almost at once. The reaction was allowed to stand for 0.5 hr at room temperature, then 1 hr in the refrigerator, and the precipitated solid was removed by filtration, washed with pyridine and ether, and dried: 9.91 g; mp 318–324°; $[\alpha]_D$ +33.0° (MeOH); λ_{max}^{Nujol} 2.94, 6.11, and 6.47 μ.

Anal. Calcd for $C_{23}H_{39}NO_4$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.24; H, 9.91; N, 3.82.

11β-Acetamido-5β-pregnan-17α-ol-3,20-dione (V).—A mixture of 5.00 g of 11β-acetamidopregnane-3α,17α,20β-triol, 150 ml of acetic acid, 150 ml of *t*-butyl alcohol, 30 ml of water, and 17.6 g of N-bromoacetamide was allowed to react in the refrigerator for 4 days. A cold, aqueous solution of 20 g of sodium sulfite and 0.5 g of sodium bicarbonate was added and the solution was evaporated to dryness at room temperature. The residue was dissolved in methylene chloride and the organic extracts were washed with water, dried, and evaporated. Treatment of the resinous residue with ethyl acetate crystallized 3.79 g as a solvate: mp 156–164° with bubbling; $[\alpha]_D$ +67.1° (MeOH); λ_{max}^{Nujol} 2.89 (sh), 2.94, 5.86, 6.09, and 6.52 μ.

Anal. Calcd for $C_{23}H_{35}NO_4 \cdot 0.5C_4H_8O_2$: C, 69.25; H, 9.07; N, 3.23. Found: C, 69.17; H, 8.80; N, 3.58.

11β-Acetamido-2,4,21-tribromo-5β-pregnan-17α-ol-3,20-dione (X).—A solution of 2.59 g of bromine in 15 ml of acetic acid was added dropwise with stirring to a solution of 2.00 g of 11β-acetamidopregnan-17α-ol-3,20-dione in 40 ml of acetic acid containing 0.5 ml of 48% aqueous hydrogen bromide. Addition was complete in 15 min, at the end of 2 hr 0.5 g of sodium bicarbonate was added and the solution was evaporated to dryness at room temperature. The residue was triturated with water and filtered to give 3.13 g of crude tribromide.

Anal. Calcd for $C_{23}H_{32}Br_3NO_4$: Br, 38.28. Found: Br, 38.16.

11β-Acetamido-21-acetoxy-1,4-pregnadien-17α-ol-3,20-dione (IXb).—A mixture of 30 ml of diethylacetamide and 0.53 g of calcium carbonate was brought to reflux, and 3.10 g of crude tribromide was added with the aid of an additional 15 ml of diethylacetamide. Refluxing was continued for 10 min; then the mixture was poured into water and extracted with methylene chloride. The organic extracts were washed with dilute sulfuric acid and water, dried, and evaporated at room temperature to an oil. This was dissolved in 100 ml of acetone containing 12 g of potassium acetate and the mixture was refluxed with stirring for 5 hr. The organic solvent was removed at room temperature and the residue was extracted with methylene chloride. The organic extracts were washed with water, dried, and evaporated. The residue was chromatographed on Florisil to give 1.20 g of crude product as an oil. Two crystallizations from ethyl acetate gave 0.5 g, mp 167–173°. The analytical sample, crystallized once more, had mp 163–167°; $[\alpha]_D$ +176.9° (dioxane); λ_{max}^{MeOH} 240 mμ (ε 12,900); λ_{max}^{Nujol} 3.02, 5.72 (sh), 5.80, 6.04, 6.15 (sh), 6.23 (sh), 6.56, 7.95, 8.13 μ. This material gave a postive TPTZ test.

Anal. Calcd for $C_{25}H_{33}NO_6$: C, 67.70; H, 7.50; N, 3.16. Found: C, 67.53; H, 7.52; N, 2.97.

3α,20-Dihydroxy-5β-pregn-9(11)-en-12-one. Side-Chain Conformations in the Light of Ultraviolet and Infrared Studies

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The unknown 3α,20α-dihydroxy-5β-pregn-9(11)-en-12-one (**4g**), the known 3α,20β-dihydroxy-5β-pregn-9(11)-en-12-one (**4c**), and some derivatives thereof have been prepared by conventional methods. Infrared and ultraviolet spectra demonstrate that the 20β-, but not the 20α-, hydroxyl group is intramolecularly hydrogen bonded to the 12-keto moiety. Conformations of the side chain of $\Delta^{9(11)}$-12-keto steroids possessing a C-20 hydroxyl group are shown.

