spectral shifts and enthalpies of hydrogen bonds, our evidence was taken to indicate that proton acceptor ability of covalently-bound halogen atoms increased in the same sequence. This order has been used by others in discussing the relative basicity of alkyl halides toward protons[6] and it therefore seems important to set forth our present modified views.

The recent accumulation of reliable thermochemical data on the strength of hydrogen bonds has made apparent the invalidity of the Badger–Bauer rule when applied to more than a limited series of closely related compounds.[4,7,8] This evidence has led us to determine the thermodynamic properties of the interaction of phenol with alkyl halides; the results (Table I) quite contradict the earlier conclusion concerning the order of hydrogen bond forming ability of covalently bound halogens.[9] Both the free energy and enthalpy of interaction tend to decrease in the order F > Cl > Br > I, the reverse of the spectral shift order. Baker and Kaeding[10] have shown that the free energies of intramolecular hydrogen bonding between hydroxyl groups and halogens in 2,6-dihalophenols increase in the order I < F < Br < Cl; however, steric factors are expected to influence the free energy of interaction in these compounds.

TABLE I

THERMODYNAMIC PROPERTIES AND SPECTRAL SHIFTS OF HYDROGEN BONDS OF PHENOL TO ALKYL HALIDES AND ALKYL CHALCOGENIDES IN CCl_4 SOLUTION[a]

Compound	$\Delta\nu$, cm.$^{-1}$[b]	$-\Delta H^0$, kcal./mole	$-\Delta F^0$, 25°, kcal./mole	$-\Delta S^0$, 25°, cal./deg. mole
Cyclohexyl fluoride	53	3.13	1.31	6.1
Cyclohexyl chloride	66	2.21	0.87	4.5
Cyclohexyl bromide	82	2.05	0.85	4.0
Cyclohexyl iodide	86	1.72	0.82	3.0
n-Butyl ether	278[c]	5.98	2.45	11.8
n-Butyl sulfide	254[c]	4.26	1.59	9.0
n-Butyl selenide	240[c]	3.72	1.46	7.6

[a] Thermodynamic properties determined in the near infrared. See D. L. Powell, Ph.D. Thesis, University of Wisconsin, 1962, for the method of calculation. [b] Taken from ref. 2, or the present work, unless noted. [c] P. von R. Schleyer and L. Robinson, Abstracts, Fourth Delaware Valley Regional Meeting, Am. Chem. Soc., Philadelphia, Pa., Jan., 1962, p. 76. The corresponding spectral shift for phenol-*n*-butyl telluride is 220 cm.$^{-1}$.

In the previous communication,[2] it was also concluded that alkyl halides were relatively weak proton acceptors in hydrogen bonding. This conclusion is unchanged by the thermodynamic data, which show that such hydrogen bonds are quite weak compared with those from phenol to oxygen or nitrogen bases (*ca.* 5–8 kcal/mole).[4,7,8] Table I includes data for the enthalpy of hydrogen bonding of phenol to the di-*n*-butyl derivatives of oxygen, sulfur and selenium; a decrease in $-\Delta H^0$ in the order given was found. The trend thus parallels that found for the alkyl halides, but it is to be noted that both sulfur and selenium are capable of forming hydrogen bonds of appreciable strength, a fact not fully recognized heretofore.

The phenomenon of hydrogen bonding is not sufficiently understood at present to explain the data of Table I. However, it is not hard to understand in qualitative terms why $\Delta\nu$ and $-\Delta H^0$ should not correlate.[11] $-\Delta H^0$ measures the total energy of the interaction A-H...B-Y, *i.e.*, the strength of the H...B bond partially compensated by the weakening of the A–H and the B–Y bonds; $\Delta\nu$ measures the weakening of the A–H bond only. If the proton donor, A–H, is kept the same, $\Delta\nu$ and $-\Delta H^0$ may correlate for minor structural changes in the proton acceptor, *e.g.*, in Y, but not necessarily for major changes, *e.g.*, in the acceptor atom, B.

(6) S. Andreades and D. C. England, *J. Am. Chem. Soc.*, **83**, 4670 (1961); J. R. Gersten, *J. Org. Chem.*, **26**, 758 (1961). *Cf.* J. E. Gordon, *J. Org. Chem.*, **26**, 738 (1961).

