TABLE I

In Vitro ACTIVITIES IN % COMPARED TO TETRACYCLINE[a]

Tetracycline	100
6-Demethyl-6-deoxytetracycline (I)	160
6-Demethyl-6-deoxytetracycline-7-diazonium sulfate hydrochloride (II)	20
7-Chloro-6-demethyl-6-deoxytetracycline[b] (III)	300
7-Acetoxy-6-demethyl-6-deoxytetracycline (IV)	120
6-Demethyl-6-deoxy-7-formyloxytetracycline (V)	32
6-Demethyl-6-deoxy-7-hydroxytetracycline (VI)	23
6-Demethyl-6-deoxy-7-fluorotetracycline (VII)	220
7-Bromo-6-demethyl-6-deoxytetracycline (VIII)	200
6-Demethyl-6-deoxy-7-iodotetracycline (IX)	120

[a] Activities were measured turbidimetrically against *Staph. aureus* by the method of E. Pelcak and A. Dornbush, *Ann. N. Y. Acad. Sci.*, **51**, 218 (1948). [b] See ref. 2.

phate buffer, pH 2.0 (20); $[\alpha]^{25}D$ −98°; R_f 0.68; $\lambda_{max.}^{0.1\ N\ HCl}$ 348, 265 mμ; log ε 4.55, 4.72.

Anal. Calcd. for $C_{23}H_{24}O_9N_2$: C, 58.5; H, 5.1; OAc, 9.1. Found: C, 58.3; H, 5.7; OAc, 9.0.

In addition to the 7-acetoxy derivative (IV), we obtained some 7-chloro-6-demethyl-6-deoxytetracycline[2] (III) and some 6-demethyl-6-deoxytetracycline[3] (I) in a ratio of 2:1:1, respectively.

6-Demethyl-6-deoxy-7-hydroxytetracycline (VI).[8,9]—A solution of 0.075 g. (0.159 mmole) of 7-acetoxy-6-demethyl-6-deoxytetracycline in 0.30 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 5 min. The solution was acidified with hydrochloric acid to pH 4.5 and the precipitate was collected by filtration, washed with water, and dried *in vacuo* at room temperature, yield 20 mg. $[\alpha]^{25}D$ −171°; R_f 0.58; $\lambda_{max.}^{0.1\ N\ HCl}$ 340, 282 mμ; log ε 3.89, 4.85.

Anal. Calcd. for $C_{21}H_{22}N_2O_8 \cdot H_2O$: C, 56.4; H, 5.4; N, 5.2. Found: C, 56.7; H, 5.8; N, 5.1.

6-Demethyl-6-deoxy-7-formyloxytetracycline Sulfate (V).—A solution of 0.30 g. (0.523 mmole) of 6-demethyl-6-deoxytetracycline-7-diazonium hydrochloride sulfate in 40 ml. of 98% formic acid was irradiated for 3 hr. at room temperature. The formic acid was removed by lyophilization and the residue was washed well with ethyl ether, yield 0.25 g. The compound absorbed at 5.75 μ (infrared) which is characteristic of formyl substitution; $\lambda_{max.}^{0.1\ N\ HCl}$ 345, 260 mμ; log ε 3.86, 4.15.

An attempted purification of this material by partition column chromatography[10] using a solvent system of heptane (8)–butanol (10)–2-methoxyethanol (6)–0.2 *M* phosphate buffer, pH 2.0 (10) yielded the hydrolyzed product, 6-demethyl-6-deoxy-7-hydroxytetracycline (VI).

6-Demethyl-6-deoxy-7-fluorotetracycline (VII).[8,9]—To a solution of 1.00 g. (1.57 mmoles) of 6-demethyl-6-deoxytetracycline-7-diazonium disulfate and 0.34 g. (3.14 mmoles) of sodium fluoroborate in 3.0 ml. water was added 250 ml. of glacial acetic acid. The solution was irradiated for 5 hr. at room temperature. The reaction mixture was lyophilized and the residue was distributed in a chloroform (4)–0.2 *M* phosphate buffer, pH 2.0 (2)–butanol (1) solution. The organic layer after evaporation to dryness was purified twice by partition column chromatography[10] using solvent systems of heptane (4)–butanol (5)–2-methoxyethanol (3)–0.2 *M* phosphate buffer, pH 2.0 (5) and heptane (60)–ethyl acetate (40)–methanol (15)–water (6); $[\alpha]^{25}D$ −83°; R_f 0.46; $\lambda_{max.}^{0.1\ N\ HCl}$ 345, 267 mμ; log ε 4.02, 4.23.

