Table I. Preparation of *o*-Hydroxyphenyl Phosphate Esters

Alcohol (ROH)	Solvent	Base	Moles of I[a]	% yield of III[b]
t-Butyl alcohol	Tetrahydrofuran	Triethylamine	1.0	83[c]
2′,3′-O-Isopropylidene-adenosine	Acetonitrile	2,6-Lutidine[g]	1.1	70[d]
2′,3′-O-Isopropylidene-uridine	Acetonitrile	2,6-Lutidine	1.0	91[e]
3′-O-Acetylthymidine	Acetonitrile	2,6-Lutidine	1.1	70[f]

[a] *I.e.*, number of molecular equivalents of I with respect to alcohol. [b] Satisfactory analytical data were obtained for all new compounds described. [c] Isolated as a crystalline triethylammonium salt, mp 116–118°. [d] Isolated as the free acid. In another preparation, the isopropylidene group was removed and the crystalline *o*-hydroxyphenyl ester of adenosine 5′-phosphate (mp 207–208°) was obtained in 75% over-all yield. [e] Isolated as the barium salt. In another preparation, the barium salt of uridine 5′-*o*-hydroxyphenyl phosphate was obtained in 75% over-all yield. [f] Isolated as crystalline ammonium thymidine 5′-*o*-hydroxyphenyl phosphate. [g] Practical 2,6-lutidine (purchased from Hopkin and Williams, Ltd.) was heated under reflux with calcium hydride and then distilled.

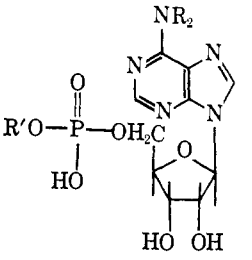
phosphorylation studies of Clark, *et al.*,[5] of converting the diesters (III) into monoesters (IV), under the conditions described, considerably increases the usefulness of *o*-phenylene phosphorochloridate (I) as a phosphorylating agent.

The latter is a colorless crystalline compound, which may easily be prepared in molar or larger quantities.[6] It reacts rapidly and apparently quantitatively with a wide range of alcohols and, as was suggested by earlier work,[2,3] *o*-hydroxyphenyl phosphate esters (III) may often be isolated from the hydrolysate of the initial products in a pure crystalline state. Some of our results are listed in Table I.

The phosphorylation of *t*-butyl alcohol was complete in 10 min at 20°, thus establishing the high reactivity of the phosphorylating agent (I). The nucleoside derivatives were allowed to react with the latter at 20° for 3 hr. The *o*-hydroxyphenyl esters, formed after the addition of water, were sufficiently stable to acidic and basic conditions to allow isopropylidene and acetyl protecting groups to be removed without concomitant dephosphorylation.

The oxidative removal of the *o*-hydroxyphenyl group was initially demonstrated with *o*-hydroxyphenyl phosphate (III, R = H) and its methyl ester (III, R = Me). When solutions of these compounds in pH 7.5 aqueous buffer[8] were treated at 20° with *ca.* 6 molar equiv of bromine,[9] rapid darkening was observed. After 5 min, examination of the respective products by paper electrophoresis and chromatography revealed that orthophosphate and methyl phosphate (IV, R = Me) were the sole phosphorus-containing components.

In a preparative-scale experiment, a solution of the triethylammonium salt of *t*-butyl *o*-hydroxyphenyl phosphate (III, R = *t*-Bu) in aqueous barium acetate was treated with 7 molar equiv of bromine. After a suitable work-up, colorless crystals of the barium salt of *t*-butyl phosphate (IV, R = *t*-Bu) were isolated in 70% yield. Similarly, oxidation of adenosine 5′-*o*-hydroxyphenyl phosphate (V, R = H; R′ = *o*-



V

HOC_6H_4) and its N^6,N^6-dimethyl derivative (V, R = Me; R′ = *o*-HOC_6H_4) in pH 7.5 aqueous buffer solution with 6 molar equiv of bromine led to adenosine 5′-phosphate (V, R = R′ = H) and its dimethyl derivative (V, R = Me; R′ = H). The respective products were obtained crystalline in 78 and 43% over-all yields, based on the 2′,3′-O-isopropylidene nucleosides[10] as starting materials. The preparations of *t*-butyl phosphate[11] and N^6,N^6-dimethyladenosine 5′-phosphate (V, R = Me; R′ = H)[12] appear to be the most convenient so far reported.