Discussion

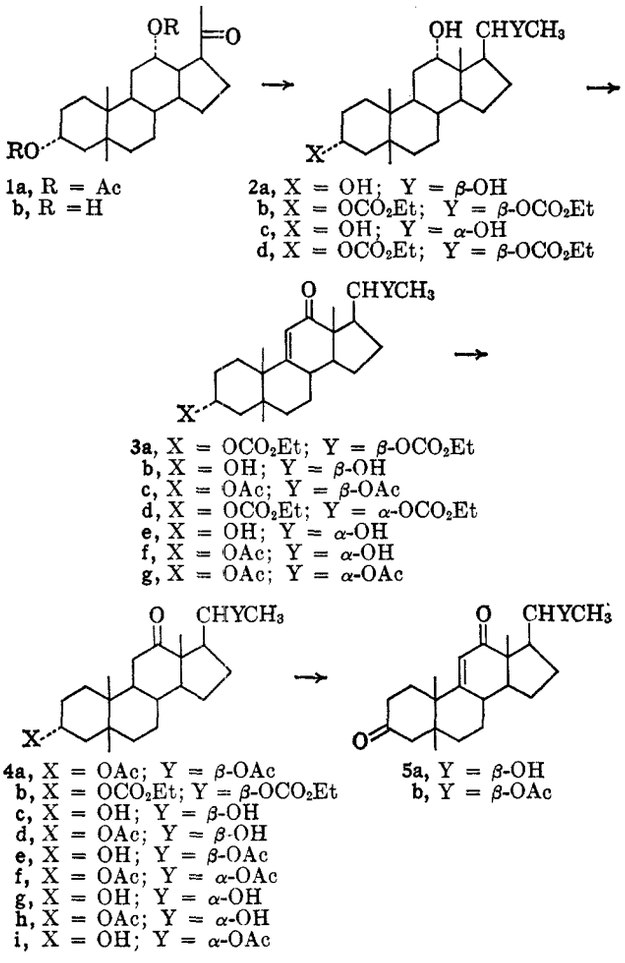
During recent studies in our laboratories, we prepared the two isomeric diolones **4c** and **4g**, of which only **4c** and its alleged diacetate have been reported recently.[1] Our interest in this type of compound was augmented by the observation that, because of the proximity of the C-20 hydroxyl and $\Delta^{9(11)}$-12-keto moieties, unique spectral evidence could be obtained regarding the conformations of the side chain of C-20 hydroxyl steroids. For this purpose, several derivatives of **4c** and **4g** were prepared, and their infrared and ultraviolet spectra were recorded.

The readily available bile acid derivative **1a** served as starting material, and was converted to the desired product as outlined in Scheme I. Reduction of **1a** with sodium borohydride followed by alkaline hydrolysis[2] afforded 3α,12α,20β-trihydroxy-5β-pregnane[1] (**2a**, 88%). Although protection of the 3α- and 20β-hydroxyl groups could be accomplished[1,2] by partial acylation of **2a** either with acetic or succinic anhydride, ethyl chlorocarbonate was employed in this work. Thus, treatment of **2a** with this reagent produced **2b**, which was oxidized with chromium trioxide in glacial acetic acid; the product, **3a**, could not be obtained in a crystalline form. Dehydrogenation of crude **3a** with selenium dioxide–glacial acetic acid[3] gave the unsaturated ketone **4b**, but crystallization could not be induced even in a chromatographically homogeneous sample. Nevertheless, basic hydrolysis of **4b** afforded the known[1] diolone **4c** in 71% over-all yield (**2b** → **3a** → **4b** → **4c**).

Alternatively, hydrolysis of the noncrystalline **3a** to **3b**, followed by acetylation to the known[4] diacetate **3c**, and dehydrogenation of the latter with selenium dioxide–glacial acetic acid gave 3α,20β-diacetoxy-5β-pregn-9(11)-en-12-one (**4a**, mp 149.5–150.5°, λ_{max}^{MeOH} 239.5 mμ). However, the same structure has been assigned recently[1] to a substance (mp 200.5–201.5°, λ_{max}^{EtOH} 244 mμ) obtained by acetylation of **4c** with a large excess of acetic anhydride–pyridine at room temperature. We have prepared the alleged diacetate (mp 206.5–207.5°, λ_{max}^{MeOH} 245 mμ) by usual acetylation of **4c**. This compound was found to be 3α-acetoxy-20β-hydroxy-5β-pregn-9(11)-en-12-one[5] (**4d**) by elemental analysis and by infrared spectroscopy, which revealed the presence of one acetoxy and one 20β-

(1) C. R. Engel and W. W. Huculak, *Can. J. Chem.*, **37**, 2031 (1959).
(2) P. L. Julian and A. Magnani, U. S. Patent 2,940,991 (1960).
(3) E. Schwenk and E. Stahl, *Arch. Biochem.*, **14**, 125 (1947); C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, p 233.
(4) G. Just and R. Nagarajan, *Can. J. Chem.*, **39**, 548 (1961).
(5) In a personal communication, Professor C. R. Engel informed us that he has also concluded that the product melting at 200.5–201.5° is in fact 3α-acetoxy-20β-hydroxy-5β-pregn-9(11)-en-12-one (**4e**). A mixture melting point of that product, kindly provided by Professor Engel, and **4e** showed no depression.