(8) Optical rotations were determined at a concentration of 0.1–0.5% in 0.1 *N* sulfuric acid.

(9) R_f values were determined in the system butanol, 0.2 *M* phosphate buffer, pH 2.

(10) The solid support for the stationary phase was diatomaceous earth (Johns-Manville Celite 547).

Anal. Calcd. for $C_{21}H_{21}N_2O_7F \cdot 2/3\ H_2O$: C, 57.0; H, 5.1; F, 4.3. Found: C, 57.1; H, 5.2; F, 3.9.

In addition to the 7-fluoro compound (VII), we obtained some IV and I.

On the Mechanism of the Arbuzov Rearrangement

FRANCIS C. BUCK[1a] AND JOHN T. YOKE, III[1b]

Department of Chemistry, University of Arizona, Tucson, Arizona

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The Arbuzov rearrangement, $P(OR)_3 \xrightarrow{RX} RP(O)(OR)_2$, is generally considered to be a two-stage reaction with an ionic intermediate[2] shown as

$$R'X + :P(OR)_3 \longrightarrow [R'P(OR)_3]^+X^-$$

$$[R'P(OR)(O-R)]^+X^- \longrightarrow R'P(O)(OR) + RX$$

If the R groups in the two starting materials are the same, then a catalytic amount of the halide is sufficient to bring about isomerization of the phosphite. If they differ, the R group of the halide ends up bound directly to phosphorus, although as the reaction proceeds two different halides are present to compete for the phosphite.

With certain aromatic phosphites it has been possible to isolate the phosphonium intermediate, but no such direct confirmation of the course of the reaction has been obtained for aliphatic derivatives. It seemed to us that a study of the conductivity of a phosphite–alkyl halide mixture would bear directly on the mechanism of the reaction, and so we have made a conductometric study of the kinetics of the reaction of tri-*n*-butyl phosphite with ethyl iodide in acetonitrile at 31°.

Experimental

Materials.—Acetonitrile (Eastman Kodak Co.) was refluxed over barium oxide for several hours and distilled from barium oxide through a Vigreux column in a system protected by a calcium hydride tube. A middle fraction was collected, b.p. 76–78° uncor. (700 mm.). The specific

(1) (a) The Rev. F. C. Buck, S.J., Boston College High School, Boston, Massachusetts. The support of this work by a N. S. F. High School Teachers Research Participation Summer Institute at the University of Arizona is gratefully acknowledged; (b) To whom inquiries should be addressed.

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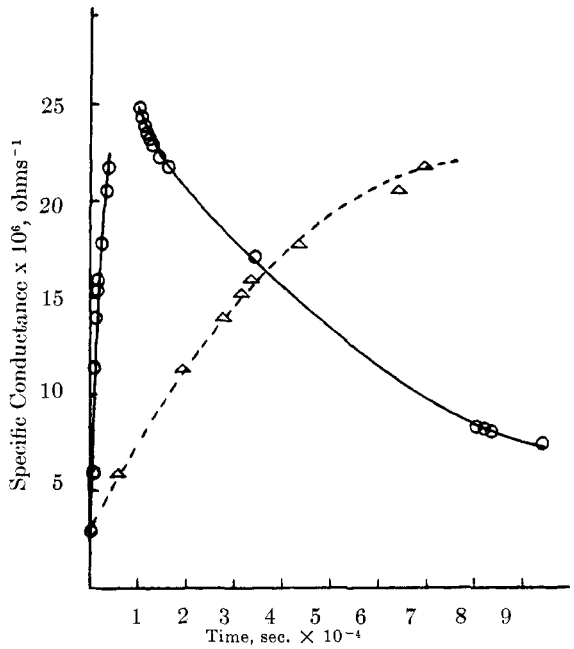

Fig. 1.—$P(OC_4H_9)_3$ and C_2H_5I in CH_3CN at 31°. The dashed line represents the initial stage rate data magnified 20 times on the time axis.

conductance of such middle fractions from several distillations ranged from 1 to 10 × 10^{-6} $ohms^{-1}$. Ethyl iodide (Matheson, Coleman and Bell) was distilled, washed with 0.1 *M* sodium thiosulfate and then twice with water, dried over calcium chloride, and redistilled. A colorless middle fraction was collected, b.p. 68–70° uncor. (700 mm.). Tri-*n*-butyl phosphite (Virginia-Carolina Chemical Corp. research sample) was distilled, b.p. 146–149° (37–38 mm.). In a weight–volume calibration of the microburet, the density was found to be 0.914 g./ml. at 31°.

