and the mixture was diluted with water and extracted with chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Crystallization of the residue from acetone–hexane gave 129 mg. of Vc having m.p. 198–200°, $[\alpha]^{28}\mathrm{D}$ +28° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{32}O_5$ (388.49): C, 71.10; H, 8.30. Found: C, 71.20; H, 8.08.

Following the procedure for obtaining 12β-hydroxy-11-ketoprogesterone (V) from Vb, acid hydrolysis of Vc also gave V. Similarly Vb could be obtained from Vc by ketalization following the same procedure described for V.

11β,12β,20β-Trihydroxypregn-4-en-3-one 11,12-Acetonide (XV) and 11β,12β,20α-Trihydroxypregn-4-en-3-one 11,12-Acetonide (XVI).—A mixture of 1.0 g. of 3-ethylenedioxy-12β-hydroxypregn-5-ene-11,20-dione and 1.0 g. of lithium aluminum hydride in 75 ml. of tetrahydrofuran freshly distilled from lithium aluminum hydride was refluxed for 3.5 hr. with stirring, then cooled, and the excess lithium aluminum hydride was decomposed by the dropwise addition of ethyl acetate. The mixture was then diluted with water and extracted with chloroform which was washed with water and evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of acetone, 0.2 ml. of 70% perchloric acid was added, and the solution was left at room temperature for 2 hr. It was then neutralized with dilute sodium bicarbonate, diluted with water, and extracted with chloroform. The chloroform was washed with water and evaporated to dryness *in vacuo*. Plate chromatography of the residue using Woelm neutral alumina (activity V) as adsorbant and chloroform as the developing solvent gave two bands detectable by ultraviolet at R_f 0.7 and 0.5 which were separated, eluted with ethyl acetate, evaporated, and crystallized from acetone–hexane. The less polar band gave 270 mg. of XVI having m.p. 152–154°, $[\alpha]^{26}\mathrm{D}$ +123° ($CHCl_3$), $\lambda_{\max}^{\text{alc}}$ 239 mμ (ϵ 16,200).

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 74.26; H, 9.35.

From the more polar band 330 mg. of XV was obtained having m.p. 178–180°, $[\alpha]^{26}\mathrm{D}$ +112° ($CHCl_3$), $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 19,100).

Anal. Calcd. for $C_{24}H_{36}O_4$ (388.53): C, 74.19; H, 9.34. Found: C, 74.33; H, 9.42.

Acetylation of XVI at room temperature for 16 hr. using acetic anhydride and pyridine gave the 20α-acetate XVII having m.p. 116–118°, $[\alpha]^{26}\mathrm{D}$ +109° ($CHCl_3$), $\lambda_{\max}^{\text{alc}}$ 238 mμ (ϵ 18,800).

Anal. Calcd. for $C_{26}H_{38}O_5$ (430.56): C, 72.52; H, 8.90. Found: C, 72.72; H, 8.93.

Reaction of XV with acetic anhydride and pyridine under these conditions gave only starting material.

Jones oxidation[5a] of either XV or XVI gave 11β,12β-dihydroxyprogesterone 11,12-acetonide (XI).

The Chemistry of 11,12-Oxygenated Progesterones. II. Hydrogen-Bonding Studies

ALLEN I. COHEN, BARBARA T. KEELER, EDWARD J. BECKER,[1] AND PATRICK A. DIASSI

The Squibb Institute for Medical Research, New Brunswick, New Jersey

Received March 2, 1965

The relationships between structure and hydrogen bonding of 11,12-oxygenated derivatives have been determined by n.m.r. and infrared spectroscopy. In the intramolecular hydrogen-bonding studies, a general correlation is found between the hydroxyl frequency and the proton chemical shift.

Hydrogen bonding in cyclic and acyclic diols has been systematically investigated by high-resolution infrared spectroscopy.[2] Jones, *et al.*,[3a] in their definitive survey, applied infrared spectroscopy to the determination of hydrogen bonding of steroidal ketols and diols. Subsequent investigations have been concerned with various aspects of hydrogen bonding in steroids[3b–d] and triterpenes.[4] The detection and identification of hydrogen bonding by infrared spectroscopy have been instrumental in the assignment of partial structures.[5]

Hydrogen-bonding studies of steroids by n.m.r. spectroscopy have, however, received little attention. In their survey of the n.m.r. of steroids, Shoolery and Rogers[6] presented spectral evidence for hydrogen bonding in a number of steroids which include the ketols, 17α-hydroxyprogesterone and 11-dehydrocorticosterone. Subsequently, there have been only scattered reports of the proton resonance of steroidal hydroxyl groups.[5b,7]

Although solution infrared and n.m.r. spectra are obtained under different conditions, the spectral results are complementary. N.m.r. spectroscopy was used extensively to assign the structure of related 11,12-oxygenated progesterones.[8] Since hydrogen bonding was encountered in these compounds, high-resolution infrared spectra of carbon tetrachloride or deuteriochloroform solutions were also obtained. The interpretation of the hydrogen-bonding phenomena which aided in the subsequent structural assignment of the derivatives is the subject of this report.