Except for unsaturated alcohols, as complications may then arise in the oxidation step, *o*-phenylene phosphorochloridate appears to be one of the most convenient and powerful phosphorylating agents available.

(5) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. Todd, *J. Chem. Soc.*, 715 (1961).

(6) Reaction between catechol and phosphorus pentachloride gives 2,2-dihydro-2,2,2-trichloro-1,3,2-benzodioxaphosphole[7] in 80% yield. When the latter is heated on a steam bath with acetic anhydride (1.1 molar equiv), a nearly quantitative yield of acetyl chloride may be collected within 20 min, by distillation (at atmospheric pressure). Distillation (under reduced pressure) of the residue gives *o*-phenylene phosphorochloridate (I) [bp 91° (0.9 mm)] in 88% yield. Thus 100–200-g quantities of I may be prepared in a few hours, starting from catechol.

(7) L. Anschütz, *Ann.*, **454**, 71 (1927).

(8) Triethylammonium bicarbonate (0.2 *M*) was found to be a suitable buffer.

(9) A 2% aqueous solution of bromine was used in all experiments.

(10) We thank Dr. Beverly Griffin for a gift of N^6,N^6-dimethyl-2′,3′-O-isopropylideneadenosine, and Mr. A. Wilcox for assistance with its phosphorylation.

(11) F. Cramer, W. Rittersdorf, and W. Bohm, *Ann.*, **654**, 180 (1962); A. Lapidot, D. Samuel, and M. Weiss-Broday, *J. Chem. Soc.*, 637 (1964).

(12) M. Ikehara, E. Ohtsuka, and F. Ishikawa, *Chem. Pharm. Bull. Japan*, **9**, 173 (1961).

T. A. Khawaja, C. B. Reese
University Chemical Laboratory
Cambridge, England
Received May 28, 1966

Electrolytic Method of Converting an Aliphatic Trichloromethyl Group into a Dichloromethyl or Monochloromethyl Group

Sir:

Few investigations have so far been made on the reduction of *gem*-chlorinated aliphatic compounds.

Table I. Reduction to the Dichloromethyl Product at a Mercury Cathode[a] at 25°

Starting material[b]	Catholyte[c]	Amp hr[d]	Product Formula	Bp, °C (mm)	Found, % C	H	Cl	N	Calcd, % C	H	Cl	N	Yield, %
$Cl(CH_2)_4CCl_3$	NH_4NO_3	5.0	$Cl(CH_2)_4CHCl_2$										92
$Cl(CH_2)_4CCl_3$	LiCl	5.0	$Cl(CH_2)_4CHCl_2$										87
$AcO(CH_2)_4CCl_3$	NH_4NO_3	5.0	$AcO(CH_2)_4CHCl_2$	94 (4)	42.48	6.42	35.78		42.23	6.08	35.62		93
$CN(CH_2)_4CCl_3$	$LiNO_3$	5.0	$CN(CH_2)_4CHCl_2$	110–112 (4)	43.62	5.72	42.62	8.41	43.39	5.46	42.69	8.48	91
$ClCH_2CH{=}CHCH_2CCl_3$	NH_4NO_3	3.5	$ClCH_2CH{=}CHCH_2CHCl_2$	62–63 (2)	34.35	4.26	61.12		34.61	4.07	61.31		64
$HOCH_2CH{=}CHCH_2CCl_3$	NH_4NO_3	5.0	$HOCH_2CH{=}CHCH_2CHCl_2$	96–97 (2)	38.60	5.33	45.47		38.75	5.20	45.75		94

[a] Platinum anode. [b] 10.0 g. [c] 0.2 mole in 90% MeOH. [d] 2.0 A.