Procedure.—The cell was a test tube with two side arm leads for the bright platinum electrodes and was mounted in the plastic lid of a water bath. The cell constant was determined by measurement of the conductivity of a standard solution of potassium chloride. The cell was fitted with a 1-ml. buret and a calcium hydride drying tube. Acetonitrile was weighed into the cell and a period of time was allowed for resistance measurements to become constant. The resistance was measured with a Model RC-16B2 bridge, Industrial Instruments Inc. A measured amount of ethyl iodide was then added from a weight burette and a measured volume of tri-*n*-butyl phosphite was added from the microburet. The reaction mixture contained 6.696 g. of (89.57 wt. %) acetonitrile, 0.327 g. (4.38 wt.%) of ethyl iodide, and 0.494 ml. (0.451 g., 6.05 wt. %) of tri-*n*-butyl phosphite. Assuming additivity of volumes, the solution was 9.21 ml. and the concentrations of ethyl iodide and tri-*n*-butyl phosphite were 0.228 *M* and 0.195 *M*, respectively. The contents of the cell were swirled, and the conductivity was measured as a function of time. After 10^5 sec., an aliquot of the reaction mixture was transferred by syringe to an infrared cell, made up to 25% concentration in carbon tetrachloride solvent, and compared with a 25% solution of acetonitrile in carbon tetrachloride as the blank, using a Perkin-Elmer Infracord. The tertiary phosphite absorption at 6.8–7.0 μ was absent, and a strong absorption at 7.9–8.0 μ characteristic of the P=O group,[3] was observed.

(3) L. W. Daasch and D. C. Smith, *Anal. Chem.*, **23**, 863 (1951).

Results

The specific conductance was calculated from the observed resistance values at various times and the data are shown in Fig. 1. The results are clearly interpretable in terms of two consecutive reactions involving the formation and then the decay of a conducting intermediate, the first step being much faster than the second. If the observed values of specific conductance are corrected for the initial conductance of 3.0 × 10^{-6} ohm^{-1}, a smooth curve drawn through the data for the initial portion of the reaction approaches a limiting value of 28.0 × 10^{-6} ohm^{-1} which may be taken to correspond to completion of the first step of the reaction and thus to a concentration of 0.195 *M* $[C_2H_5P(OC_4H_9)_3]^+I^-$. Using this rather crude relation between corrected conductance and concentration, an approximate analysis of the kinetic data may be undertaken. Supposing that the second step of the reaction is sufficiently slow to be neglected in treating the initial rate data, and taking the attack of the phosphite on the alkyl halide to be a S_N2 process, a second-order rate constant was calculated by the equation[4] and the

$$k = \frac{1}{t(a-b)} \ln \frac{b(a-x)}{a(b-x)}$$

results are given in Table I. The supposition of second-order kinetics for the first step of the reaction seems justified.

TABLE I

TEST FOR A SECOND-ORDER CONSTANT—INITIAL STAGE RATE DATA

$a = [C_2H_5I]_0 = 0.228\ M$; $b = [P(OC_4H_9)_3]_0 = 0.195\ M$. $x = [C_2H_5P(OC_4H_9)_3I] = 0.195\ M \times$ spec. cond./28.0 × 10^{-6}

t, sec.	Specific[a] conductance × 10^6	*x*	*k*, l./mole sec. × 10^3
3.00 × 10^2	3.0	0.021	2.00
9.60 × 10^2	8.4	.059	1.84
1.38 × 10^3	11.0	.077	2.10
1.56 × 10^3	12.4	.087	2.19
1.68 × 10^3	13.0	.091	2.20
2.16 × 10^3	14.8	.103	2.07
3.24 × 10^3	17.5	.122	1.94
3.48 × 10^3	18.8	.131	2.22
		Mean	2.07

[a] Corrected for initial conductance.