Experimental

The method of preparation and the chemical and physical properties of these compounds have been described in the preceding paper.[8] Testosterone and 17α-hydroxyprogesterone were obtained from the Squibb collection. The n.m.r. spectra were obtained by transferring a known quantity of steroid to a 1-ml. volumetric flask and diluting to mark with deuteriochloroform containing 0.5 % (v./v.) tetramethylsilane as an internal refer-

---

(1) Deceased January 23, 1965.

(2) (a) L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger, Jr., and L. Eberson, *J. Am. Chem. Soc.*, **86**, 650 (1964); (b) L. P. Kuhn, *ibid.*, **74**, 2492 (1952); (c) *ibid.*, **76**, 4323 (1954); (d) *ibid.*, **80**, 5950 (1958); (e) L. P. Kuhn and R. A. Wires, *ibid.*, **86**, 2161 (1964); (f) L. P. Kuhn and R. E. Bowman, *Spectrochim. Acta*, **17**, 650 (1961); (g) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959); (h) A. R. H. Cole and P. R. Jefferies, *ibid.*, 439 (1956); (i) R. D. Stolow, P. M. McDonagh, and M. M. Bonaventura, *J. Am. Chem. Soc.*, **86**, 2165 (1964).

(3) (a) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *ibid.*, **74**, 2820 (1952); (b) M. K. Birmingham, H. Traikov, and P. J. Ward, *Steroids*, **1**, 463 (1963); (c) F. V. Brutcher, Jr., and W. Bauer, Jr., *J. Am. Chem. Soc.*, **84**, 2236 (1962); (d) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1957).

(4) A. R. H. Cole and G. T. A. Müller, *ibid.*, 1224 (1959).

(5) (a) M. E. Wall and S. Serota, *Tetrahedron*, **10**, 238 (1960); (b) M. E. Wall, F. I. Carroll, and G. S. Abernethy, Jr., *J. Org. Chem.*, **29**, 604 (1964); (c) R. Nagarajan and G. Just, *Can. J. Chem.*, **39**, 1274 (1961); (d) J. Fajkos, J. Joska, and F. Šorm, *Collection Czechoslov. Chem. Commun.*, **29**, 652 (1964); (e) S. Rakhit and Ch. R. Engel, *Can. J. Chem.*, **40**, 2163 (1962).

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

(7) (a) L. L. Smith, M. Marx, J. J. Carbarini, T. Foell, V. E. Origoni, and J. J. Goodman, *J. Am. Chem. Soc.*, **82**, 4616 (1960); (b) F. v. Werder, K. Bruckner, K. H. Bork, H. Metz, B. Hampel, and H. J. Mannhardt, *Chem. Ber.*, **94**, 2110 (1962); (c) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961); (d) T. Takahashi, *Agr. Biol. Chem.* (Tokyo), **27**, 633 (1963); (e) K. Kuriyama, E. Kondo, and K. Tori, *Tetrahedron Letters*, 2057 (1963); (f) A. I. Laskin, J. Fried, A. I. Cohen, C. Meyers, P. Grabowich, B. Junta, R. M. Palmere, and P. A. Diassi, *Steroids*, **5**, 57 (1965).

(8) E. J. Becker, R. M. Palmere, A. I. Cohen, and P. A. Diassi, *J. Org. Chem.*, **30**, 2169 (1965).

