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1,4-Carbonyl-Carbonyl Interactions

It is well known that natural (20-normal) steroids containing a carbonyl group at the 22-position can be isomerized to the 20-iso compounds, usually to the greater part. This is true for 22-carbonyl steroids unsubstituted at C-16 as well as for such compounds bearing a 16α-acetoxy or a 16-cycloethylenedioxy grouping (for leading references, see [1]).

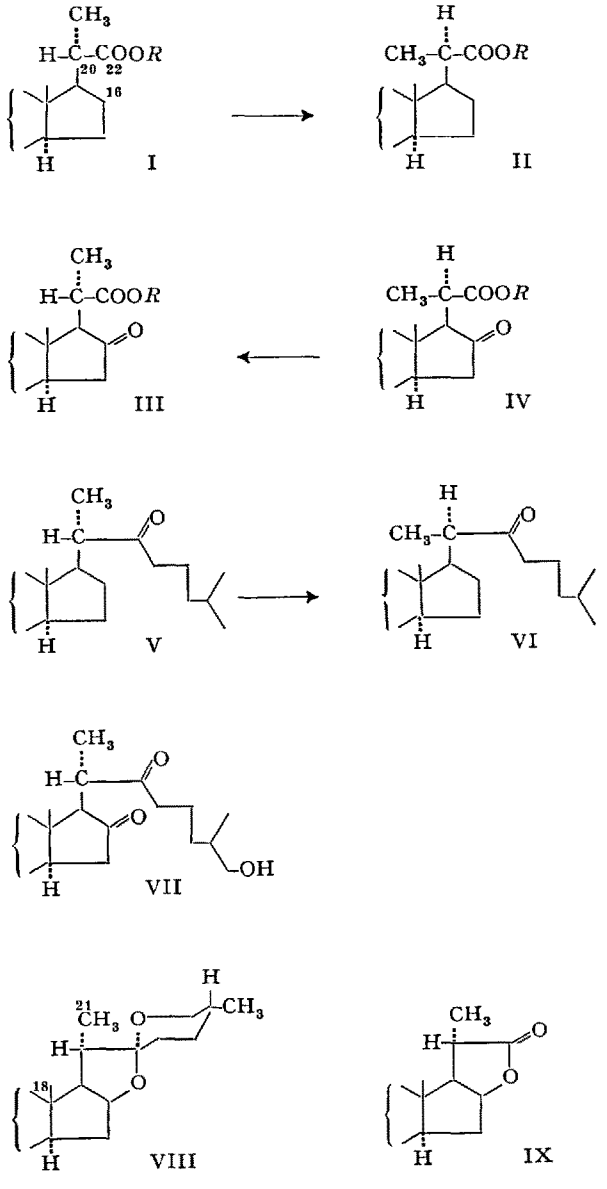
We have recently remarked[1] on the surprising fact that when an additional keto group is introduced at C-16 into a 22-carbonyl steroid, the stability relationship is reversed and the 20-normal configuration becomes the more stable. Thus, whereas esters of 16-unsubstituted bisnorcholanic acids (type I) can be inverted with base to the 20-iso compounds (II)[2,3], the 16-keto ester, methyl 3,16-diketobisnorcholanate (III), cannot be inverted and in fact is obtained quantitatively from the 20-iso ester IV by treatment with base and re-esterification[1]. Similarly, whereas 22-ketocholesterol (V) can be inverted to the 20-iso epimer VI[4], 16,22-diketo-27-hydroxycholesterol (kryptogenin) (VII) appears to possess the stable configuration at C-20[1].

In the case where the 20-position forms part of a ring, as in the steroidal sapogenins of type VIII or in the derived lactones IX, the natural 21α-methyl configuration (as shown) is the stable one. This is in keeping with expectation, since the 21-methyl group is fixed in space in these substances and there is considerable interference between the 18β- and 21β-methyl groups in the corresponding unnatural 20-iso compounds[3].

A likely explanation for the observed stability of the 16,22-dicarbonyl compounds III and VII appeared to us to involve the existence of an intramolecular field effect between the two carbonyl dipoles in these compounds, which would favour the carbonyl groups being close to each other. In this spatial arrangement, interference between the 21- and 18β-methyl groups would occur in the 20-iso but not in the 20-normal (21α-methyl) series, the situation paralleling that which exists in the cyclic systems VIII and IX.

We have now found indications that this type of field effect is in fact operative, by a study of the infrared spectra. These show that interaction between the 16- and 22-carbonyl groups in compounds of type III and VII does occur, as indicated by the raising of the carbonyl frequencies compared with the normal values.