SCHEME I



1a, R = Ac
b, R = H

2a, X = OH; Y = β-OH
b, X = OCO_2Et; Y = β-OCO_2Et
c, X = OH; Y = α-OH
d, X = OCO_2Et; Y = β-OCO_2Et

3a, X = OCO_2Et; Y = β-OCO_2Et
b, X = OH; Y = β-OH
c, X = OAc; Y = β-OAc
d, X = OCO_2Et; Y = α-OCO_2Et
e, X = OH; Y = α-OH
f, X = OAc; Y = α-OH
g, X = OAc; Y = α-OAc

4a, X = OAc; Y = β-OAc
b, X = OCO_2Et; Y = β-OCO_2Et
c, X = OH; Y = β-OH
d, X = OAc; Y = β-OH
e, X = OH; Y = β-OAc
f, X = OAc; Y = α-OAc
g, X = OH; Y = α-OH
h, X = OAc; Y = α-OH
i, X = OH; Y = α-OAc

5a, Y = β-OH
b, Y = β-OAc

hydroxyl group. These assignments will be discussed conclusively later in this paper.

It was also found that **4a** could be prepared in good yield only after prolonged heating (steam bath) of **4c** in excess acetic anhydride–pyridine, whereas room temperature acetylation of **4c** produced **4d** and **4a** in 90–95 and 5–10% yield, respectively. Finally, the isomeric monoacetate **4e** was prepared by partial methanolysis of **4a**. Oxidation of **4e** to **5b** and hydrolysis of the latter afforded **5a**.

The preparation of compounds in the 20α series was carried out in a similar manner. Lithium aluminum hydride reduction of **1b** in ether gave the isomeric triols **2a** and **2c** in 5.3 and 78% yield, respectively.[4] These triols could be completely separated by tlc, since the 20β isomer was moved faster than the 20α isomer [$R_f(20\beta):R_f(20\alpha) = 2$]. The detection of contaminating isomers in the triols used throughout this work was thus ensured by this separation; moreover, the ratio of the reduction products of **1b** could now be determined as approximately[6] 85:15% in favor of the 20α-triol **2c**.

Conversion of the triol **2c** to **4g** was carried out as described above for the 20β series (**2c** → **2d** → **3d** → **3e** → **3g** → **4f** → **4g**) without isolation of intermediates **2d** and **3d**. Partial hydrolysis of **4f** gave **4i** (80%), whereas partial acetylation of **4g** afforded a mixture from which **4h** and **4f** were isolated in 25 and 46% yield, respectively.

(6) For different ratios of 20α and 20β isomers, see ref 4.

In contrast to the behavior of the 20β-hydroxyl group, the 20α-hydroxyl could be easily acetylated at room temperature (**4g** → **4f**, **4h** → **4f**). Thus, the acetylation and hydrolysis experiments established the following order of reactivity of the hydroxyl groups in compounds of structure **4**: $3\alpha > 20\alpha \gg 20\beta$. Obviously, the 20β-hydroxyl group resists acetylation because (a) it is sterically hindered in the particular conformation in which it exists; and (b) it is involved in strong intramolecular bonding[7] (see information given later in this paper) with the $\Delta^{9(11)}$-12-keto moiety.

Molecular rotations of the compounds synthesized and changes in rotation accompanying acetylation at positions 3α, 20α, and 20β agree (Table I) with the well-established patterns[8] and support the structures assigned to the monoacetates **4d**, **4e**, **4h**, and **4i**. Thus, acetylation of the 3α- and 20β-hydroxyl groups increased the molecular rotation by 100–106 and 16–33°, respectively, whereas acetylation of the 20α-hydroxyl group resulted in a small decrease (18–33°).

Derivatives **4e** and **4i**, possessing one hydroxyl group at position 3α, absorbed near 3620 cm^{-1} (ϵ_a 35–40) in good agreement with the frequency and intensity of the free hydroxyl absorption.[9] The monoacetate **4h**, having one hydroxyl group at position 20α, showed a sharp free hydroxyl absorption at 3600 cm^{-1} (ϵ_a 25) accompanied by a broad, weak band near 3350 cm^{-1}; **4g** absorbed at 3600 cm^{-1} (ϵ_a 70) for the 3α- and 20α-hydroxyl groups, but showed also a weak peak near 3370 cm^{-1}. Since the broad absorption accompanied the free 20α-hydroxyl band and was found to be concentration dependent, it should be due to polymeric intermolecular hydrogen bonding.[9] In contrast, **4d** and **5a**, having a 20β-OH, each exhibited only one strong and sharp band at 3360 (ϵ_a 155) and 3365 cm^{-1} (ϵ_a 166), respectively. In addition, **4c** showed two absorption peaks at 3600 (ϵ_a 40) and 3355 cm^{-1} (ϵ_a 160), corresponding to the 3α- and 20β-hydroxyl groups, respectively. The position and intensity of the strong peak near 3360 cm^{-1} were independent of concentration demonstrating complete intramolecular hydrogen bonding between the 20β-hydroxyl and $\Delta^{9(11)}$-12-keto moieties.