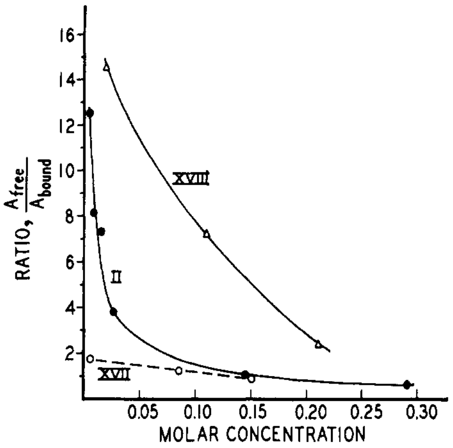


Figure 1.—The variation of the ratio of absorbances of the free and bound hydroxyl absorbances as a function of the solution concentration: ●, 11-keto-12α-hydroxyprogesterone (II); ○, 17α-hydroxyprogesterone (XVII); △, testosterone (XVIII).

ence. Appropriate dilutions of this solution were made to study concentration dependency of the hydroxyl proton chemical shifts. No special precautions were taken to remove any acid which might be present in the solvent. The n.m.r. spectra were obtained with a Varian A-60 spectrometer scanned at a rate of 2 c.p.s. The repeatability of τ is within 0.01 p.p.m. and that of the coupling constant J is within 0.3 c.p.s. The probe, a room temperature type, operates at approximately 33°. Deuterium exchange was performed by adding 0.05 ml. of deuterium oxide to a sample tube containing 0.35 ml. of test solution, shaking several times to mix the two immiscible phases, and then allowing the deuterium oxide to rise above the deuteriochloroform layer. The infrared spectra were obtained from solutions prepared by dissolving the appropriate weights in either carbon tetrachloride or deuteriochloroform. The Perkin-Elmer Model 237 Grating Infracord was operated at the normal slit program (25) and at the slow scanning speed. After obtaining the spectrum, a polystyrene film was inserted and the 2850- and 1603-cm.$^{-1}$ peaks were recorded on the chart and, if necessary, the frequencies of the pertinent bands were corrected. The repeatability of the measured wave length is 5 cm.$^{-1}$. Either 10-mm. quartz cells transmitting to 2500 cm.$^{-1}$ or sodium chloride cavity cells of various thicknesses were used. The temperature of the nonthermostatically controlled cells was approximately 35°.

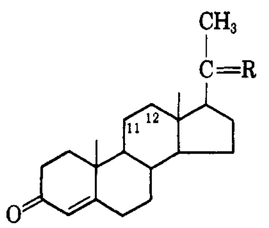
The hydroxyl proton chemical shifts of the 11,12-oxygenated progesterones[9] are tabulated in Table I and that of the 3-ethylene ketal derivatives are tabulated in Table II. The pertinent hydroxyl and carbonyl infrared frequencies are presented in Table III.

Discussion

Bonding of Ketols.—Each of the n.m.r. spectra of the 11,12-ketoprogesterones (VII, II and V) gave evidence for hydrogen bonding[10] and, of the three derivatives at *ca.* 0.2 M concentrations, the axial hydroxyl of 12α-hydroxy-11-ketoprogesterone (II) had a proton resonance at the lowest field (τ 5.67). The carbon tetrachloride infrared spectra of the two equatorial ketols, 11α-hydroxy-12-ketoprogesterone (VII) and 12β-hydroxy-11-ketoprogesterone (V) showed the expected concentration-independent intramolecular hydrogen bonding at 3450 and 3461 cm.$^{-1}$, respectively.

TABLE I

HYDROXYL PROTON RESONANCES OF 11,12-OXYGENATED PROGESTERONES

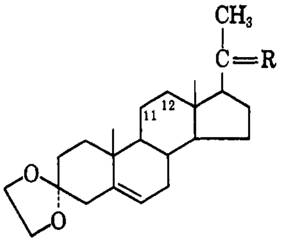


	Substituent			Concn.,	Hydroxyl	
Compd.	C-11	C-12	R	M	Position	τ value
VII	α-OH	=O	O	0.2	11	6.07 (d, 4.3)[a]
				0.01	11	6.09 (m)
II	=O	α-OH	O	0.23	12	5.67 (d, 3.5)
				0.16	12	5.94 (m)[b]
				0.08	12	6.40 (d, 4)
V	=O	β-OH	O	0.2	12	6.13 (d, 4.7)
				0.01	12	6.14 (d, 4.5)
IV	β-OH	α-OH	O	0.2	11, 12	>7.5
IVa	β-OH	α-OAc	O	0.08	11	>7.5
XIII	β-OH	β-OH	O	0.22	11, 12	7.72 (s), 4.41 (s)
				0.11	12	4.40 (s)
					11	7.25 (s)
XIV	α-OH	α-OH	O	0.21	12	6.78 (d, 3.5)
					11	7.29 (s)
				0.11	12	7.02 (d, 3.5)
					11	7.6 (s)
VI	α-OH	β-OH	O	0.19	12	4.85 (s)
					11	7.07 (s)
				0.095	12	4.85 (s)
					11	7.13 (s)
VIa	α-OAc	β-OH	O	0.20	12	5.53 (d, 2.3)
				0.10	12	5.53 (d, 2.3)
XV	β-OH 11,12-Acetonide	β-OH	α-H, β-OH	0.17	20	5.87 (s)
XVI	β-OH 11,12-Acetonide	β-OH	α-OH, β-H	0.19	20	>7.5
XVII	17α-OH		O	0.30	17	6.89 (s)
				0.15	17	7.26 (s)
				0.075	17	7.20 (s)

[a] s, singlet; d, doublet; m, multiplet; J in c.p.s. [b] A proton of an AB coupling pattern.