In Table I are recorded the infrared carbonyl bands in the 1700 cm^{-1} region of a number of steroidal 22-monoketones (X–XIV). All of these compounds, whether substituted at C_{16} or at C_{27}, absorb at 1704 (± 2) cm^{-1}, the normal value[5]. In Table II, the corresponding infrared bands of several 16,22-diketones (XV–XX) are listed. It can be seen that all of these substances show two bands. The one at 1731 (± 1) cm^{-1}, due to the 16-keto group, is normal for an α-substituted cyclopentanone, α-methylcyclopentanone (XXII) showing the ketone band at 1730 cm^{-1} (Table III). However, the other band at 1714 (± 2) cm^{-1}, due to the 22-carbonyl group, has been displaced upwards by ca. 10 cm^{-1} compared with the values for the 22-monoketones listed in Table I[6]. This effect clearly demonstrates that an interaction between the two carbonyl groups is operative.



[1] N. Danieli, Y. Mazur, and F. Sondheimer, Chem. & Ind. *1958*, 1725.

[2] H. Wieland, O. Schlichting, and R. Jacobi, Z. physiol. Chem. *161*, 80 (1926). – M. Sorkin and T. Reichstein, Helv. chim. Acta *27*, 1631 (1944); *28*, 875 (1945).

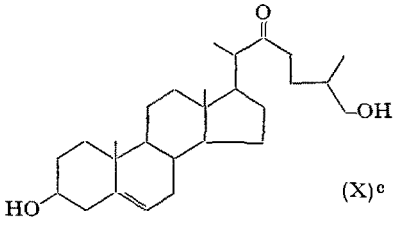
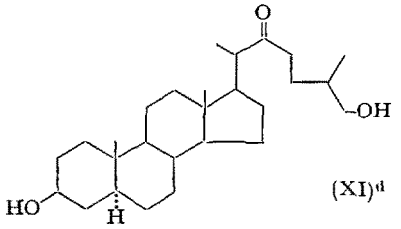
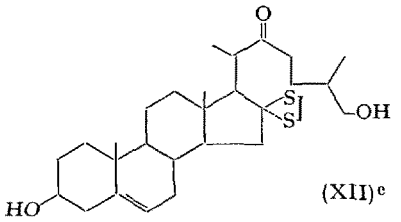
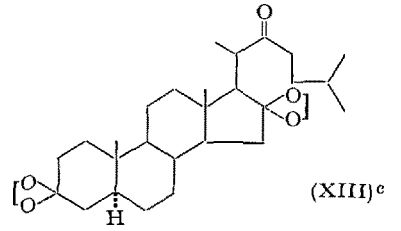
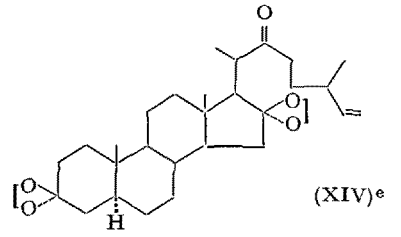
[3] J. W. Corcoran and H. Hirschmann, J. Amer. chem. Soc. *78*, 2325 (1956) and references to earlier work cited there.

[4] R. Hayatsu, Pharm. Bull. (Japan) *5*, 452 (1957).

[5] R. N. Jones and F. Herling, J. org. Chem. *19*, 1252 (1954).

