

$C_{26}H_{24}P_2$ : C, 78.39; H, 6.03; P, 15.58. Found: C, 78.29; H, 5.63; P, 15.68.

The pale yellow distillate was partitioned between oxygen-free 10% sodium bicarbonate solution and ethyl ether. The aqueous phase on acidification gave benzoic acid (0.65 g.). The ether phase was dried over anhydrous sodium sulfate and upon evaporation yielded diphenylvinylphosphine (0.25 g.), characterized as its methiodide.

(2-Acetoxyethyl)diphenylphosphine (Ic).—(2-Acetoxyethyl)diphenylphosphine (2.8 g.), a colorless oil, 1720  $cm^{-1}$  ( $C=O$ ), was obtained from 2.3 g. of (2-hydroxyethyl)diphenylphosphine in an entirely similar manner to the procedure described for the synthesis of Id. This compound was characterized as its methiodide, colorless prisms (ethanol-ether), m.p. 107–108°. *Anal.* Calcd. for  $C_{17}H_{20}IO_2P$ : C, 49.27; H, 4.83; I, 30.68; P, 7.49. Found: C, 49.04; H, 5.00; I, 30.91; P, 7.33.

Pyrolysis of (2-Acetoxyethyl)diphenylphosphine.—Attempted distillation of Ic (4.2 g.) at 0.35 mm. produced similar results to those obtained with Id. When the bath temperature reached 147°, a violent exothermic reaction occurred with the distillation of a colorless oil. The bath temperature was raised slowly to 180°, but no further reaction occurred. The brown residue yielded *s*-ethylenebis(diphenylphosphine) (1.9 g.) as colorless prisms, m.p. 141–142°, and from the colorless distillate diphenylvinylphosphine (0.4 g.), b.p. 110° (0.22 mm.), and acetic acid (0.61 g.) were obtained.

1,1,4,4-Tetraphenyl-1,4-diphosphoniacyclohexane Diiodide.—(2-Benzoyloxyethyl)diphenylphosphine (2.1 g.) was left at room temperature under nitrogen for 15 days. During the course of this period it had changed to a pale yellow, opaque solid.

This mixture was partitioned between ethyl ether (40 ml.) and 2 *N* hydrochloric acid (15 ml.). From the ether phase 0.31 g. of benzoic acid was isolated. To the filtered aqueous solution a 10% sodium iodide solution (10 ml.) was added. The precipitated 1,1,4,4-tetraphenyl-1,4-diphosphoniacyclohexane diiodide was removed, washed well with distilled water, and dried. A white insoluble amorphous powder remained, m.p. 316–318°. *Anal.* Calcd. for  $C_{28}H_{28}I_2P_2$ : C, 49.00; H, 4.21; P, 9.25; mol. wt. (on dichloride), 497. Found: C, 49.34; H, 4.77; P, 9.13; mol. wt. (isometric molecular weight determination), 403.

Decomposition of (2-Acetoxyethyl)diphenylphosphine by the Catalytic Effect of (2-Acetoxyethyl)methyldiphenylphosphonium Iodide.—(2-Acetoxyethyl)diphenylphosphine was unchanged, as assessed by its infrared spectra, on standing at room temperature for 15 days. However, the addition of 20 mg. of (2-acetoxyethyl)methyldiphenylphosphonium iodide to 500 mg. of this tertiary phosphine resulted in the polymerization of the compound to a brown solid in the same length of time. The infrared spectrum was characteristic of a quaternary phosphonium compound and could not be explained on the basis of merely the catalytic amount which had been added.

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## The Determination of Polar Substituent Constants for the Dialkoxy- and Diarylphosphono and Trialkyl- and Triarylphosphonium Groups

D. J. MARTIN AND C. E. GRIFFIN

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213*

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The syntheses of five phosphorus-substituted acetic acids have been carried out and the acidity of each has been determined. By application of a linear free energy correlation, approximate polar substituent constants ( $\sigma^*$ ) for each of the phosphorus substituents have been determined. These studies indicate that the di-*n*-butoxyphosphono, diethoxyphosphono, and diphenylphosphono groups ( $\sigma^* = 1.74, 2.18, \text{ and } 1.68$ ) are comparable in electron-acceptor properties with carboalkoxy groups, while the tri-*n*-butyl- and triphenylphosphonium substituents ( $\sigma^* = 3.75 \text{ and } 4.70$ ) possess electron-acceptor properties comparable with those of quaternary ammonium groups.