TABLE II

HYDROXYL PROTON RESONANCES OF 3-ETHYLENE KETAL 11,12-OXYGENATED PROGESTERONES



	Substituents			Concn.,	Hydroxyl	
Compd.	C-11	C-12	R	M	Position	τ value
VIIb	α-OH	=O	$O_2(CH_2)_2$	0.2	11	5.8–6.1
Vb	=O	β-OH	$O_2(CH_2)_2$	0.2	12	4.94 (s)[a]
Vc	=O	β-OH	O	0.2	12	5.8–6.1
X	α-OH	α-OH	$O_2(CH_2)_2$	0.1		[b]
IX	β-OH	β-OH	$O_2(CH_2)_2$	0.15	12	4.65 (s)
					11	7 35 (s)
VIb	α-OH	β-OH	$O_2(CH_2)_2$	0.16	12	4.99 (s)
					11	7.18 (s)
				0.08	12	5.00 (s)
					11	7.20 (s)
				0.04	12	5.00 (s)
					11	7.21 (s)
VIc	α-OAc	β-OH	$O_2(CH_2)_2$	0.13	12	5.16 (s)

[a] s, singlet. [b] Masked by ketal proton resonances and not detected.

---

[9] The numbering of the compounds is the same as that of the compounds named in ref. 8.

[10] In the proton resonance of steroids there are a considerable number of ring protons that occur at fields greater than τ 7.5. Steroids involved in linear intermolecular bonding have proton resonances near τ 8 and therefore are not normally observed. At greater concentration (*ca.* 0.5 M),[8] however, these bands have appeared at lower fields near τ 7. In practice, at 0.2 M concentration, hydrogen-bound hydroxyl protons, other than those linear intermolecularly bound, appear at fields lower than τ 7.5.

TABLE III

INFRARED HYDROXYL AND CARBONYL FREQUENCIES OF 11,12-OXYGENATED DERIVATIVES

			Hydroxyl frequencies, cm.$^{-1}$					Carbonyl frequencies		C-3,
Compd.	Solvent	Concn., M	Free	Intramolecular		Intermolecular	$\frac{A_{free}}{A_{bound}}$	Position	cm.$^{-1}$	cm.$^{-1}$
VIb	CCl_4	0.002			3450			12	1710	
Vb	CCl_4	0.002			3438			11	1703	
Vc	CCl_4	0.0025			3453			11, 20	1708	
X	CCl_4	0.002		3561	3450					
IX	CCl_4	0.002		3558	3430					
VIb	CCl_4	0.002		3558	3438					
	CCl_4	0.001		3556	3436					
	$CDCl_3$	0.008		3550	3400					
	$CDCl_3$	0.05		3550	3410					
VIc	CCl_4	0.002			3438			Acetate	1747	
VII	CCl_4	0.003			3450			12, 20	1714	1680
II	CCl_4	0.001	3600			3400	15	11, 20	1722	1680
	$CDCl_3$	0.29	3600			3400	0.62	11, 20	1717	1667
	$CDCl_3$	0.145	3600			3400	101	11, 20	1711	1672
	$CDCl_3$	0.029	3600			3400	3.8	11, 20	1722	1683
	$CDCl_3$	0.015	3600			3400	7.3	11, 20	1711	1669
	$CDCl_3$	0.009	3605			3400	8.1	11, 20	1711	1672
	$CDCl_3$	0.003	3597			3400	12.5	11, 20	1706	1672
V	CCl_4	0.005			3461			11, 20	1711	1682
IV	CCl_4	<0.001	3600					*a*	*a*	*a*
XIII	CCl_4	0.002		3533	3383			20	1690	1678
XIV	CCl_4	0.001		3583	3550			20	1703	1670
	$CDCl_3$	0.14		3570	3533	3450		20	1700	1661
	$CDCl_3$	0.03		3580	3550			*a*	*a*	*a*
	$CDCl_3$	0.003		3580	3550			*a*	*a*	*a*
VI	CCl_4	0.003		3558	3406			20	1700	1686
VIa	CCl_4	0.0025			3415			20	1711	1682
								Acetate	1744	
XV	CCl_4	0.002			3500			*a*	*a*	*a*
XVI	CCl_4	0.0025	3620					*a*	*a*	*a*
XVII	CCl_4	0.0015	3611		3500		1.4	20	1711	1683
	$CDCl_3$	0.15	3600		3480		0.89	20	1706	1687
	$CDCl_3$	0.075	3600		3480		1.2	20	1706	1667
	$CDCl_3$	0.003	3600		3500		1.7	20	1706	1667
XVIII	$CDCl_3$	0.21	3606			3450	2.9			*a*
	$CDCl_3$	0.11	3608			3450	7.2			*a*
	$CDCl_3$	0.02	3608			3450	14.5			*a*
	$CDCl_3$	0.01	3608							*a*