(7) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, 1960, pp. 82–85 and 348 ff.

(8) E. D. Becker, *Spect. Acta*, **17**, 436 (1961); H. Dunken and H. Fritsche, *Zeit. Chem.*, **1**, 127, 249 (1961).

(9) Added in proof: some measurements similar to those reported here have recently been presented in preliminary form, M.-L. Josien, *Pure Appl. Chem.*, **4**, 33 (1962).

(10) A. W. Baker and W. W. Kaeding, *J. Am. Chem. Soc.*, **81**, 5904 (1959); also see J. H. Richards and S. Walker, *Trans. Faraday Soc.*, **57**, 412 (1961).

(11) We are indebted to Dr. H. J. Bernstein, National Research Council, Ottawa, for this observation. Dr. Bernstein (private communication) has demonstrated a simple relationship between $\Delta\nu/\Delta H^0$ for a given acceptor and the ionization potential for acceptor atoms in related molecules.

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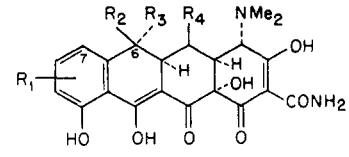
RECEIVED MAY 31, 1962

THE TOTAL SYNTHESIS OF 6-DEMETHYL-6-DEOXYTETRACYCLINE

Sir:

The molecular structures of oxytetracycline (Ia) and chlorotetracycline (Ib) were elucidated in our laboratories a decade ago.[1] Since that



I

	Ia	Ib	Ic
R_1	H	Cl (7)	H
R_2	OH	OH	H
R_3	Me	Me	H
R_4	OH	H	H

time, the tetracycline antibiotics have emerged as a unique class, whose characteristic chemotherapeutic activity is strictly dependent upon the main-

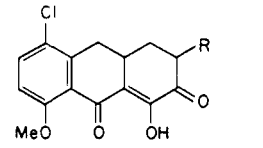
(1) (a) F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, K. J. Brunings and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 3708 (1952); F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **75**, 5455 (1953). *Cf.* also S. Hirokawa, Y. Okaya, F. M. Lovell and R. Pepinsky, *Z. Krist.*, **112**, 439 (1959). (b) C. R. Stephens, L. H. Conover, F. A. Hochstein, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *J. Am. Chem. Soc.*, **74**, 4976 (1952); 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).

tenance of all of the structural and stereochemical features of the expression I.[2]

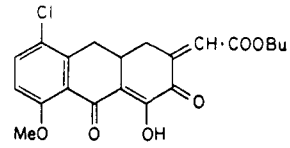
We now wish to record the first total synthesis of a member of this group[3]—the fully biologically active prototype of the series,[4] 6-demethyl-6-deoxytetracycline (Ic).[5]

Dimethyl succinate and methyl 3-methoxybenzoate were condensed in dimethylformamide solution with sodium hydride as catalyst to afford dimethyl α-(3-methoxybenzoyl)-succinate [b.p. 160–163° (0.5 mm.); $n^{25}D$ 1.5220. Found: C, 59.91; H, 5.79]. This was transformed by Michael addition of methyl acrylate in methanol with Triton B as catalyst into the viscous oily dimethyl β-carbomethoxy-β-(3-methoxybenzoyl)-adipate, which without further purification was converted by hot aqueous sulfuric and acetic acids into β-(3-methoxybenzoyl)-adipic acid [m.p. 109–110°. Found: C, 60.05; H, 5.81; neut. equiv., 141]. Hydrogenation over 10% palladium/charcoal in glacial acetic acid at 200 psi. yielded β-(3-methoxybenzyl)-adipic acid [dimethyl ester, b.p. 165–168° (0.5 mm.); $n^{25}D$ 1.5045]. Chlorination in glacial acetic acid at 15° converted the acid to crude β-(2-chloro-5-methoxybenzyl)-adipic acid, which in liquid hydrogen fluoride at 15° underwent cyclodehydration to give, mainly, 5-chloro-8-methoxy-1-tetralone-3-propionic acid [m.p. 181–182°. Found: C, 59.51; H, 5.42; Cl, 12.60].