As expected, intramolecular hydrogen bonding caused a significant shift (by 23–31 cm^{-1}) toward the lower frequencies of the ν (C=O) vibration, which is normally located at 1671–1676 cm^{-1} ($CHCl_3$) or at 1680–1684 cm^{-1} (CCl_4) in steroidal $\Delta^{9(11)}$-12-ketones.[10] Thus, all compounds possessing a 20β-OH (**4d**, **4c**, and **5a**) absorbed strongly at 1650–1656, whereas their acetates (**4a**, **4e**, and **5b**) exhibited the ν (C=O) near 1680 cm^{-1} in methylene chloride solutions (Table I). In contrast, no similar displacement was observed in the 20α series, indicating that intramolecular hydrogen bonding is unimportant in this case (Table I).

A consistent and significant displacement also occurred in the ultraviolet spectra, in which the normal $\Delta^{9(11)}$-12-keto absorption is located near 240 mμ in ethanol solution.[11] Table I revealed clearly that a

(7) For examples of similar interaction, see M. E. Wall, F. I. Carroll, and G. S. Abernethy, Jr., *J. Org. Chem.*, **29**, 604 (1964); also, M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960).

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 177, 614.

(9) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956); K. Nakanishi, "Infrared Absorption Spectroscopy, Practical," Holden-Day, Inc., San Francisco, Calif., and Nankodo Co., Ltd., Tokyo, 1962, pp 30–33.

(10) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

(11) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

TABLE I

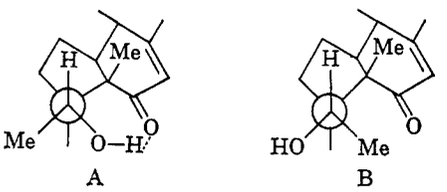
PHYSICAL PROPERTIES OF EPIMERIC 3α,20-DIHYDROXY-5β-PREGN-9(11)-EN-12-ONES

Compd	Substituents 3α	20β	20α	M_D ($CHCl_3$)	Δ_{prop}^{phys}	ΔM_D (OAc − OH) 3α	20β	20α	λ_{max}^{MeOH} [a]	$-\Delta\lambda$ 20β	20α	ε	$-\Delta\varepsilon$ 20β	20α	ν (OH) CH_2Cl_2	ν (OH) CCl_4	$\Delta\nu$ CH_2Cl_2	ε CH_2Cl_2	ε CCl_4	ν ($\Delta^{9(11)}$-12-ketone) CH_2Cl_2	ν ($\Delta^{9(11)}$-12-ketone) CCl_4	$\Delta\nu$ (ketone) CH_2Cl_2	$\Delta\nu$ (ketone) CCl_4
4a	OAc	OAc		524					239.5			13,100								1679	1689		
					4a–4d		+33			+5.5			+900									+24	+23
4d	OAc	OH		491					245			14,000			3370	3400	−230	155	170	1655	1666		
					4d–4c	+105																	
4c	OH	OH		386					246			13,800			3600[d]		−240	40		1650			
					4c–4e		+32			+5.5			+1100		3360[e]			160				+31	
4e	OH	OAc		418					240.5			12,700						35		1681			
					4a–4e	+106									3620					1671	1685	−2	+5
4f	OAc		OAc	396					240.5			12,600											
					4f–4h			−18			+1			+300									
4h	OAc		OH	414					239.5			12,300			3600	3630		25	25	1673	1680		
					4h–4g	+101																	
4g	OH		OH	313					241			12,000			3600			70		1670		+4	
					4i–4g			−33			0			+200									
4i	OH		OAc	280					241			11,800			3600			37		1674			
					4f–4i	+116																	
5a	=O	OH		330					243.5			14,100											
					5b–5a		+16			+5.5			+2000		3365		−235	165		1656		+23	
5b	=O	Ac		346					238			12,100								1679	1690		

[a] λ given in millimicrons. [b] ν given in reciprocal centimeters. [c] Based on free ν (OH) at 3600 cm^{-1}. [d] 3α-OH. [e] 20β-OH.

bathochromic shift of this absorption by 5.5 mμ and a small but definite increase of the molecular extinction coefficient by 900–2000 occurred, when a 20β- but not a 20α-hydroxyl group was present in the molecule. Obviously, the bathochromic displacement is due to intramolecular hydrogen bonding which, in the 20β series, decreases the energy of excitation from the ground to the more polar excited state (N → V) by stabilizing the latter.