The Hammett equation has been applied successfully to the acid dissociation constants of substituted arylphosphonic acids by Jaffé, Freedman, and Doak<sup>1</sup> and, more recently, to arylphosphinic acids by Quin and Dysart.<sup>2</sup> This relationship has been extended to arylphosphonic and arylphosphinic acids containing acidic (carboxylic, phenolic) substituents, permitting the determination of the Hammett substituent constants for the  $-PO_3H^-$  ( $\sigma_m = 0.25, \sigma_p = 0.17$ ),<sup>1</sup>  $-PO_3^{2-}$  ( $\sigma_m = -0.02, \sigma_p = -0.16$ ),<sup>1</sup> and  $-PO_2H^-$  ( $\sigma_p = 0.14$ )<sup>2</sup> groups. By a similar treatment, Freedman and Jaffé have determined the substituent constants ( $\sigma_m = 0.55, \sigma_p = 0.60$ ) for the diethoxyphosphono [ $-P(O)(OC_2H_5)_2$ ] group.<sup>3</sup> These substituent-constant values clearly indicate that the  $-PO_3H^-$ ,  $-PO_2H^-$ , and  $-P(O)(OC_2H_5)_2$  groups are moderately electron attracting, while the  $-PO_3^{2-}$  group is weakly electron repelling.

In the course of studies carried out in this laboratory on the base-catalyzed reactions of organophosphorus compounds,<sup>4</sup> an accurate assessment of the inductive effects of certain phosphorus substituents became desirable. Presumably, inductive effects account for the magnitudes of the Hammett constants of the groups cited above, but the effects of  $d\pi-p\pi$  bonding cannot be completely discounted in these aromatic systems. Even though the effects of such bonding are probably quite small and possibly negligible, it was of interest to consider the application of linear free energy correlations to systems in which  $d\pi-p\pi$  bonding would be completely absent. Recently the Taft equation was found to apply satisfactorily to the acid dissociation constants of alkylphosphonic acids, but the attempted determination of polar (inductive) substituent constant ( $\sigma^*$ ) values by application of this

(1) H. H. Jaffé, L. D. Freedman, and G. O. Doak, *J. Am. Chem. Soc.*, **75**, 2209 (1953).

(2) L. D. Quin and M. R. Dysart, *J. Org. Chem.*, **27**, 1012 (1962).

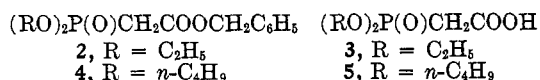
(3) L. D. Freedman and H. H. Jaffé, *J. Am. Chem. Soc.*, **77**, 920 (1955).

(4) (a) D. J. Martin and C. E. Griffin, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965; Abstracts, p. 58S; (b) D. J. Martin, Ph.D. Thesis, University of Pittsburgh, 1965; (c) R. H. Churi and C. E. Griffin, unpublished results.

relationship to bisphosphonic acids was unsuccessful.<sup>5</sup> Since it has been demonstrated that the acidities of carboxylic acids (RCOOH) are satisfactorily correlated by the Taft equation ( $-\text{p}K_a = 1.721\sigma^*_R - 4.65$ ),<sup>6</sup> it was anticipated that a study of the acidities of phosphorus-substituted acetic acids might provide an alternative approach to the determination of the inductive substituent constants of the desired phosphorus-containing groups. Such an approach should be applicable to the determination of  $\sigma^*$  values for the dialkoxyposphono [ $-\text{P}(\text{O})(\text{OR})_2$ ], dialkyl(aryl)phosphono [ $-\text{P}(\text{O})\text{R}_2$ ], and trialkyl(aryl)phosphonium [ $(-\text{PR}_3)^+$ ] groups, since the synthesis of acetic acids possessing these substituent groups should be easily achieved by established procedures.

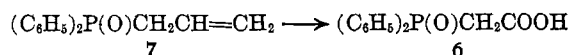
#### Preparation of Phosphorus-Substituted Acetic Acids.

—Triethyl phosphite and benzyl chloroacetate (**1**) underwent an Arbuzov reaction at 175° to yield diethyl carbobenzyloxymethylphosphonate (**2**). Hydrogenolysis of **2** in absolute ethanol over 10% palladium on charcoal gave the desired acetic acid, diethyl carboxymethylphosphonate (**3**). The di-*n*-butyl analog **5** of **3**



was prepared in a similar manner from **1** and tri-*n*-butyl phosphite. This reaction sequence was first employed by Magerlein and Kagan<sup>7</sup> for the preparation of the diisopropyl analog of **3**.