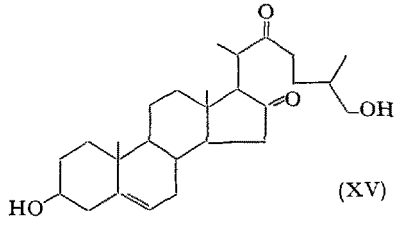
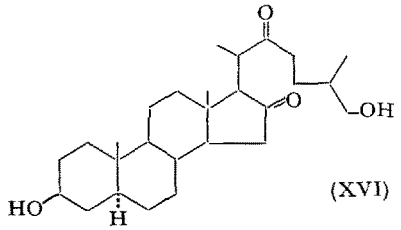
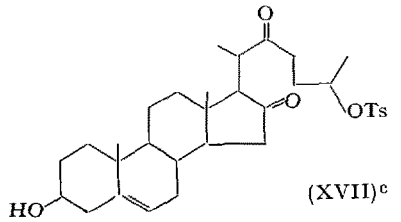
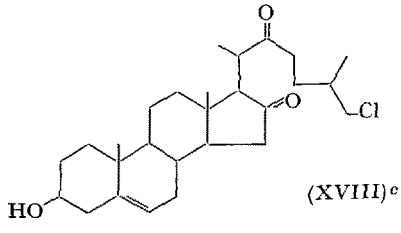
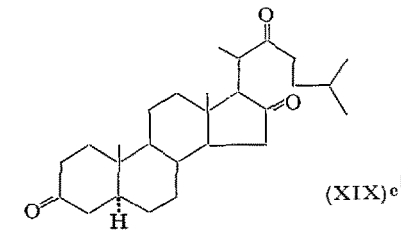
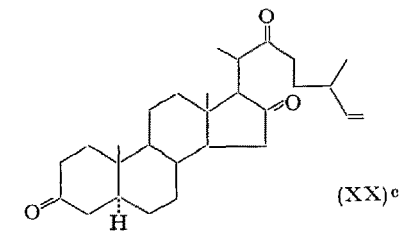
[6] In the compounds (XIX) and (XX) in Table II, the band at 1716 cm^{-1} is due both to the 22- and to the 3-carbonyl group. Since the normal values for these individual functions are 1704 cm^{-1} (Table I) and ca. 1708 cm^{-1}, the observed values have also been displaced upwards by ca. 10 cm^{-1}.

Table I

Compound [a]	$\nu_{max}(CHCl_3)$ [b]
 (X)[c]	1703 cm^{-1}
 (XI)[d]	1706 cm^{-1}[d]
 (XII)[e]	1703 cm^{-1}
 (XIII)[e]	1705 cm^{-1}
 (XIV)[e]	1705 cm^{-1}

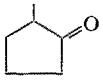
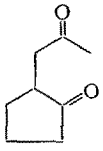
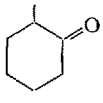
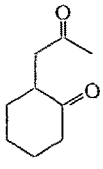
[a] All compounds possess the natural configuration at C-20.
[b] All values determined by ourselves, except where stated otherwise.
[c] Prepared in these Laboratories.
[d] I. SCHEER, M. J. THOMPSON, and E. MOSETTIG, J. Amer. chem. Soc. *79*, 3218 (1957).
[e] Y. MAZUR and F. SONDHEIMER, J. Amer. chem. Soc. *81*, 3161 (1959).

Table II

Compound [a]	$\nu_{max}(CHCl_3)$ [b]
 (XV)	1714, 1732 cm^{-1}
 (XVI)	1714, 1731 cm^{-1}
 (XVII)[c]	1715, 1732 cm^{-1}
 (XVIII)[c]	1713, 1732 cm^{-1}
 (XIX)[c]	1716, 1730 cm^{-1}
 (XX)[c]	1716, 1730 cm^{-1}

[a] All compounds possess the natural configuration at C-20.
[b] All values determined by ourselves.
[c] Prepared in these Laboratories.

Table III

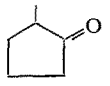
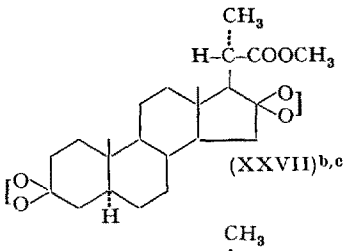
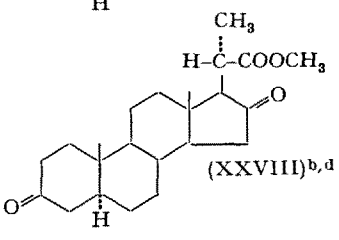
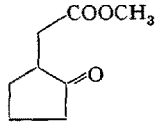
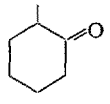
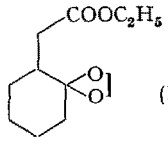
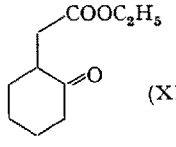
Compound		$\nu_{max}(CHCl_3)$ [a]
CH_3COCH_3	(XXI)	1712 cm^{-1}
	(XXII)	1730 cm^{-1}
	(XXIII)[b]	1721, 1731 cm^{-1}
	(XXIV)	1703 cm^{-1}
	(XXV)[c]	1708 cm^{-1}
$CH_3COCH_2CH_2COCH_3$	(XXVI)	1712 cm^{-1}

[a] All values determined by ourselves.
[b] H. PAUL and I. WENDEL, Chem. Ber. *90*, 1342 (1957).
[c] H. E. BAUMGARTEN, P. L. CREGER, and C. E. VILLARS, J. Amer. chem. Soc. *80*, 6609 (1958).