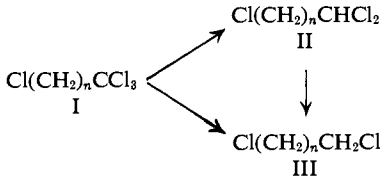
Table II. Reduction to the Monochloromethyl Product at a Mercury Cathode[a] at 25°

Starting material[b]	Catholyte[c]	Amp hr[d]	Product Formula	Bp, °C (mm)	Found, % C	H	Cl	Calcd, % C	H	Cl	Yield, %
$Cl(CH_2)_4CCl_3$	Me_4NCl	7.0	$Cl(CH_2)_5Cl$								90
$Cl(CH_2)_4CHCl_2$	Me_4NCl	5.0	$Cl(CH_2)_5Cl$								95
$HO(CH_2)_4CCl_3$	Me_4NCl	7.0	$HO(CH_2)_5Cl$								93
$HOOC(CH_2)_3CCl_3$	$Me_2NH \cdot HCl$	9.0	$HOOC(CH_2)_4Cl$								92
$CN(CH_2)_4CCl_3$	Me_4NCl	7.0	$CN(CH_2)_5Cl$								96
$AcOCH_2CH{=}CHCH_2CCl_3$	$Me_2NH \cdot HCl$	9.0	$AcOCH_2CH{=}CHCH_2CH_2Cl$	81 (4)	51.41	6.95	21.84	51.71	6.82	21.81	93
$HOCH_2CH{=}CHCH_2CCl_3$	Me_4NCl	7.0	$HOCH_2CH{=}CHCH_2CH_2Cl$	80 (6)	49.61	7.53	29.41	49.80	7.52	29.40	91
$Cl(CH_2)_3CH{=}CCl_2$	Me_4NCl	5.0	$Cl(CH_2)_3CH{=}CHCl$	59–61 (20)	43.00	5.91	50.98	43.21	5.80	51.02	63

[a] Platinum anode. [b] 10.0 g. [c] 0.2 mole in 90% MeOH. [d] 2.0 A.

Nesmeyanov, *et al.*,[1] and Ladd and Sargent[2] have reported that $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes are catalytically reduced to α,α,ω-trichloroalkanes and dimeric α,ω-dichloroalkanes. However, $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes have not been reported to be reduced to monomeric α,ω-dichloroalkanes.

Our communication presents a successful electrochemical method of reducing an aliphatic trichloromethyl group selectively to either a monochloromethyl or dichloromethyl group.



When $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes (I) are reduced electrolytically at the mercury cathode using ammonium nitrate as a cathodic supporting electrolyte, α,α,ω-trichloroalkanes (II) are formed in good yields. On the other hand, α,ω-dichloroalkanes (III) are formed quantitatively from I or II when tetramethylammonium chloride is used in place of ammonium nitrate. Thus, $\alpha,\alpha,\alpha,\omega$-tetrachloroalkanes can be converted to either α,ω-dichloroalkanes or α,α,ω-trichloroalkanes by properly selecting the cathodic electrolyte. This fact may be explained by the difference of reduction potential of the electrolytes used. No appreciable amount of the dimeric product was formed in contrast to catalytic reduction.[1,2]

The results of reduction of the trichloromethyl to the dichloromethyl group are shown in Table I and to the monochloromethyl group in Table II.

1,1,1,5-Tetrachloropentene-3 is converted to 1,1,5-trichloropentene-3 when ammonium nitrate is used as a catholyte (Table I). The trichloromethyl group is reduced to dichloromethyl more readily than the allylic chlorine under these conditions. Further reduction of 1,1,5-trichloropentene-3 to 1,5-dichloropentene-3 was unsuccessful, since the allylic chlorine was reduced simultaneously.

1,1,5-Trichloropentene-1,[3] however, is reduced to 1,5-dichloropentene-1 in the presence of tetramethylammonium chloride as a catholyte.