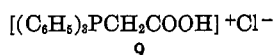
Diphenyl(carboxymethyl)phosphine oxide (**6**) was prepared by a mild oxidation (potassium permanganate-sodium iodate)<sup>8</sup> of diphenylallylphosphine oxide<sup>9</sup> (**7**). Attempted oxidation of **7** with hot aqueous potas-



sium permanganate was apparently too vigorous since neither **6** nor starting material could be isolated from the reaction mixture. A sample of **6** was also prepared for comparison by the carbonation of the lithium salt of diphenylmethylphosphine oxide following the procedure of Richards and Banks<sup>10</sup>; the two samples were identical in all respects.

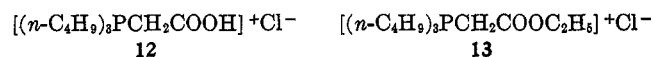
In an attempt to prepare dimethyl(carboxymethyl)phosphine oxide (**8**), trimethylphosphine oxide was converted to its anion with *n*-butyllithium and the anion was carbonated. P.m.r. studies showed that **8** was formed during the carbonation reaction, but it could not be completely separated from the unreacted phosphine oxide. Several other routes were examined in attempts to prepare a dialkyl(carboxymethyl)phosphine oxide, but all were unsuccessful.

Triphenyl(carboxymethyl)phosphonium chloride (**9**) was obtained by the reaction of triphenylphosphine and chloroacetic acid.<sup>11</sup> A sample of **9** was also pre-



pared by hydrolysis of the corresponding benzyl ester,  $[(\text{C}_6\text{H}_5)_3\text{PCH}_2\text{COOCH}_2\text{C}_6\text{H}_5] + \text{Cl}^-$  (**10**); the ester was prepared by the reaction of **1** and triphenylphosphine. Both samples of **9** were identical in all respects. The melting point (218–219°) of **9** was in agreement with that reported by Denney and Smith<sup>11</sup>; however, it is suspected that the observed melting point is that of triphenylmethylphosphonium chloride (**11**), the thermal decomposition product of **9**. A sample of **9** has been observed to decompose slowly in the solid state with the evolution of carbon dioxide to yield **11** on standing at room temperature. The decomposition could be followed readily by p.m.r. spectroscopy. The ratios of the integrated intensities of the methylene protons of **9** and the methyl protons of **11** indicated 14.2 and 27.7% decomposition of **9** after 1 and 2 months, respectively. Because of its instability, determinations of the acidity of **9** were only carried out on freshly prepared samples which gave satisfactory analyses and p.m.r. spectra.

Tri-*n*-butyl(carboxymethyl)phosphonium chloride (**12**) was prepared by two routes: reaction of tri-*n*-butylphosphine with chloroacetic acid and by the acidic hydrolysis of the ester **13**, formed by reaction of tri-*n*-butylphosphine and ethyl chloroacetate. **12** did not exhibit instability of the type shown by **9**.



All of the compounds prepared in this study gave satisfactory elemental analyses and their infrared and p.m.r. spectra (including relative intensities) were in complete accord with the postulated structures. The p.m.r. spectra of compounds **9**, **10**, and **11** have been reported previously.<sup>12</sup>

**Determination of Substituent Constants.**—The acid dissociation constants of the phosphorus-substituted acetic acids (**3**, **5**, **6**, **9**, and **12**) prepared in this study were determined by potentiometric titration in water at 25°, employing standard methods.<sup>13</sup> The acidity of one additional acid,  $(\text{C}_6\text{H}_5)_2\text{P}(\text{S})\text{CH}_2\text{COOH}$  (**14**), the thiono analog of **6**, was also determined. Owing to its limited solubility in water, the acidity of **14** was determined in 50% ethanol; for purposes of comparison, the acidity of **6** was also determined in this solvent mixture. Using the  $\sigma^*-\rho^*$  relationship established by Taft<sup>6</sup> for the ionizations of carboxylic acids,  $\sigma^*$  values for the substituent groups ( $-\text{CH}_2\text{PZ}_3$ ) were calculated. No  $\sigma^*$  value based on the ionization constant of **14** was calculated, since the  $\rho^*$  value for the ionization of carboxylic acids in 50% ethanol has not been determined. