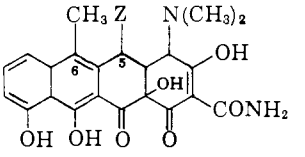
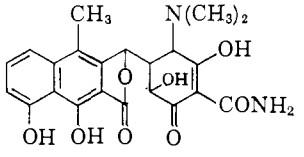


XVIII, Z = H
XIX, Z = OH

cycline (XV).[9] [M.p. 205° (dec.) $\lambda_{max}^{MeOH \cdot 0.01\ N\ HCl}$ 253 and 345 mμ log ε 4.37 and 4.19. *Anal.* found for $C_{22}H_{22}O_8N_2 \cdot HCl \cdot 0.5H_2O \cdot 0.5CH_3OH$: C, 54.0; H, 5.3; N, 5.4; Cl^-, 6.9; H_2O, 1.9; OCH_3, 3.1]. That XV possesses the methylene structure is deduced from spectral properties, from formation of formaldehyde on ozonolysis,[7] and from its conversion by treatment with hot aqueous acid to the apoterramycins (XX)[10] via the intermediate acid unstable (XIX) 5a,6-anhydro-5-hydroxytetracycline.[10]



XX

Chlorination of *11a-chloro-6-methylene-5-hydroxytetracycline* (XII) with N-chlorosuccinimide in liquid hydrogen fluoride, then hydrosulfite reduction of the intermediate *dichloro derivative* XIII, yields (XVII) *7-chloro-6-methylene-5-hydroxytetracycline* [$\lambda_{max}^{CH_3OH \cdot 0.01\ N\ HCl}$ 245, 347 mμ, log ε 4.34, 4.10. *Anal.* Found for $C_{22}H_{21}N_2O_8Cl$: C, 55.3; H, 4.4; N, 5.6; Cl, 7.5]. The assignment of structure to XVII is based on composition, spectral data, and the observation that an exhaustive methylation–oxidation sequence converts it to 6-chloro-3-methoxyphthalic anhydride.[11]

The 6-methylenetetracyclines (XIV, XV, XVI, XVII) described herein show broad *in vitro* antimicrobial activity.[12] Illustrative are the biological assay data shown in Table I.

TABLE I

Compound	Biological assay, 5-hydroxytetracycline units per mg.[13]
Tetracycline (II)	1000
5-Hydroxytetracycline (III)	1000
6-Methylenetetracycline (XIV)	1200
6-Methylene-5-hydroxytetracycline (XV)	2300
7-Chloro-6-methylene-5-hydroxytetracycline (XVII)	6300

(9) Similarly 7-chlorotetracycline (IV) has been converted to *7-chloro-6-methylenetetracycline* (XVI).

(10) Both the α and β forms of apoterramycin are obtained—*cf.* F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5455 (1953).

(11) S. Kushner, J. H. Boothe, J. Morton, J. Petisi and J. H. Williams, *ibid.*, **74**, 3710 (1952).

(12) We are indebted to Drs. A. R. English, T. J. McBride and B. A. Sobin for permission to disclose their unpublished biological studies.

(13) Based on the standard 5-hydroxytetracycline biological assay against *Klebsiella pneumoniae*, *cf.* R. C. Kersey, *J. Am. Pharm. Assoc.*, **39**, 252 (1950). We are indebted to Mr. J. J. Smith and his associates for these assays.

Of particular potential significance is 6-methylene-5-hydroxytetracycline (XV), a compound which shows evidence of superior therapeutic effect in animals as compared to earlier tetracyclines.[12]

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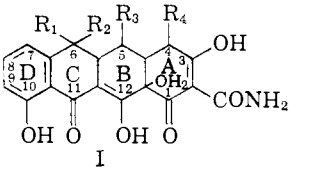
RECEIVED MAY 8, 1961

FLUOROTETRACYCLINES. I. PERCHLORYL FLUORIDE STUDIES IN THE TETRACYCLINE SERIES

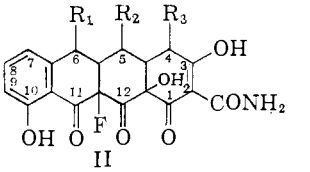
Sir:

Interaction of perchloryl fluoride[1] under suitable conditions[2] with a variety of tetracyclines (Ia-Ih) has resulted in two classes of active methylene fluorination products (II and III). These substances are of unusual interest as intermediates for further transformations and as model substances in more clearly defining various questions of stereochemistry and reaction mechanism in the tetracycline series.