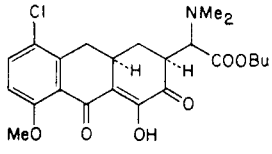
The sodium hydride-induced condensation of the corresponding ester, methyl 5-chloro-8-methoxy-1-tetralone-3-propionate [m.p. 102–103°; $\lambda\lambda_{max}$ mμ (ϵ), 223 (24,700), 255 (7,900), 326 (4,500) in MeOH/0.01 *N* HCl. Found: C, 60.88; H, 5.91; Cl, 11.3], with dimethyl oxalate in dimethylformamide containing one equivalent of methanol produced methyl 8-chloro-1,2,3,9,9a,10-hexahydro-4-hydroxy-5-methoxy-3,10-dioxoanthracene-2-carboxylate (II)[6] [m.p. 201–203° (dec.). Found: C, 58.53; H, 4.43; Cl, 10.10]. The β-keto ester was hydrolyzed and decarboxylated in hot aqueous hydrochloric-acetic acid solution to 8-chloro-1,2,3,9,9a,10-hexahydro-4-hydroxy-5-methoxy-3,10-dioxoanthracene (III)[6] [m.p. 173–175° (dec.); $\lambda\lambda_{max}$ mμ (ϵ) 270 (3,400), 342 (12,300) in MeOH/0.01 *N* HCl; 399 (14,400) in MeOH/0.01 *N* NaOH. Found: C, 61.59; H, 4.64; Cl, 12.01]. Magnesium methoxide-catalyzed condensation of the anthracene derivative III with *n*-butyl glyoxylate in refluxing toluene gave *n*-butyl 8-chloro-3,9,9a,10-tetrahydro-4-hydroxy-5-methoxy-3,10-dioxo-$\Delta^{2(1H),\alpha}$-anthracene-2-acetate (IV)[6] [m.p. 127.5–128° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), 285 (6,100), 366 (13,700) in MeOH/0.01 *N* HCl; 240 (12,200), 318 (5,100), 440 (10,100) in MeOH/0.01 *N* NaOH. Found: C, 62.58; H, 5.55; Cl, 8.87], which combined with dimethylamine at −10° to yield stereospecifically



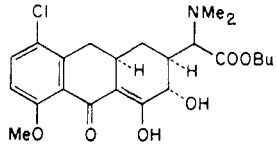
II : R = COOMe
III : R = H



IV

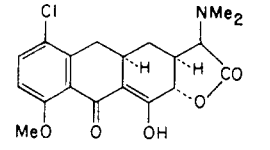


V

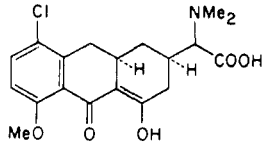


VI

the labile base V.[6] The latter was reduced by excess sodium borohydride in dimethoxyethane at low temperature to *n*-butyl-8-chloro-1,2,3,9,9a,10-hexahydro-3,4-dihydroxy-5-methoxy-10-oxo-anthracene-2-(α-dimethylamino)-acetate (VI)[6] [B.HCl, m.p. 190–192° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), 269 (4,100), 350 (13,600) in MeOH/0.01 *N* HCl; 263 (6,400), 360 (14,100) in MeOH/0.01 *N* NaOH. Found: C, 56.88; H, 6.44; N, 2.70; Cl, 14.4]. The corresponding lactone VII[6] [B.HCl, m.p. (solvate with 1/3$CHCl_3$) 222–225° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), 275 (3,900), ~320 (9,500), 347 (10,800) in MeOH/0.01 *N* HCl; 261 (6,000), 359 (15,300) in MeOH/0.01 *N* NaOH. Found: C, 51.33; H, 4.76; N, 3.00; Cl, 24.0] was formed from the hydroxy ester by the action of *p*-toluenesulfonic acid in refluxing toluene. Zinc dust reduction of the lactone in 97% formic acid gave the acid VIII[6] [m.p. 235–237° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), 223 (15,500), 267 (4,200), 345 (14,000) in MeOH 0.01 *N* HCl; 224 (16,100), 265 (4,800), 347 (14,600) in MeOH/0.01 *N* NaOH. Found: C, 60.29; H, 5.87; N, 3.49; Cl, 9.7], which was hydrogenolyzed over palladium/charcoal in ethanol in the presence of triethylamine to give 1,2,3,9,9a,10-hexahydro-4-hydroxy-5-methoxy-10-oxoanthracene-2-(α-dimethylamino)-acetic acid IX[6] [m.p. 210–211° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), 265 (4,700), 338 (14,700) in MeOH/0.01 *N* HCl; 264 (5,500), 340 (15,900) in MeOH/0.01 *N* NaOH. Found: C, 65.83; H, 6.65; N, 4.12].



