β-diol (**16**) was isolated in 5% yield from thin layer chromatograms of the mother liquor as colorless needles: mp 144–146° (ether–petroleum ether); infrared spectrum (in $CHCl_3$), 3620 cm^{-1} (OH); nmr spectrum (in $CDCl_3$), 10-CH_3 band at δ 1.76, 13-CH_3 singlet at 0.86, 17β-CH(β-OH)CH_3 methyl doublet (J = 6 cps) at 1.15, and 5β-H and 20α-H at 3.88 (narrow band) and 3.75 (broad), respectively.

Anal. Calcd for $C_{17}H_{28}O_2$ (264.41): C, 77.22; H, 10.67. Found: C, 77.06; H, 10.79.

B.—Oxidation of 2 g of des-A-pregn-9-ene-5β,20β-diol (**15**) (mp 155–164°) in 200 ml of chloroform with 25 g of highly active manganese dioxide gave 1.85 g of oily product, with an ultraviolet absorption at 250 mμ (ε 4970) and 292.5 mμ (ε 4410). In addition to 20β-hydroxy-des-A-pregn-9-en-5-one (**17**), chromatographic separation of this product gave a 15% yield of 20β-hydroxy-des-A-pregna-9,11-dien-5-one (**21**) as colorless needles: mp 158–159° (aqueous methanol); $[\alpha]^{25}D$ −73.4° (c 0.5, in C_2H_5OH); infrared spectrum (in $CHCl_3$), 3610 (–OH), 1650 and 1600 cm^{-1} (dienone); uv spectrum (in 95% C_2H_5OH), λ_{max} 292.5 mμ (ε 24,300); nmr spectrum (in $CDCl_3$), 10-CH_3 doublet (J = 2 cps, indicating long-range coupling) at δ 1.85, 13-CH_3 singlet at 0.91, 17β-CH(β-OH)CH_3 methyl doublet (J = 6 cps) at 1.20, and AB quartet for C_{11} and C_{12} olefinic protons (J = 10 cps) centered at 6.66, with $\Delta\delta_{AB}$ = 0.60 ppm.

Anal. Calcd for $C_{17}H_{24}O_2$ (260.38): C, 78.42; H, 9.29. Found: C, 78.68; H, 8.92.

C.—To a solution of 1 g of **17** in 50 ml of methanol at 5° was added 1 g of sodium borohydride, and the reaction mixture was stirred for 1.5 hr at this temperature. Glacial acetic acid was added to the cold solution until the pH was 7; the solution was diluted with chloroform, washed with water, dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue gave 758 mg of crude **15**, mp 155–162°. The mother liquor residue (222 mg), which appears (thin layer chromatogram) to be a (1:1) mixture of diols **15** and **16**, was oxidized with manganese dioxide (Code No. 37, General Metallic Oxides) to an oil (202 mg), which appears (thin layer chromatogram) to contain **16** and **17** but no **15**. From this oil by thin layer chromatography, 56 mg of crude crystalline **16** was obtained. Recrystallization from ether–petroleum ether gave colorless needles, mp and mmp 144–146°.

20β-Acetoxy-des-A-pregn-9-en-5-one (**19**) had mp 118–119°, $[\alpha]^{25}D$ +11.9° (c 0.88 in $CHCl_3$). The infrared spectrum (in $CHCl_3$) had bands at 1725 (acetoxy carbonyl), 1660 (conjugated ketone), and 1605 cm^{-1} (double bond); the uv spectrum (in 95% C_2H_5OH) showed λ_{max} 248 mμ (ε 16,150); nmr spectrum (in $CDCl_3$) showed 10-CH_3 at δ 1.80, 13-CH_3 at 0.80, 17β-CH(β-OAc)CH_3 methyl doublet at 1.17 (J = 6 cps), and acetoxy methyl at 2.03.

Anal. Calcd for $C_{19}H_{28}O_3$ (304.41): C, 74.96; H, 9.27. Found: C, 75.04; H, 9.30.

Registry No.—**1**, 80-75-1; **3**, 10110-77-7; **5**, 15259-95-7; **6**, 10110-78-8; **7**, 15259-97-9; **8**, 15259-98-0; **9**, 10110-79-9; **10**, 10072-88-5; **12**, 10116-24-2; **13**, 10110-54-0; **14**, 15314-09-7; **15**, 15285-88-8; **16**, 15260-03-4; **17**, 10110-81-3; **17** semicarbazone, 15266-89-4; **18**, 15267-19-3; **19**, 15266-90-7; **20**, 15266-91-8; **21**, 15266-92-9.

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A Study of Tautomerism in Arylazopyrazolones and Related Heterocycles with Nuclear Magnetic Resonance Spectroscopy

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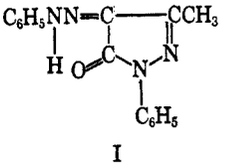
Nuclear magnetic resonance was used to determine the tautomeric forms of arylazo-3-, -4-, and -5-pyrazolones and several related azo heterocycles in chloroform. The assignments of the hydrazone structure to the 5-pyrazolones and the hydroxy structure to the 3- and 4-pyrazolones are supported by infrared data. Several conclusions emerge from the nmr spectra: (a) in the heterocyclic systems studied the hydrazone NH resonance comes 3–5 ppm lower than the azohydroxy OH resonance and (b) it appears that the hydrazone NH resonance of structurally similar azo heterocycles fall within a 2-ppm range.

Azopyrazolones have been known and used for over 100 years, but the structures of these compounds have been examined only within the last decade. The structure of arylazo-5-pyrazolones in solution has now been established,[1] but arylazo-3-pyrazolones, arylazo-4-pyrazolones, and many similar azo heterocycles have not yet been investigated.

Nmr spectroscopy has been very valuable in studies of tautomerism, but when the tautomers in question contain NH and OH protons it is frequently difficult to assign unambiguously a given acidic proton resonance to a particular functional group. The first objective of the present work, therefore, was to evaluate the applicability of nmr to the determination of the structures of azo heterocycles in solution. Since the structure of arylazo-5-pyrazolones was already known and the structures of the tautomerically simpler 3-pyrazolones were easily determined by infrared, this objective was at least partially accomplished by a study of various derivatives of these compounds. The second and related objective was to establish the structures of azo-4-pyrazolones and related azo heterocycles.

The Structure of Azopyrazolones in Chloroform.—Although there has been some disagreement about the structure of 1,3-disubstituted 4-arylazo-5-pyrazolones in solution, a recent spectroscopic investigation[1] argues convincingly for the phenylhydrazone structure (I) as the predominant form in chloroform.



I

Two reasonable tautomeric forms (not involving charge separation) can be written for 1,5-disubstituted 4-arylazo-3-pyrazolones. The infrared spectra of numerous 4-arylazo derivatives in chloroform exhibit only one absorption, at 1600 ± 15 cm^{-1}, in the region be-

(1) H. Yasuda and H. Midorikawa, *J. Org. Chem.*, **31**, 1722 (1966).