Model inspection demonstrates that interaction between the C-18 angular and C-21 methyl groups of the steroids in question prevents free rotation of the side chain around the C-17–C-20 bond. Consequently, only one conformation (A) is permissible for the 20β-OH compounds in which the hydroxyl group is intramolecularly hydrogen bonded, and the bulky C-21 and C-18 methyl groups are as far apart as possible. On the other hand, since steric hindrance is strong enough to prevent intramolecular hydrogen bonding between the 20α-OH and C-12 keto moieties, the rotational energy barrier must be greater than 5 kcal/mole,[12] and the 20α-OH compounds should exist predominantly[13] in the conformation showed in B.



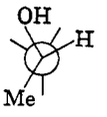
Experimental Section[14]

3α,12α,20β-Trihydroxy-5β-pregnane (2a).—A solution of sodium bicarbonate (6 g) in water (50 ml) was added with stirring to a solution of **1a** (100 g) in methanol (700 ml), and the mixture was warmed to 30°. Sodium borohydride (6 g) in water (40 ml) was then added over a period of 15 min. After the solution had been stirred for 1 hr, the mixture was refluxed for 15 min and filtered, and the filtrate was refluxed for 1 hr. The solution was concentrated to incipient crystallization, cooled, and filtered to give the triol **2a**, 64.5 g, mp 230–234°. A second crop (8.03 g, mp 236–238°) was obtained by further concentration of the mother liquor. The two crops were combined and recrystallized from acetone to give pure **2a**: 70.8 g, 80%, mp 235–237°, $[\alpha]_D$ +34°; lit.[1] mp 236°, $[\alpha]_D$ +31°.

3α,20β-Dicarbethoxy-12α-hydroxy-5β-pregnane (2b).—Ethyl chlorocarbonate (62 ml) was added dropwise with stirring and cooling to a solution of **2a** (52 g) in dioxane (200 ml) and pyridine (60 ml) in 20 min. The mixture was stirred at room temperature for 1 hr, dissolved in water–methylene chloride (1000:250 ml) and acidified with concentrated hydrochloric acid, and the organic layer was separated. The water phase was extracted

(12) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall Inc., Englewood Cliffs, N. J., 1963, p 128; L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 449.

(13) The referee pointed out that in conformation B there is a rather strong interaction between the 12-keto group and the 21-methyl group and suggested that the most favorable conformation should be close to C



This possibility cannot be excluded, although nonbonded interactions, particularly between the hydroxyl group and the 16β-hydrogen and 18-methyl groups, become also strong in this case.

(14) Infrared spectra were recorded on a Beckman IR-4 spectrophotometer. Ultraviolet spectra were taken on a Beckman DK-2 recording spectrophotometer. Optical rotations were measured in chloroform solutions at 25–27°, at concentrations of 0.3–0.6%, and have been approximated to the nearest degree. Melting points are not corrected. Microanalyses were performed by Mr. E. Thommen, Basel, Switzerland.

with methylene chloride, and the combined extracts were washed with water, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The oily residue was crystallized from hexane to furnish **2b** (31.7 g, mp 123–125°) in 42.5% yield. The filtrate was evaporated *in vacuo* to give an oil (46.5 g) which contained a substantial amount of **2b** (*ca.* 70%, tlc) and was processed separately (see following experiment). The analytical sample was prepared by two recrystallizations from ether–hexane: mp 126.5–128°, $[\alpha]_D$ +64°.

Anal. Calcd for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23. Found: C, 67.45; H, 9.19.

3α,20β-Dihydroxy-5β-pregnan-12-one (3b).—A solution of **2b** (29.1 g, 0.06 mole) in glacial acetic acid (300 ml) was oxidized by chromic oxide (6.1 g) at room temperature for 20 hr to furnish an oil (29 g) which resisted all attempts at crystallization. This oil (26.9 g) was dissolved in methanol (500 ml), potassium hydroxide (14 g) in water (40 ml) was added, and the mixture was refluxed for 2.5 hr. The solution was then evaporated on a steam bath until a considerable amount of crystals had formed. The mixture was diluted with water (600 ml), and the solid was filtered off and dried: mp 220–223°, yield 16.9 g, 90% (**2b** → **3a** → **3b**).

Oxidation of the oil containing an appreciable amount of **2b** (see previous experiment), followed by hydrolysis and purification by column chromatography on silica gel, yielded an additional amount of **3b** (13.7 g, mp 220–223°) raising the over-all yield to 61.5% (**2a** → **2b** → **3a** → **3b**). A sample was recrystallized once from acetone to give pure **3b**: mp 222–223°, $[\alpha]_D$ +106°; lit.[3] mp 222–223°, $[\alpha]_D$ +131°.

3α,20β-Diacetoxy-5β-pregnan-12-one (3c).—A solution of the ketone **3b** (13.7 g, 41 mmoles) in pyridine (50 ml) and acetic anhydride (40 ml) was heated on a steam bath for 30 hr. The mixture was worked up as usual to give 13.25 g (78%) of the diacetate **3c**: mp 141–142°, $[\alpha]_D$ +142°; lit.[3] mp 136–137°, $[\alpha]_D$ +179°. A second crop (2.6 g, mp 138–140°) increased the yield to 92.5%.