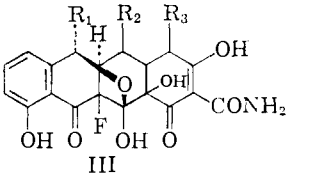
I

Ia, $R_1 = R_2 = R_3 = H$, $R_4 = NMe_2$
Ib, $R_1 = Me$, $R_2 = H$, $R_3 = OH$, $R_4 = NMe_2$
Ic, $R_1 = Me$, $R_2 = OH$, $R_3 = H$, $R_4 = NMe_2$
Id, $R_1 = Me$, $R_2 = R_3 = OH$, $R_4 = NMe_2$
Ie, $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = NMe_2$
If, $R_1 = Me$, $R_2 = OH$, $R_3 = R_4 = H$
Ig, $R_1 = Me$, $R_2 = R_3 = OH$, $R_4 = H$
Ih, $R_1 = R_2 = R_3 = R_4 = H$



II

IIa, $R_1 = R_2 = H$, $R_3 = NMe_2$
IIb, $R_1 = Me$, $R_2 = OH$, $R_3 = NMe_2$
IIc, $R_1 = R_2 = R_3 = H$



III

IIIa, $R_1 = Me$, $R_2 = H$, $R_3 = NMe_2$
IIIb, $R_1 = Me$, $R_2 = OH$, $R_3 = NMe_2$
IIIc, $R_1 = R_2 = H$, $R_3 = NMe_2$
IIId, $R_1 = Me$, $R_2 = R_3 = H$
IIIe, $R_1 = Me$, $R_2 = OH$, $R_3 = H$

(1) *Cf.* C. E. Inmann, R. E. Oesterling and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

(2) These include: (i) passage of the gas (excess) into a cold methanolic solution of the antibiotic and one equivalent of sodium methoxide; (ii) a similar procedure substituting water as the solvent and two equivalents of alkali. Procedure (i), when applied to basic compounds, results directly in a crystalline precipitate of the hydrochlorate salt of the fluorinated product.

TABLE I

	Compound	λ_{max}	log ϵ	Composition	Analyses, % C	H	N	F	Yield, %
IIa	11a-Fluoro-6-demethyl-6-deoxytetracycline	270, 350	4.45, 3.71	$C_{21}H_{21}N_2O_7F \cdot 0.5\ H_2O$	57.1	4.91	6.17	4.03	70
IIb	11a-Fluoro-6-deoxy-5-hydroxytetracycline	269, 345	4.12, 3.59	$C_{22}H_{23}N_2O_8F \cdot HCl \cdot 0.5\ H_2O$	51.99	5.22	5.36		53
IIc	11a-Fluoro-6-demethyl-6-deoxy-dedimethyl-aminotetracycline	265, 348	4.40, 3.57	$C_{19}H_{16}NO_7F$	58.2	4.3	3.4	5.1	69
IIIa	11a-Fluorotetracycline 6,12-hemiketal	265, 336	4.45, 3.71	$C_{22}H_{25}N_2O_9F \cdot H_2O$	54.97	5.19	5.85		56
IIIb	11a-Fluoro-5-hydroxy-tetracycline-6,12-hemi-ketal	265, 335	4.41, 3.72	$C_{22}H_{23}N_2O_9F \cdot 2H_2O$	51.23	5.29	5.73		83
IIIc	11a-Fluoro-6-demethyl-tetracycline-6,12-hemi-ketal	264, 337	4.40, 3.67	$C_{21}H_{21}N_2O_8F \cdot H_2O$	53.98	4.91	5.80		15
IIId	11a-Fluoro-dedimethyl-aminotetracycline-6,12-hemiketal	265, 345	4.29, 3.57	$C_{20}H_{18}NO_8F \cdot 0.5$ MeOH	56.80	4.44	3.65		34
IIIe	11a-Fluoro-5-hydroxy-dedimethylaminotetra-cycline-6,12-hemiketal	263, 335	4.41, 3.72	$C_{20}H_{18}NO_9F \cdot H_2O$	56.79	4.85	3.34		42

Simple 11a-fluorotetracyclines (II) have been obtained smoothly only in cases where no C.6 hydroxyl is present. As examples, 6-demethyl-6-deoxytetracycline (Ia),[3,4] 6-deoxy-5-hydroxytetracycline (Ib)[3] and 6-dimethyl-6-deoxy-dedimethylaminotetracycline (Ih)[4b] are converted in good yield to the ketonic derivatives IIa, IIb and IIc (see Table I for analytical data) by procedures i or ii (Footnote 2). The structures of derivatives of this type are readily apparent from composition, ultraviolet absorption (a composite of an 8-hydroxytetralone chromophore[5] plus the tetracycline A-ring absorption maximum)[5,6] infrared ketonic absorption (5.72 μ in KBr), and the observation that mild reduction (metal combinations, catalytic hydrogenation, etc.) readily regenerates starting material. Unlike several previously reported 11a-bromotetracyclines[4,7] compounds of type II are quite stable substances and provide valuable intermediates for substitution reactions in which protection of the 11–12 enol system is desirable.