A typical experiment is as follows. An electrolysis cell (11 cm in height and 7.5 cm in diameter) was fitted with a mercury cathode (1 kg) and a platinum anode (2.5 × 2.0 cm) which was separated with the usual porcelain diaphragm. 1,1,1-Trichloro-5-cyanopentane (10.0 g), tetramethylammonium chloride (21.9 g), and methanol containing 10% (v/v) water (200 ml) were placed in the cathode compartment, while a 1 *N* aqueous solution of tetramethylammonium *p*-toluenesulfonate (30 ml) was placed in the anode compartment. A constant current (2.0 amp) was passed through the stirred solution for 3.5 hr (theoretically 2.4 hr) at 25°. The cathode solution was diluted with 5 vol of water and extracted with chloroform. After removal of chloroform, 6.1 g of 1-chloro-5-cyanopentane was obtained by distillation (bp 87° (3 mm), yield 94%) and was identified by gas chromatography and infrared spectroscopy with the same compound prepared independently.[4]

(1) A. N. Nesmeyanov, L. I. Zakharkin, and T. A. Kost, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 657 (1955) *Chem. Abstr.*, 50, 7061*f* (1956).

(2) E. C. Ladd and H. Sargent, U. S. Patent 2,644,835 (July 7, 1953).

(3) A. N. Nesmeyanov and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 505 (1951).

(4) O. J. Magidson and A. M. Grigowsky, *Chem. Ber.*, 69, 403 (1936).

Since many aliphatic trichloromethyl compounds and their derivatives are now readily available by telomerization reaction of olefins with carbon tetrachloride or chloroform, the electrochemical reduction described above opens a route to the simple preparation of α,ω-bifunctional aliphatic compounds.

Masanori Nagao, Naotake Sato
Takekazu Akashi, Toichi Yoshida
Central Research Laboratories, Ajinomoto Company, Inc.
Kawasaki, Japan
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Optical Rotatory Properties of Diketopiperazines

Sir:

We wish to present results from optical rotatory dispersion (ORD) and spectral studies on two diketopiperazines, a hitherto uninvestigated class of compounds. These diketopiperazines are the simplest and most rigid among cyclic polypeptides and thus would be expected to display: (a) the n–π* Cotton effect of the peptide band arising from local rigidity,[1] and (b) aspects of "exciton" interactions among peptide chromophores, a familiar phenomenon in the α-helix.[2]

The ORD studies on L-alanyl-L-alanyldiketopiperazine (LALADKP) and L-alanyl-L-seryldiketopiperazine (LALSDKP) (Cyclo Chemical Corp., Los Angeles, Calif.) were done using a Cary Model 60 spectropolarimeter. In the concentration range (10^{-4} to 2×10^{-3} *M*) of measurements, the samples showed no concentration dependence of ultraviolet absorption or rotation. However, infrared measurements on LALADKP in dioxane revealed triplet amide I bands, implying association of the compounds in dioxane, and probably also in acetonitrile, in which the rotatory dispersion is very similar. However, competitive hydrogen bonding should prevent any DKP association in ethanol and water solutions.[3]

The ultraviolet spectra of LALADKP and LALSDKP were measured in solvents of different polarities. From both theory[4] and analogous experiments on a lactam,[1] we had hoped to observe the n–π* peptide band. However, this was not observed, and the failure may be due to smaller oscillator strength for this band compared to the lactam, or to masking by the very broad π–π* band centered below 1950 A.