3α,20β-Diacetoxy-5β-pregn-9(11)-en-12-one (4a). A. From 3α,20β-Diacetoxy-5β-pregnan-12-one (3c).—To a solution of **3c** (15 g) in glacial acetic acid (150 ml), selenium dioxide (6 g) was added and the mixture was refluxed for 18 hr. After an additional amount of selenium dioxide (6 g) had been added, the mixture was refluxed for 6 hr, filtered hot, cooled to room temperature, and diluted by slow addition of water (500 ml). The crystalline precipitate was filtered off, washed with water, and dried to give pale yellow crystals: 11.78 g, 79%, mp 140–142°. On recrystallization from ether–hexane gave **4a**: 9.8 g, 65%, mp 144–146°.

The analytical sample was prepared by purification through a column of silica gel and crystallization from ether: mp 149.5–150.5°; $[\alpha]_D$ +126°; $\nu_{max}^{CCl_4}$ 1738 (diacetate), 1689, and 1607 cm^{-1} [$\Delta^{9(11)}$-12-ketone]; λ_{max}^{MeOH} 239.5 mμ (ε 13100).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.96; H, 8.69.

B. From 3α,20β-Dihydroxy-5β-pregn-9(11)-en-12-one (4c).—A solution of **4c** (1 g) in pyridine (10 ml) and acetic anhydride (4 ml) was heated on a steam bath for 54 hr to yield the diacetate **4a** (mp 145–147°, 1.08 g) in 86% yield.

3α,20β-Dihydroxy-5β-pregn-9(11)-en-12-one (4c). A. By Hydrolysis of 4a.—To a solution of **4a** (5.9 g) in methanol (200 ml), potassium hydroxide (4 g) in water (10 ml) was added. The mixture was refluxed for 4.5 hr, concentrated, and diluted with water to yield **4c**: mp 243–246°, 4.1 g, 93%. Two recrystallizations from acetone gave pure **4c**: mp 247–249°, $[\alpha]_D$ +116°, λ_{max}^{MeOH} 246 mμ (ε 13,800); lit.[1] mp 242–243°, λ_{max}^{MeOH} 242 mμ (ε 11,000).

B. From 3α,20β-Dicarbethoxy-5β-pregnan-12-one (3a → 4b → 4c).—Crude noncrystalline **3a** (2.8 g) in glacial acetic acid (25 ml) was dehydrogenated with selenium dioxide (1.8 g) at reflux temperature for 24 hr to yield a glassy residue, which did not crystallize. This residue was purified by column chromatography on silica gel (110 g). Despite the fact that a chromatographically pure product (tlc) was obtained, all attempts to induce crystallization failed. The product was then hydrolyzed in MeOH–KOH to produce crystalline **4a** [mp 245–247°, λ_{max}^{MeOH} 246 mμ (ε 13,700)] in 71% over-all yield.

3α-Acetoxy-20β-hydroxy-5β-pregn-9(11)-en-12-one (4d).—Acetylation of **4c** (1.66 g, 5 mmoles) in pyridine (15 ml) and acetic anhydride (2 ml) at room temperature for 20 hr afforded the 3α-monoacetate (**4d**), mp 205–207°, in 78% yield. Two recrystallizations from acetone–hexane gave the analytical sample: mp 206.5–207.5°; $[\alpha]_D$ +131°; $\nu_{max}^{CH_2Cl_2}$ 3370 (bonded OH), 1737 (3α-acetate), 1655, and 1601 cm^{-1} [$\Delta^{9(11)}$-12-ketone].

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.65; H, 9.27.

3α-Hydroxy-20β-acetoxy-5β-pregn-9(11)-en-12-one (4e).—A solution of the diacetate **4d** (2.08 g, 5 mmoles) in methanol (100 ml) containing 1.1 ml of 25% methanolic sodium methoxide was allowed to stand at room temperature for 4 hr. The solution was then diluted with water (30 ml), neutralized with dilute hydrochloric acid, and evaporated *in vacuo* to a small volume. The product (1.8 g) was crystallized from acetone: mp 205–209°, yield 1.3 g, 70%. Pure **4e** was obtained by an additional crystallization from acetone: mp 205–207°; $[\alpha]_D$ +112°; λ_{max}^{MeOH} 240.5 mμ (ε 12,700); $\nu_{max}^{CH_2Cl_2}$ 3250 (3α-hydroxyl), 1726 cm^{-1} (20β-acetate).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.81; H, 9.18.

20β-Acetoxy-5β-pregn-9(11)-en-3,12-dione (5b).—A solution of **4e** (0.37 g) in pyridine (4 ml) was added to chromic oxide–pyridine reagent (0.3 g and 3 ml) and the mixture was stirred at room temperature overnight. The mixture was diluted with water, extracted with ether, and the combined extracts were washed with water. The solution was evaporated to dryness and the residue was recrystallized once from acetone–hexane to give the analytical sample: mp 149–151°, yield 0.26 g, 71%, $[\alpha]_D$ +93°.