This type of interaction between the keto groups in 1,4-diketones is not restricted to steroids, as appears from the data presented in Table III. Thus, α-acetonylcyclopentanone (XXIII) (which contains the same type of system as the 16,22-diketo steroids) exhibits the cyclopentanone band at the normal position at 1731 cm^{-1} [compared with 1730 cm^{-1} for α-methylcyclopentanone (XXII)], but the alicyclic carbonyl band at 1721 cm^{-1} has been displaced upwards by ca. 9 cm^{-1} compared with an ordinary acyclic ketone such as acetone (XXI) (1712 cm^{-1}). On the other hand, the corresponding six-membered ring analog α-acetonylcyclohexanone (XXV) and the acyclic analog acetonylacetone (XXVI) both show carbonyl bands at normal positions.

The postulated type of 1,4-carbonyl-carbonyl interaction is operative also with 1,4-keto-esters, as is aparent from an examination of their infrared spectra (though not as markedly as with the 1,4-diketones). It can be seen from the data in Table IV that in methyl 3,16-diketobisnorcholanate (XXVIII) the superimposed ester and 16-keto band at 1734 cm^{-1} is ca. 5 cm^{-1} higher than would be expected from the superposition of the ester band in the corresponding dicycloethylene ketal (XXVII) (1727 cm^{-1}) and the ketone band in α-methylcyclopentanone (XXII) (1730 cm^{-1}). Again the effect is not restricted to steroids and, in the analogous ethyl α-cyclopentanone-acetate (XXX), the superposed ester and cyclopentanone band at 1733 cm^{-1} is ca. 5 cm^{-1} higher than would be expected from the superposition of the bands of the individual functions (1726 and 1730 cm^{-1}). On the other

Table IV

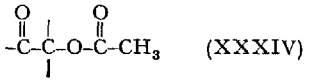
Compound		$\nu_{max}(CHCl_3)$ [a]
	(XXII)	1730 cm^{-1}
	(XXVII)[b,c]	1727 cm^{-1}
	(XXVIII)[b,d]	1710, 1734 cm^{-1}
$CH_3COOC_2H_5$	(XXIX)	1726 cm^{-1}
	(XXX)[e]	1733 cm^{-1}
	(XXIV)	1703 cm^{-1}
	(XXXI)[f]	1725 cm^{-1}
	(XXXII)[g]	1704, 1724 cm^{-1}
$CH_3COCH_2CH_2COOC_2H_5$	(XXXIII)	1712, 1726 cm^{-1}

[a] All values determined by ourselves.
[b] J. W. CORCORAN and H. HIRSCHMANN, J. Amer. chem. Soc. *78*, 2325 (1956).
[c] Y. MAZUR and F. SONDHEIMER, J. Amer. chem. Soc. *81*, 3161 (1959).
[d] N. DANIELI, Y. MAZUR, and F. SONDHEIMER, Chem. & Ind. 1725, (1958).
[e] *Cf.* A. KÖTZ, Liebigs Ann. *350*, 238 (1906).
[f] Prepared in these Laboratories.
[g] Kindly presented by Dr. A. MEISELS.

hand, the corresponding six-membered ring analog (XXXII) and the acyclic analog ethyl levulinate (XXXIII) show carbonyl bands at normal positions.

It therefore appears that the interaction between the carbonyl groups both in 1,4-diketones and in 1,4-keto-esters occurs only when one ketone is in a five-membered ring, presumably because the latter renders the system more rigid.

The presently described carbonyl-carbonyl interactions in 1,4-dicarbonyl compounds are probably of the same type as exist in α-acetoxy-ketones of type (XXXIV), which may also be considered as 1,4-dicarbonyl systems. Thus, in 21-acetoxy-20-keto-steroids the ketone band as well as the ester band is raised by ca. 20 cm^{-1} over the normal values[5,7,8] while in 17α- and 17β-acetoxy-20-keto-steroids the ketone band is raised by ca. 8 cm^{-1} (the acetate band being essentially unaffected)[8,9]. Similar effects have been found in steroidal 12-acetoxy-11-ones and 11-acetoxy-12-ones[10].



(XXXIV)

It has already been postulated by JONES *et al.*[8,11] that the anomalous infrared spectra of these α-acetoxy-ketones are due to the existence of a field effect between the two carbonyl groups and BELLAMY and WILLIAMS[12] have provided evidence for this by pointing out that the anomaly is markedly dependant on steric factors. The steric nature of this effect is also shown well by our finding (Table V) that whereas the expected raising of the infrared carbonyl bands occurs with acetol acetate (XXXVI) (+ 21 cm^{-1} for the ketone band; + 21 cm^{-1} for the ester band) it is considerably less marked in acetol pivalate (+ 11 cm^{-1} and 18 cm^{-1}, respectively) in which the extra methyl groups prevent the carbonyl dipoles from being as close to each other as in the acetate.