In all cases in which the starting tetracycline contains a C.6 hydroxyl, more involved products result from the perchloryl fluoride reaction. In the numerous cases studied, for example: tetracycline (Ic),[6] 5-hydroxytetracycline (Id),[5] 6-demethyltetracycline (Ie),[8] dedimethylaminotetracycline (If)[9] and dedimethylamino-5-hydroxytetracycline[5,9] (Ig), pure compounds have been consistently obtained whose properties clearly indicate the 11a-fluoro-6,12-hemiketal structure (IIIa to IIIe, respectively, *cf.* Table I).[10] These derivatives show composition and ultraviolet absorption characteristics similar to those of the simple 11a-fluoro compounds II, but unlike the former, show no indication of ketonic infrared absorption below 6 (KBr pellet). Also, in contrast with the previous case, reductive removal of the 11a-fluorine is relatively more difficult. For example, 11a-fluorotetracycline hemiketal (IIIa) requires catalytic hydrogenolysis at 5,000 psi. and 30–100° for significant reconversion to tetracycline, whereas compound IIa is reduced readily at atmospheric pressure and 20°. Metal combination reduction of IIIa with zinc dust and hydrochloric acid readily regenerates starting material, although zinc dust and acetic acid reduction does not work smoothly on compounds of this type, due to competing reductive degradation.[5,6]

The formation of hemiketals such as III uniquely establishes the previously suggested[5] stereochemical assignment at C.6 and C.5a in the tetracycline series since 6,12-hemiketal ring formation is sterically possible only in the case where the C.5a hydrogen and the C.6 hydroxyl are *trans*. The further requirement follows that the C.11a fluorine be *cis* to the C.5a hydrogen. The isolation of compound IIIc is noteworthy in that it provides, for the first time, rigorous experimental evidence that the C.6 hydroxyl in 6-demethyltetracycline[8] analogs has the same stereochemistry as in the parent series. Of particular theoretical significance is the observation that 11a-fluoro compounds of type III (in sharp contrast to the parent tetracyclines) do not undergo C.5a–C.6 dehydration even in boiling methanolic hydrochloric acid. This, and several related experiments,[12] strongly suggest that the ready dehydration C-ring aromatization

(3) C. R. Stephens, K. Murai, H. H. Rennhard, L. H. Conover and K. J. Brunings, *J. Am. Chem. Soc.*, **80**, 5324 (1958).

(4) (a) J. J. Beereboom, J. J. Ursprung, H. H. Rennhard and C. R. Stephens, *ibid.*, **82**, 1003 (1960); (b) R. K. Blackwood, unpublished work.

(5) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953).

(6) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **76**, 3568 (1954).

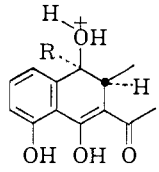
(7) A. Green, R. G. Wilkinson and J. H. Boothe, *ibid.*, **82**, 3947 (1960).

(8) J. R. D. McCormick, N. O. Sjolander, V. Hirsch, E. R. Jensen and A. P. Doerschuk, *ibid.*, **79**, 4561 (1957).

(9) C. R. Stephens, U. S. Patent No. 2,786,077, March 19, 1957.

(10) Amorphous, less stable by-products also were obtained in most instances, in addition to the main product. The isolation of fluorinated hemiketals of this type, particularly IIId and IIIe, is to be contrasted with recent bromination studies on dedimethylaminotetracycline reported by Green, Wilkinson and Boothe (ref. 7) in which a simple 11a-bromo analog (with 5.8μ ketonic absorption) was reported.

commonly observed[5,6,8] in the tetracycline series requires *more than* a *trans relationship*[11] of the C.6 oxygen function and the C.5a hydrogen. A logical conclusion is that a transition state such as IV is necessary for the unusually facile elimination observed.



IV

11a-Halo-hemiketals such as III have proven to be of fundamental significance in opening up a new field of tetracycline chemistry, parts of which are described in the accompanying communication.[12]

(11) This conclusion tends to weaken earlier stereochemical arguments in the tetracycline series based solely on dehydration rates (*cf.* C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, W. J. Stein, C. F. Wolf and J. H. Williams, *J. Am. Chem. Soc.*, **74**, 4981 (1952) and J. R. D. McCormick, P. A. Miller, J. A. Growich, J. Reichenthal, N. O. Sjolander and A. P. Doerschuk, *ibid.*, **80**, 5572 (1958).

(12) R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Schach von Wittenau and C. R. Stephens, *ibid.*, **83**, 2775 (1961).