[a] Not measured.

In dilute (<0.001 M) carbon tetrachloride solution, the infrared spectrum of II exhibited the stretching frequency of both a nonbonded axial hydroxyl (3600 cm.$^{-1}$) and a low-intensity bonded hydroxyl band at 3400 cm.$^{-1}$. The infrared spectrum in deuteriochloroform of II also showed both a free and bound hydroxyl bands, the latter of which could be defined as intermolecular, since the ratio of the absorbances were concentration dependent (*cf.* Figure 1). In the n.m.r., on dilution, the hydroxyl proton resonance of II was shifted to higher field. Thus, the proton resonance is dependent upon the number of molecules with intermolecularly bound hydroxyl protons.

17α-Hydroxyprogesterone (XVII) is an example of a compound exhibiting free and intramolecularly bound infrared hydroxyl bands which have been shown by Jones, *et al.*,[3a] to be concentration independent. This was confirmed over a wider concentration range in this study (*cf.* Figure 1). Testesterone (XVIII), a model for intermolecular hydrogen bonding, has a less marked concentration dependence of the ratio of free and bound hydroxyl absorbances than II. Figure 1 shows the dependence of A_{free}/A_{bound} as a function of the concentration of II, XVIII, and XVII. This concentration dependence suggests that II intermolecularly bonds by cyclic dimerization.[11] Further, the isomeric ketol having an axial hydroxyl group, methyl 11β-hydroxy-12-ketocholanate,[12] has free and bound hydroxyl bands, the absorbance ratio being concentration independent at 3600 and 3450 cm.$^{-1}$, respectively. Cyclic dimerization in this case is prevented by the steric hindrance of the β side of the steroid nucleus and the spectrum is interpreted as the nonbonding (*trans*) and bonding (*cis*) forms of the hydroxyl group.[3a] The n.m.r. spectrum of a 0.15 M solution of methyl 11β-hydroxy-12-ketocholanate has a hydroxyl proton resonance at τ 7.38 ($J_{11,OH}$ = 4 c.p.s.).

The equatorial hydroxyl group of 12β-hydroxylated steroids has been reported[5b,c] to bond intramolecularly to the 20-carbonyl group. Thus, the 12β-hydroxyl of Vc and V may intramolecularly bond at either the 11- or the 20-carbonyl. The bonding site could not be determined from the infrared spectra because the hy-

---

[11] Cole and Müller[4] observed a weak hydroxyl band at 3436 cm.$^{-1}$ in the α-ketol cerin and suggest the cyclic dimer as the possible bonding form. Jones, *et al.*,[3a] have observed that 17β-hydroxyisoprogesterone exhibits concentration dependent bound and free hydroxyl infrared bands similar to II which may also be attributed to dimeric hydrogen bonding.

[12] Kindly supplied by Dr. O. Wintersteiner of this laboratory.