VII



VIII

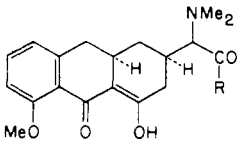
(2) For an excellent summary of structure-activity relationships in the tetracycline antibiotic series, *cf.* J. R. D. McCormick, E. R. Jensen, P. A. Miller and A. P. Doerschuk [ref. 5b]. The definition of the variable substituents R_1–R_4 contained in this paper is subject to amplification in the light of subsequent discoveries; *cf.* the methylene-tetracyclines reported by R. K. Blackwood, J. J. Beereboom, H. H. Rennhard, M. Schach von Wittenau and C. R. Stephens [*J. Am. Chem. Soc.*, **83**, 2773 (1961)].

(3) Outstanding earlier progress toward this objective has been achieved in a number of laboratories, notably by H. Muxfeldt, W. Rogalski and K. Striegler [*Angew. Chem.*, **72**, 170 (1960)] and by T. L. Fields, A. S. Kende and J. H. Boothe [*J. Am. Chem. Soc.*, **82**, 1250 (1960); **83**, 4612 (1961)]; *cf.* also Yu. A. Arbuzov, Yu. A. Berlin, Yu. P. Volkov, M. N. Kolosov, Yu. A. Ovchinnikov, Hsieh Yü-Yüan, T'ao Chêng-e and M. M. Shemyakin [*Antibiotiki*, **6**, 585 (1961)].

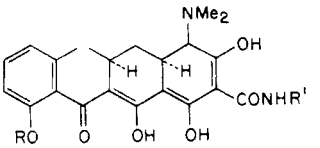
(4) Drs. R. Riggio, A. R. English and T. J. McBride have reported privately that 6-demethyl-6-deoxytetracycline possesses therapeutic efficacy equivalent to that of tetracycline itself against bacterial infections of man and laboratory animals.

(5) (a) J. J. Beereboom, J. J. Ursprung, H. H. Rennhard and C. R. Stephens, *J. Am. Chem. Soc.*, **82**, 1003 (1960); (b) J. R. D. McCormick, E. R. Jensen, P. A. Miller and A. P. Doerschuk, *ibid.*, **82**, 3381 (1960).

(6) Alternative enolic structure(s) of course are possible.