Table V

Compound	$\nu_{max}(CHCl_3)$[a]
CH_3COCH_3 (XXI)	1712 cm^{-1}
$CH_3COOC_2H_5$ (XXIX)	1726 cm^{-1}
$(CH_3)_3COOCH_3$ (XXXV)	1718 cm^{-1}
$CH_3COCH_2OCOCH_3$ (XXXVI)[b] . .	1733, 1747 cm^{-1}
$CH_3COCH_2OCOC(CH_3)_3$ (XXXVII)[b]	1723, 1736 cm^{-1}

[a] All values determined by ourselves.

[b] Prepared in these Laboratories by reaction of α-chloro-acetone with the corresponding potassium alkoxide.

All the infrared data discussed clearly point to the existence of an intramolecular field effect between the carbonyl groups in certain 1,4-dicarbonyl compounds. Although the exact nature of this effect is still not well understood, it must operate between the dipoles across space and is clearly different in nature from inductive and mesomeric effects which are transmitted through the chain.

We thank Dr. S. PINCHAS, Weizmann Institute of Science, who determined most of the infrared spectra on a Perkin-Elmer model 12 C single-beam spectrophotometer (sodium chloride optics).

Y. MAZUR* and F. SONDHEIMER

Daniel Sieff Research Institute, Weizmann Institute of Science, Rehovoth (Israel), January 5, 1960.

Zusammenfassung

Es wird gezeigt, dass die IR-Spektren gewisser 1,4-Diketone und 1,4-Ketoester abnorm hohe Carbonylfrequenzen aufweisen, was auf das Vorhandensein eines intramolekularen Feldeffekts zwischen den beiden Carbonylgruppen in diesen Verbindungen hindeutet. Die ungewöhnlichen Stabilitätsverhältnisse an C-20 der 16,22-Dicarbonyl-Steroide sind vermutlich auf die gleiche 1,4-Carbonyl-Carbonyl-Einwirkung zurückzuführen.

* At present Fellow of the School for Advanced Studies, Massachusetts Institute of Technology, Cambridge, Mass., U.S.A.

[7] R. N. JONES, P. HUMPHRIES, and K. DOBRINER, J. Amer. chem. Soc. *72*, 956 (1950).

[8] R. N. JONES, P. HUMPHRIES, F. HERLING, and K. DOBRINER, J. Amer. chem Soc. *74*, 2820 (1952).

[9] R. B. TURNER, J. Amer. chem. Soc. *75*, 3489 (1953).

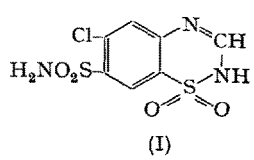
[10] J. ELKS, G. H. PHILLIPS, T. WALKER, and L. J. WYMAN, J. chem. Soc. *1956*, 4330.

[11] R. N. JONES and C. SANDORFY, *Chemical Applications of Spectroscopy* (Interscience, New York 1956).

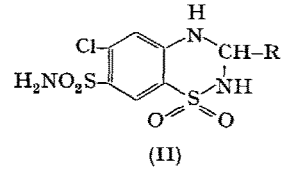
[12] L. J. BELLAMY and R. L. WILLIAMS, J. chem. Soc. *1957*, 861.

3-Haloalkyl-Dihydrobenzothiadiazine Dioxides as Potent Diuretic Agents

The class of compounds based on the 1,2,4-benzothiadiazine nucleus became important from the standpoint of pharmacological activity with the discovery that 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (I) was a potent, orally effective diuretic agent of low toxicity[1].



(I)



(II)

As part of a program directed towards structural modifications of I, with the view of finding other agents of increased activity along with superior electrolyte excretion patterns, we have prepared a series of compounds

[1] F. C. NOVELLO and J. M. SPRAGUE, J. Amer. chem. Soc. *79*, 2028 (1957). The generic name of this compound is chlorothiazide.

[2] G. DE STEVENS, L. H. WERNER, A. HALAMANDARIS, and S. RICCA JR., Exper. *14*, 463 (1958). The generic name of this compound is hydrochlorothiazide.

[3] Hahnemann Medical College and Hospital, *Symposium on Edema*, Philadelphia, Pa., December 7 to 11 (1959).