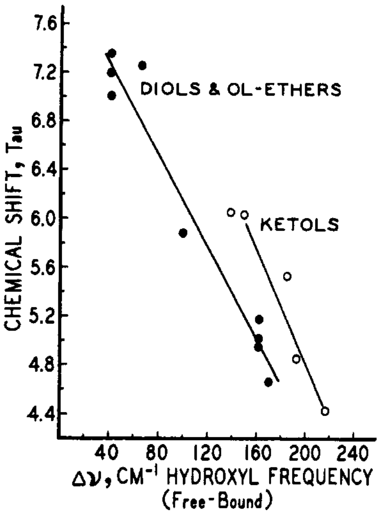


Figure 2.—The variation of the hydroxyl chemical shift as a function of $\Delta\nu$ (cm.$^{-1}$) of the hydroxyl infrared band: ●, hydroxyls bonded to an ether oxygen or hydroxyl oxygen; ○, hydrogen bonding of ketols.

droxyl stretching frequency of the model compounds bonded to either the 11-carbonyl or the 20-carbonyl[13] are not significantly different, and the carbonyl stretching frequencies are not indicative of the bonding site.[14] An inference that the 12β-hydroxyl of V (and Vc) does bond to the vicinal carbonyl, however, could be made from the n.m.r. data. The hydroxyl proton resonance in Vc appears near τ 6.1 at a similar position to the 11α,12-ketol (VII), whereas compounds known to have 12β-hydroxy-20-carbonyl intramolecular bonding have the resonance at lower fields (τ 4.4–5.1).[15] Further, the 21-methyl proton resonance of compounds Vc and V appears at τ 7.66 and 7.69, respectively, and the resonance of the 11,12β-acetonides VIII and XI appears at τ 7.69,[8] whereas the band for 12β-hydroxy derivatives bonded to the 20-carbonyl is at τ 7.75–7.80.[16]

The hydroxyl frequency of the α-ketol bisketal Vb occurs at 3438 cm.$^{-1}$ and hydroxyl proton resonance is observed at τ 4.94. Perturbation of four of the ketal protons in Vb (τ 6.07, singlet, C-3 ketal; τ 6.02, multiplet, C-20 ketal) and data cited in the discussion concerning bonding in ol–ethers show that bonding in this compound is between the hydroxyl and a ketal oxygen and not between the carbonyl and hydroxyl groups.

Bonding of Diols and Ol–Ethers.—The 11-acetate of the 11α,12β-diol bisketal VIc shows an intramolecularly bound hydroxyl (τ 5.16, 3438 cm.$^{-1}$) similar to the α-ketol bisketal Vb. The spectral data of the diol bisketals IX and VIb indicate the 12β-hydroxyl group intramolecularly hydrogen bonds to the oxygen or the 20-ketal (IX, τ 4.65, 3430 cm.$^{-1}$; VIb, τ 5.00, 3438 cm.$^{-1}$). The deshielding of the C-20 ethylene ketal protons supports this conclusion, since the nonbonded ketal oxygen derivatives, VIIb and X, exhibit only a broadened singlet eight-proton resonance at τ 6.07. Finally, the ease of hydrolysis of the C-20 ethylene ketal of Vb to form Vc[17] under conditions where other C-20 ketals are stable suggests that the 12β-hydroxyl, through hydrogen bonding, anchimerically assists the hydrolysis.

The 11,12β-diol progesterones XIII and VI exhibit a second intramolecularly bound hydroxyl due to bonding of the 11-hydroxyl to the oxygen of 12β-hydroxyl the hydrogen of which is bound to C-20 carbonyl. The corresponding bisketals IX and VIb also exhibit a second intramolecularly bound hydroxyl to the oxygen of the 12β-hydroxyl group. The hydrogen bonding of the 11-ol in these derivatives is anticipated[2a–d] in *cis* axial–equatorial or *trans* diequatorial diols. The *trans* diaxial diol IV and the acetylated derivative IVa yield spectra with no hydrogen bonding (3600 cm.$^{-1}$, τ >7.5).

The carbon tetrachloride solution infrared spectrum of the 11α,12α-diol XIV has two hydroxyl stretching frequency bands at 3583 and 3550 cm.$^{-1}$, the separation which is expected for *cis*-1,2-diol cyclohexane derivatives.[2a–d] In 0.14 *M* deuteriochloroform solution, a lower frequency band appears at 3450 cm.$^{-1}$ which indicates that intermolecular bonding occurs at higher concentrations. The concentration dependence is also observed in the two hydroxyl proton bands that are present in the n.m.r. spectra. Again the α side of the steroid is amenable to intermolecular bonding. At a 0.002 *M* concentration, in carbon tetrachloride, the 11α,12α-diol bisketal X has three hydroxyl bands (sh 3590 weak, 3561 strong, 3450 cm.$^{-1}$ medium). A $\Delta\nu$ of 111 cm.$^{-1}$ is much greater than expected[2a–d] for 1,2-*cis*-cyclohexyl diols. The 3450-cm.$^{-1}$ band might possibly be due to intermolecular bonding. However, no additional infrared data to substantiate this was obtained.