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RECEIVED MAY 8, 1961

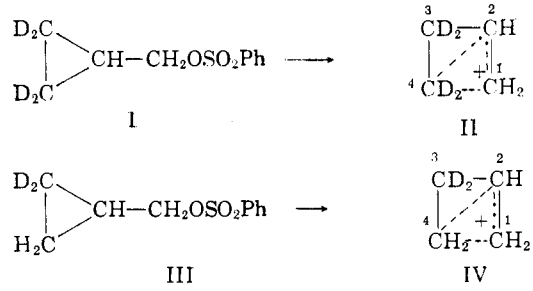
THE NON-EQUIVALENCY OF METHYLENE RING CARBON ATOMS IN THE SOLVOLYSIS OF CYCLOPROPYLMETHYL DERIVATIVES

Sir:

In a recent communication[1] we have reported that no isotope effect was observed in the solvolysis of I. It was pointed out that the formation of a non-classical carbonium ion of the bicyclobutonium ion type (II)[2] implies a rehybridization of the carbon–deuterium bonding orbitals and that therefore an isotope effect should occur in the solvolysis of I if such an intermediate was formed in the rate determining process.[3]

This view was criticized[4] on the grounds that carbon–hydrogen bonds in cyclopropane were nearly sp^2 hybridized.[5] Thus, in the process of ionization leading to II the carbon–deuterium bonds on carbon 4 would tend to become more sp^2 but more sp^3 on carbon 3. The sum of these processes is therefore a negligibly small net rehybridization and a lack of an isotope effect in the solvolysis of I should not be surprising even if II is formed in the rate determining process.

In this communication we wish to report some experimental evidence which indicates the correctness of this criticism. The compound III was synthesized and its acetolysis and ethanolysis rate constants determined. An *inverse* isotope effect was found to occur ($k_H/k_D = 0.962 \pm 0.015$ resp. 0.957 ± 0.007). These results can be well understood if it is considered that the reaction with III can proceed through a transition state resembling the intermediate IV. The formation of IV is associated with a rehybridization of the carbon–deuterium bonding orbitals toward more p character and represents therefore the reaction path of minimum activation energy.[6] Thus, in the solvolysis of III the energy gained in the above change in hybridization is not compensated by the reverse process as with I, with the result of an over-all rate increase.



The occurrence of an isotope effect in the solvolysis of III and the lack of such an effect in the reaction with I demonstrate in a striking manner the non-equivalency of carbon atoms 3 and 4 in the transition state as implied in the formulation of bicyclobutonium ions.[2]

Full experimental details of this and the previously reported work[1] will be presented in a forthcoming publication.

(6) S. Seltzer, *Chemistry and Industry*, 1313 (1959); D. B. Denney and N. Tunkel, *ibid.*, 1383 (1959).

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RECEIVED APRIL 25, 1961

FERRATE(VI) FORMATION BY HYDROGEN PEROXIDE IN PRESENCE OF ETHYLENEDIAMINETETRAACETATE

Sir:

Recently it was reported[1] that an unidentified purple complex was formed when hydrogen peroxide was added to an alkaline solution of disodium dihydrogen ethylenediaminetetraacetate (EDTA), containing a small amount of suspended $Fe(OH)_3$ (solid). Our studies with iron chemistry indicate that this complex ion is ferrate (FeO_4^{--}), in some solvated form.

We have prepared the complex ion approximately $1 \times 10^{-3}M$ by addition of an excess of 30% H_2O_2 solution to a cool (ice bath) solution of KOH ($2\text{–}7M$), EDTA ($>0.02M$) and $Fe(OH)_3$ ($>2 \times 10^{-3}M$). The excess $Fe(OH)_3$ was removed by filtration through a glass frit and the absorption spectrum was recorded from 3600 to 8000Å. One broad maximum was observed at 5180Å. and two minima, one at 4070 and one at 7750Å. Maximum and minimum absorption therefore was observed at slightly higher wave lengths than usually is noted for ferrate solutions.[2,3] This probably is due to the formation of a somewhat

(1) S. Borčić, M. Nikoletić and D. E. Sunko, *Chemistry and Industry*, 527 (1960).

(2) R. H. Mazur, W. N. White, D. A. Semenow, C. C. Lee, M. S. Silver and J. D. Roberts, *J. Am. Chem. Soc.*, **81**, 4390 (1959).

(3) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *ibid.*, **80**, 2326 (1958).

(4) E. F. Cox, M. C. Caserio, M. S. Silver and J. D. Roberts, *ibid.*, **83**, 2719 (1961).

(5) C. A. Coulson and W. Moffitt, *Phil. Mag.*, **40**, 1 (1949).

(1) F. R. Duke and T. W. Haas, *J. Phys. Chem.*, **65**, 304 (1961).

(2) Z. G. Kaufman and J. M. Schreyer, *Chem. Anal.*, **45**, 22 (1956).

(3) R. H. Wood, *J. Am. Chem. Soc.*, **80**, 2038 (1958).