Anal. Calcd for $C_{23}H_{37}O_4$: C, 74.16; H, 8.66. Found: C, 73.98; H, 8.73.

20β-Hydroxy-5β-pregn-9(11)-en-3,12-dione (5a).—Methanolysis of **5b** (0.69 g) in methanol (30 ml) and sodium methoxide (1 ml of a 25% solution) at reflux temperature for 2.5 hr yielded crude **5a**: 0.5 g, 81%, mp 193–195°. The pure sample was obtained by two crystallizations from acetone: mp 200–201°, $[\alpha]_D$ +100°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.25; H, 9.23.

3α,12α,20α-Trihydroxy-5β-pregnane (2c).—Diol **1b** (12.2 g, mp 173–175°) was reduced with lithium aluminum hydride in ether as described previously.[3] The residue obtained was crystallized repeatedly from chloroform to yield pure **2c**, mp 219.5–221°, $[\alpha]_D$ +48°, in 65.4% yield (8.02 g) (lit.[3] mp 225–226°, $[\alpha]_D$ +46°). All filtrates were combined and evaporated to dryness, and the residue obtained (4.1 g) was recrystallized from acetone. The pure triol **2a** (0.65 g), mp 236–238°, was isolated in 5.3% yield.

The acetone filtrates were combined again and evaporated to dryness, and the residue was recrystallized repeatedly from chloroform to give an additional amount of **2c**: 1.55 g, 12.6%, mp 219.5–221°. Tlc on silica gel G (ascending technique, MeOH–$CHCl_3$, 1:9 v/v) of all combined residues (1.79 g) showed a mixture that consisted of 35% 20α- and 65% 20β-triols. Thus, **2c** and **2a** were produced at an approximate rate of 85:15 in favor of the 20α isomer **2c**.

3α,20α-Dihydroxy-5β-pregnan-12-one (3f) (2c → 2d → 3d → 3e).—Triol **2c** (6.6 g) was acylated with ethyl chlorocarbonate (8 ml) in pyridine and the crude product was oxidized to **3d** in chromic oxide–acetic acid. Hydrolysis of crude **3d** afforded **3e**: 4.35 g, 65%, mp 260–263°. Pure **3e** was obtained by two recrystallizations from ethanol: mp 264–266°, $[\alpha]_D$ +113°; lit.[15] mp 260–261°, $[\alpha]_D$ 120°.

3α,20α-Diacetoxy-5β-pregnan-12-one (3g).—A mixture of **3f** (1.55 g), pyridine (10 ml), and acetic anhydride (8 ml) was heated on a steam bath for 15 min and allowed to stand at room temperature overnight. Slow addition of water precipitated crystalline **3g**: 1.85 g, 95%, mp 212–214°. One crystallization from ethanol gave the pure product: mp 213–214.5°, $[\alpha]_D$ +108°; lit.[11] mp 212–212.5°, $[\alpha]_D$ +103°.

3α,20α-Diacetoxy-5β-pregn-9(11)-en-12-one (4f). A. From 3g.—The diacetate **3g** (1.85 g) was treated with selenium dioxide–acetic acid as described previously in the preparation of **3a** to yield **4f**, mp 179–180°, in 82% yield. A sample was recrystallized once from ether–hexane for analysis and had mp 180–181°, $[\alpha]_D$ +95°.

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.88; H, 8.72.

B. From 4g.—This compound was acetylated under the same conditions as those described for the preparation of **4d** to

(15) R. Nagarajan and G. Just, *Can. J. Chem.*, **39**, 1274 (1961).

yield the diacetate **4f**, mp 180–181°, $[\alpha]D$ +96°, in 90% yield.

3α,20α-Dihydroxy-5β-pregn-9(11)-en-12-one (4g).—Methanolysis of **4f** (280 mg) in methanolic sodium methoxide at reflux for 2 hr yielded the free diol **4g**: mp 222–224°, 235 mg, 95%. The product was recrystallized once from acetone–hexane: mp 226–227°, $[\alpha]D$ +94°, yield 206 mg, 88%.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.76.

3α-Acetoxy-20α-hydroxy-5β-pregn-9(11)-en-20-one (4h).—A solution of **4g** (0.43 g) in pyridine (10 ml) and acetic anhydride (0.26 ml) was allowed to stand at room temperature for 24 hr. The crude product obtained was chromatographed on silica gel. Elution with benzene–acetone (97:3 to 95:5) gave the diacetate **4f** (250 mg, mp 180–182°) in 46% yield. Further elutions with benzene–acetone (93:7) afforded **4h**: mp 157–158° (from methanol–water), $[\alpha]D$ +110°, yield 120 mg, 25%.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.75; H, 9.12.