Finally, hydrogen-bonding studies were instrumental in assigning the stereochemistry of the epimeric 11β,12β,20-triol 11,12-acetonides XV and XVI. Compound XV, assigned to the 20β-ol configuration, exhibits an intramolecularly bound hydroxyl (3500 cm.$^{-1}$, τ 5.87). The 20α-ol epimer has a free hydroxyl (3620 cm.$^{-1}$, τ >7.5). Examination of the Drieding models of both epimers shows that intramolecular hydrogen bonding in the 20α-ol is sterically hindered by the C-18 and the C-21 methyl groups.

Infrared and N.m.r. Correlations.—The expression, $\Delta\nu$, the difference between 3600 cm.$^{-1}$ [18] and the intramolecularly bound hydroxyl frequency, is plotted as a function of the n.m.r. proton resonance of the hydroxyl group in Figure 2. The hydroxyls bonded to an ether oxygen or hydroxyl oxygen are represented by closed circles, while hydrogen bonding of ketols is represented by open circles. Although the infrared and n.m.r. spectra were obtained under different conditions of solvent, concentration, and temperature, there appears

---

[13] The hydroxyl stretching frequencies of the equatorial ketols VIIb and VII are both at 3450 cm.$^{-1}$, while the hydroxyls bonded in 12β-hydroxy 20-carbonyl derivatives have been reported to fall between 3430 and 3450 cm.$^{-1}$,[5b,c] The 11,12β-diols XIII and VI had slightly lower bound hydroxyl stretching frequencies (3383 and 3406 cm.$^{-1}$).

[14] It would have been instructive to note a significant change in the carbonyl frequencies. At the resolution attainable with our instrument, however, both the 11- and 20-carbonyls absorbed at the same frequency (1710 cm.$^{-1}$). In general, the carbonyl frequency changes due to hydrogen bonding were small. In carbon tetrachloride, with one exception, the observed bonded and nonbonded saturated carbonyl frequencies were 1700 to 1714 cm.$^{-1}$.

[15] These chemical shifts were noted in the following 12β-hydroxyprogesterones: 15α-hydroxy, τ 5.08; 9α-fluoro, τ 5.11; and compounds XIII and VI (*cf.* Table I).

[16] The model compounds are cited in ref. 15.

[17] See Experimental.[8]

[18] As defined, $\Delta\nu$ is the difference in frequency of the bonded and nonbonded hydroxyls of α,β-diols.[2b] For purposes of evaluation in this study, 3600 cm $^{-1}$ is taken as a reasonable frequency of a nonbonded cyclic secondary hydroxyl.

to be proportionality between the deshielding of the hydroxyl proton and the lowering of the intramolecularly bound hydroxyl frequency.[19,20] Dilution causes only secondary effects in the chemical shifts.[21]

Kuhn[2b] derived an expression in which $\Delta\nu$ is inversely related to the distance between the hydroxyl proton and the bonding oxygen. Using the modified expression,[3c] the respective calculated bond distances for diols and ol–ethers with a $\Delta\nu$ of 160–170, 100, 67, and 42–46 cm.$^{-1}$ are 1.6, 1.8, 2.0, and 2.3 Å. This compares favorably with the distances measured on Drieding models of 1.3, 1.6, 2.4, and 2.4 Å., respectively. The largest $\Delta\nu$ (160–170) is caused by the bonding of a 12β-hydroxyl with a C-20 ethylene ketal oxygen and represents an extremely small bonding distance.

The respective $\Delta\nu$ for the 11,12-ketols VII and V is 140–150 and 180–217 for the 12β-hydroxy-20-keto derivatives. No general equation for the dependence of ketol frequencies and bonding distances has yet been derived. However, if the dependence of $\Delta\nu$ with bonding distance also holds in ketols, the bonding distance in 12β-hydroxy 20-ketones should be less than in the 11,12-ketols VII and V (2.2 Å.).

[19] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 15.

[20] In ref. 19, p. 406, the authors suggest similar correlation of infrared and n.m.r. data.

[21] See ref. 19, p. 413.