IX : R = OH
X : R = OCOOCHMe$_2$
XI : R = CH(COOEt)CONHBu^t



XII : R = Me, R' = Bu^t
XIII : R = R' = H

The acid IX was converted to the corresponding isopropylcarbonic mixed anhydride X[6] [m.p. 132° (dec.). Found: C, 64.32; H, 6.77; N, 3.41] in the usual manner, and condensed with the magnesium derivative of ethyl N-*tert*-butylmalonamate[7] in acetonitrile to yield the crude acylmalonamate XI.[6] The latter, by direct treatment with excess sodium hydride in dimethylformamide at 120°, gave 2-N-*tert*-butylcarbamoyl-4-dimethylamino-4,4a,5,5a,6,11 - hexahydro - 1,3,12 - trihydroxy - 10-methoxy - 11 - oxonaphthacene (XII)[6] [m.p. 215–216° (dec.); $\lambda\lambda_{max}$ mμ (ϵ), (initial) 254 (12,900), 325 (9,300), ~420 (21,600), 436 (26,700), ~456 (22,400) in MeOH/0.01 *N* HCl. Found: C, 66.95; H, 6.80; N, 6.04]. Hydrolysis and dealkylation of XII in hot 48% hydrobromic acid gave 4-dimethylamino-4,4a,5,5a,6,11-hexahydro-1,3,10,12-tetrahydroxy-11-oxonaphthacene-2-carboxamide (XIII)[6] [m.p. 223–224° (dec.). Found: C, 63.27; H, 5.51; N, 6.73]. The highly characteristic and time-variable ultraviolet spectrum [$\lambda\lambda_{max}$ mμ (ϵ), (initial) 260 (12,900), 326 (10,300), ~408 (16,600), 429 (23,600), 451 (20,100) in MeOH/0.01 *N* HCl; 247 (13,600), ~262 (13,000), 378 (9,500), ~447 (17,900), 470 (24,500), 495 (22,900) in MeOH/0.01 *N* NaOH] and the paper-chromatographic behavior [ethyl acetate/nitromethane/chloroform, ethyl acetate/chloroform/pyridine, nitromethane/chloroform/pyridine/pH 3.5 paper, pyridine/toluene/water/pH 4.2 paper] of the synthetic substance were identical in all respects with the corresponding properties of an optically active sample of the same structure (XIII), prepared by degradation of 6-demethyl-6-deoxytetracycline.[8] When the synthetic (XIII), in the presence of cerous chloride (1 mole/mole) was subjected to the action of molecular oxygen in dimethylformamide/methanol solution, brought to apparent pH ~5 with glycine/sodium hydroxide, it was transformed into racemic 6-demethyl-6-deoxytetracycline (Ic), [B.HCl.0.5H$_2$O, m.p. 225–226° (dec.). Found: C, 54.94; H, 5.46; N, 5.66]. The characteristic ultraviolet spectrum [$\lambda\lambda_{max}$ mμ (ϵ), 267 (19,300), 347 (15,500) in MeOH/0.01 *N* HCl; 248 (16,600), ~261 (15,600), ~284 (10,100), 383 (18,300) in MeOH/0.01 *N* NaOH] and the paper chromatographic behavior [toluene/pyridine/water, nitromethane/1-butanol/toluene/pyridine, ethyl acetate/nitromethane/chloroform, ethyl acetate/chloroform/pyridine, ethyl acetate/water] of this racemic substance were identical in all respects with the corresponding properties of an authentic sample of 6-demethyl-6-deoxytetracycline.[5] It is of much interest that the synthetic racemic material was found to be exactly half as active as the levorotatory antibiotic of natural provenance when assayed turbimetrically against *K. pneumoniae*.

Acknowledgment.—The authors are indebted to Mr. E. J. Bianco for the preparation of intermediates.

(7) Ethyl N-*tert*-butylmalonamate was prepared from ethyl cyanoacetate and isobutylene by Dr. J. W. McFarland of these laboratories.

(8) R. K. Blackwood, H. H. Rennhard and C. R. Stephens, *J. Am. Chem. Soc.*, **82**, 5194 (1960).

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BOOK REVIEWS

Molecular Structure. The Physical Approach. By J. C. D. BRAND, Ph.D., D.Sc., Lecturer in Chemistry in the University of Glasgow, and J. C. SPEAKMAN, Ph.D., D.Sc., Senior Lecturer in Chemistry in the University of Glasgow. St. Martin's Press, Inc., 175 Fifth Avenue, New York 10, N. Y. 1960. viii + 300 pp. 15.5 × 23.5 cm. Price, $6.00.

When a reviewer begins with the phrase, "should be in the hands of every graduate student," the reader may be forgiven for suspecting either nepotism or a quote from a dust jacket. With the book under review, however, the comment is justified. The authors set out to provide an introduction to the study of the structures and properties of molecules in their ground electronic state, and have succeeded admirably. Although the book is designed for the general chemical reader rather than the specialist, each chapter with its bibliography could serve as excellent point of departure for the beginner in that field. The book as a whole would make a good text for a one-semester course in molecular structure determination.

After an introduction and one of the most lucid introductions to molecular and crystallographic symmetry that the reviewer has encountered, successive chapters deal with elementary wave mechanics, molecular rotation and dipole moments, nuclear magnetic resonance, molecular vibration, polarizability and Raman spectroscopy, X-ray diffraction and electron diffraction. Electronic spectra and electron spin resonance are excluded by the stated limits of the book, and neutron diffraction is treated briefly in the chapter on X-rays. The discussion of group theory begun in the symmetry chapter is continued in an appendix.