The ORD of the two diketopiperazines in various solvents are shown in Figures 1 and 2. In the solvents studied, both DKP's exhibit a negative Cotton effect around 2300 A, which shows a long-wave shift with decreasing solvent dielectric constant. The exceptional result in acetonitrile may well be due to association. The general solvent dependence and location of this Cotton effect lead us to conclude that this is due to the n–π* transition of the peptide chromophore. Further, LALADKP displays another minimum around 2050 A in the hydroxylic solvents, preceding a much larger maximum below 1950 A. It appears most consistent to interpret the dispersions in Figure 2 as the result of three Cotton effects, a negative one around 2200 A,

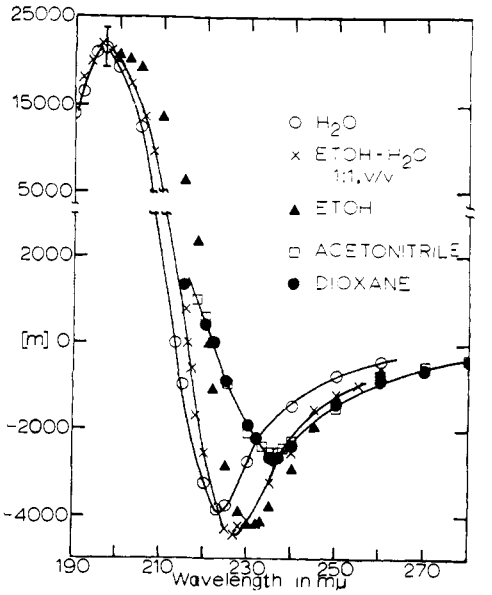

Figure 1. ORD of L-alanyl-L-seryldiketopiperazine at room temperature. The mean residue rotation, [*m*], = 0.79[α]. No refractive index corrections have been made.

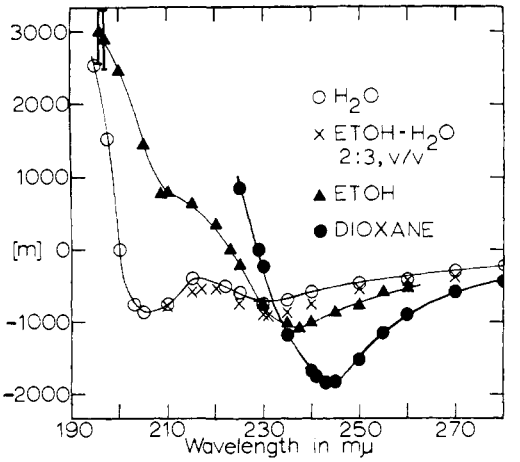

Figure 2. ORD of L-alanyl-L-alanyldiketopiperazine at room temperature. [*m*] = 0.71[α]. No refractive index corrections have been made.

another negative one around 2000 A, and a large positive one below 1950 A. The locations, signs, and relative magnitudes of the latter two Cotton effects strongly suggest their origin to be due to exciton split π–π* transition of the peptide, analogous to the α-helix.[5] It should be pointed out that the data of LALSDKP are consistent with two Cotton effects; it is very likely, however, that the trough around 2050 A in Figure 1 is here masked by the large negative n–π* Cotton effect and the much larger positive one below 1950 A. In general, the rotations of LALSDKP are larger than those of LALADKP, presumably because the latter is more symmetric than the former.

The six-membered dipeptide ring of these diketopiperazines is very nearly coplanar,[6] permitting one to inspect each peptide group independently. Application of the quadrant rule[1,7] predicts: (a) a negative

(1) B. J. Litman and J. A. Schellman, *J. Phys. Chem.*, **69**, 978 (1965).
(2) G. Holzwarth and P. Doty, *J. Am. Chem. Soc.*, **87**, 218 (1965).
(3) J. S. Franzen and R. E. Stephens, *Biochemistry*, **2**, 1321 (1963).
(4) N. S. Bayliss, *J. Chem. Phys.*, **18**, 292 (1950); *J. Phys. Chem.*, **58**, 1002 (1954).
(5) Drs. F. A. Bovey and F. P. Hood of the Bell Telephone Laboratories have observed a negative n–π* Cotton effect and also a pronounced exciton splitting in L-prolyl-L-prolyldiketopiperazine. We thank them for a preprint of their forthcoming paper.
(6) R. B. Corey, *J. Am. Chem. Soc.*, **60**, 1598 (1938).