3α-Hydroxy-20α-acetoxy-5β-pregn-9(11)-en-12-one (4i).—Partial methanolysis of **4f** (0.62 g) in methanol (30 ml) containing sodium methoxide (3.2 ml of a 2.5% solution) at room temperature for 2 hr was followed by neutralization with dilute hydrochloric acid, dilution with water, and concentration at reduced pressure. The crude **4i** (0.53 g, 94%, mp 172–174°) was purified by column chromatography on silica gel and crystallization from ether–hexane: yield 0.45 g, 80%, mp 177.5–178.5°, $[\alpha]D$ +75°.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.60; H, 9.11.

The Hemipicrates of 3-Amino- and 3-Methylamino-2-oxazolidinone[1]

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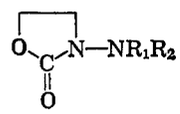
3-Amino-2-oxazolidinone gave a monopicrate or a hemipicrate depending on reaction conditions, while 3-methylamino-2-oxazolidinone gave only a hemipicrate. Conversely, the 3-ethylamino, 3-anilino, and 3-dimethylamino analogs yielded only monopicrates. A number of infrared correlations have been made for the oxazolidinones and their picrates with particular emphasis on hydrogen-bonding effects. It is proposed that in the hemipicrates 1 mole of amine is bound as an amine salt and the second mole is bound by an unusually strong amine–nitro hydrogen bond.

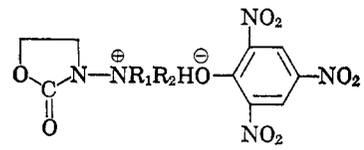
The formation of a hemipicrate between 2 moles of a nitrogen-containing organic compound and 1 mole of picric acid is a known but uncommon reaction. About 50 compounds exhibit this behavior, including aliphatic and aromatic amines, nitrogen heterocycles, and amino-nitrogen heterocycles. Several of these materials also form monopicrates. However, to the best of our knowledge, no attempt to explain the mode of bonding in hemipicrates has been made.

During the course of some work on 3-amino-2-oxazolidinone[2] (I), it was found that I gave both a monopicrate and a hemipicrate. This report describes the preparation of the picrates of I and of several 3-substituted amino-2-oxazolidinones (II–VII). Infrared data have been obtained on the oxazolidinones and their picrates with special emphasis on hydrogen bonding and some postulates have been made on the possible types of bonding in these specific picrates.

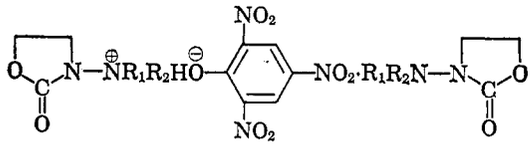


I, $R_1 = R_2 = H$
II, $R_1 = H$; $R_2 = CH_3$
III, $R_1 = H$; $R_2 = C_2H_5$
IV, $R_1 = H$; $R_2 = C_6H_5$
V, $R_1 = H$; $R_2 = COCH_3$
VI, $R_1 = R_2 = CH_3$
VII, $R_1 = R_2 = COCH_3$

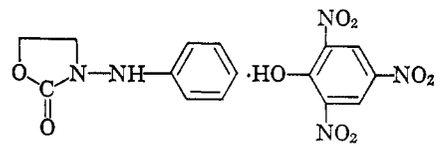
Treatment of I with excess picric acid gave a compound whose infrared spectrum was consistent with an amine salt (VIII). When recrystallization of VIII was attempted from ethanol, the hemipicrate IX was obtained,[3] along with some of the original monopicrate VIII and some free picric acid. The hemipicrate IX was also prepared by the reaction of VIII with I and by the direct reaction of 2 moles of I and 1 mole of picric acid. Conversely, the reaction of IX and picric acid gave VIII.[4] The equimolar reaction of I and picric acid yielded a mixture of both picrates.



VIII, $R_1 = R_2 = H$
XI, $R_1 = H$; $R_2 = C_2H_5$
XII, $R_1 = R_2 = CH_3$



IX, $R_1 = R_2 = H$
X, $R_1 = H$; $R_2 = CH_3$



XIII

The fact that the monopicrate VIII was not completely converted to the hemipicrate IX on heating in ethanol suggested that the buildup of free picric acid might be inhibiting the reaction. This was confirmed when VIII was recrystallized unchanged from ethanol containing 1 equiv of picric acid.

(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, under Contract NOrd 18728, and was monitored by the Bureau of Naval Weapons, RMMP, under Contract NOw 65-0277-c.

(2) G. Gever, U. S. Patent 2,625,402 (1953); *Chem. Abstr.*, **48**, 12179 (1954).

(3) A. L. Remizov and N. V. Khremov-Borisov [*Zh. Obshch. Khim.*, **23**, 794 (1953)] have reported a similar reaction for 4-morpholineacetic acid.

(4) M. de Jong and J. P. Wibaut [*Rec. Trav. Chim.*, **49**, 237 (1930)] have described a similar reaction for pyrrolidine.