The second step of the reaction, representing the decay of the conducting species, might in terms of the proposed mechanism involve a second-order nucleophilic attack of iodide on the phosphonium ion, or the existence of an ion pair might lead to apparent first-order kinetics. Using the relation developed above between specific conductance and concentration of the ionic intermediate, tests were made for the order of the reaction by plotting the

(4) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., New York, 1950, Chap. 1.

logarithm, and the reciprocal, of the concentration of intermediate *vs.* time. The first relation was nearly linear while the second was not, indicating that the second step of the reaction is a first-order process. The data are shown in Table II.

TABLE II
TEST FOR A FIRST-ORDER CONSTANT—LATTER STAGE RATE DATA

$10^5/t$, sec.$^{-1}$[a]	Specific[b] conductance $\times 10^6$	$[C_2H_5P(OC_4H_9)_3I]$	k, sec.$^{-1}$, $\times 10^5$
9.60	21.8	0.152	2.4
9.17	21.3	.149	2.5
8.93	20.8	.145	2.7
8.48	20.5	.143	2.6
8.20	20.4	.142	2.6
8.06	20.2	.141	2.6
7.70	19.9	.139	2.6
6.71	19.2	.134	2.5
6.10	18.8	.131	2.4
5.72	18.6	.130	2.3
2.92	14.2	.099	2.0
1.24	5.4	.038	2.1
1.21	5.3	.037	2.0
1.19	5.2	.036	2.0
1.05	4.6	.032	1.9
		Mean	2.3

[a] Uncorrected for time required for initial build-up of the conducting intermediate. [b] Corrected for initial conductance.

While a more rigorous mathematical treatment of the rate data for these consecutive reactions would be possible, such a treatment does not seem justified in terms of the precision of the experimental data and particularly the approximations made in relating conductance to concentration. The value of the work lies in its confirmation of the existence of a phosphonium ion intermediate in the Arbuzov rearrangement of simple aliphatic tertiary phosphites and its indication of the relative rates of the two steps.

It might be thought that when different alkyl groups are present in the halide and phosphite starting materials a mixture of products would be obtained since a second alkyl halide is generated in the course of the reaction.[5] It now appears that the first step of the reaction is so much faster than the second that by the time appreciable amounts of the second alkyl halide are formed in the reaction mixture, the phosphite ester has been largely converted to the phosphonium intermediate and is no longer available. This is in accord with work showing that in one example of such a system only a single product was obtained, in 95% yield.[6]

Acknowledgment.—We thank Dr. John P. Schaefer for making the conductivity bridge available.

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16β-Methyldesoxycorticosterone Acetate (16β-Methyl DOCA)

G. G. NATHANSOHN, F. DONADELLI, E. TESTA, AND G. F. ODASSO

Laboratories of Lepetit S.p.A., Milan, Italy

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Two different syntheses of 16α-methyldesoxycorticosterone acetate have been reported some years ago by one of the authors and his co-workers[1,2] and by Petrow and Williamson.[3] The lack of any mineralcorticoid activity of this methylated DOCA derivative prompted us to advance the hypothesis that the 16α-methyl group is responsible for abolishing the sodium retention activity of 16α-methyl-9α-fluoroprednisolone (dexamethasone) when compared with the nonmethylated parent compound. This hypothesis was also supported by the results of Wieland and co-workers[4] in the case of aldosterone, which by 16α-methylation completely lost its typical mineralcorticoid activity.

In prosecution of the work in this field it seemed interesting to investigate whether the 16β-methylation of DOCA would also be accompanied by the loss of the sodium retention activity. In this case the former hypothesis should also be valuable to explain the absence of activity on the electrolyte balance of the new 16β-methylcorticoids (16β-methylprednisolone[5,6] and 16β-methylprednisone[7]).

The attempts to prepare 16β-methyl-DOCA according to both procedures previously described for the preparation of the 16α-methyl isomer failed; the 21-iodo intermediate seems to be very unstable and could not be converted by usual methods into the 21-acetate. Therefore we started from the known[8] pregna-5,16-diene-3β,21-diol-20-one 21-acetate (I), in which the 21-acetoxy group was already present. Compound I was converted with diazomethane to the 16α,17-diazomethylene derivative II.

Pyrolysis of this compound afforded 16-methylpregna - 5,16 - diene - 3β,21 - diol - 20 - one 21-acetate (III), which was reduced with hydrogen (Raney nickel catalyst) to 16β-methylpregn-5-ene-3β,21-diol-20-one 21-acetate (IV). It is well known that this hydrogenation gives preferentially

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