Formation and Identification of *cis*- and *trans*-Dihydroxyimidazolidinones from Ureas and Glyoxal

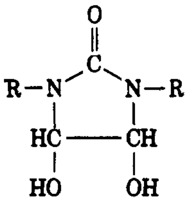
SIDNEY L. VAIL, ROBERT H. BARKER, AND P. GARY MENNITT

Southern Regional Research Laboratory,[1,2] Department of Chemistry, Tulane University, New Orleans, Louisiana, and U. S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Maryland

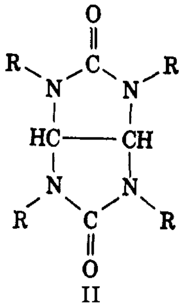
Received January 14, 1965

The additions of N,N′-dimethylurea and urea to glyoxal under both acidic and basic conditions to form 4,5-dihydroxy-2-imidazolidinones have been studied. Rates for the formation of *cis*- and *trans*-4,5-dihydroxy-1,3-dimethyl-2-imidazolidinone and for conversion of the pure isomers to an equilibrium mixture at various pH values were examined by n.m.r. It is probable that equimolar amounts of the *cis* and *trans* isomers are formed initially by a nonstereospecific addition, but the less stable *cis* isomer is rapidly converted to *trans* under the conditions of the reaction. The resulting equilibrium mixture of products is predominantly the *trans* isomer.

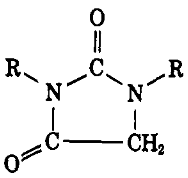
The addition of ureas to glyoxal produces several different heterocyclic compounds. 4,5-Dihydroxy-2-imidazolidinones (I) generally are isolated from base-catalyzed additions, synthesis of both Ia[3] and Ib[4] having been reported. Separation of the geometric isomers was indicated[4a] for the latter compound (Ib); however, the isomers were not assigned a configuration, nor was there described an adequate procedure by which they could be isolated. Several 1-alkyl and 1-aryl derivatives of I have been reported in the patent literature,[5] but characterization of the products was incomplete. In acid-catalyzed additions glycolurils (II) and/or hydantoins (III) are the reported products[6]; however, formation of III (R = CH_3) has not been found[7] in acid-catalyzed additions using N,N′-dimethylurea.



Ia, R = H
b, R = CH_3



II



III

The base-catalyzed addition of ureas to glyoxal is thought to be preceded by the abstraction of a proton from the urea. The resulting nucleophile attacks the glyoxal to produce the linear intermediate IV. Cycliza-

---

[1] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Inquiries should be directed to this laboratory to the attention of S. L. V. or R. H. B.

[2] The mention of trade names and firms does not imply their endorsement by the Department of Agriculture over similar products or firms not mentioned.

[3] See, for example, (a) H. Pauly and H. Sauter, *Ber.*, **63B**, 2063 (1930); (b) Badische Anilin- and Soda-Fabrik Akt., British Patent 717,287 (Oct. 27, 1954); (c) E. Torke and J. König (to Phrix-Werke A. G.), U. S. Patent 2,876,062 (March 3, 1959); (d) H. B. Goldstein and M. A. Silvestri (to Sun Chemical Corp.), U. S. Patent 3,049,446 (Aug. 14, 1962); (e) D. D. Gagliardi, W. J. Jutras, Jr., and E. Stern (to Gagliardi Research Corp.), Belgian Patent 616,785 (May 15, 1962); *Chem. Abstr.*, **58**, 1467c (1963). In general, these patents agree that Ia is isolated under neutral or basic conditions; however, there is not general agreement on the results when the addition is acid catalyzed.

[4] (a) S. L. Vail, P. J. Murphy, Jr., J. G. Frick, Jr., and J. D. Reid, *Am. Dyestuff Reptr.*, **50**, 550 (1961); (b) S. L. Vail and P. J. Murphy, Jr. (to U. S. Department of Agriculture), U. S. Patent 3,112,156 (Nov. 26, 1963); (c) M. T. Beachem and W. K. Van Loo, Jr. (to American Cyanamid Co.), Belgian Patent 614,586 (Sept. 3, 1962); *Chem. Abstr.*, **58**, 10348c (1963); (d) W. A. Burris (to American Cyanamid Co.), U. S. Patent 3,091,617 (May 28, 1963); the dimethyl ether of Ib is reported in this reference.

[5] Badische Anilin- and Soda-Fabrik Akt., British Patent 783,051 (Sept. 18, 1957).

[6] (a) F. B. Slezak, H. Bluestone, T. A. Magee, and J. H. Wotiz, *J. Org. Chem.*, **27**, 2181 (1962); (b) J. Nematollahi and R. Ketcham, *J. Org. Chem.*, **28**, 2378 (1963); (c) E. Ware, *Chem. Rev.*, **46**, 403 (1950).

[7] Our attempts to prepare III (R = CH_3) from N,N′-dimethylurea and glyoxal yielded only II (R = CH_3). A literature search indicated that formation of III (R = CH_3) from these reactants has not been reported.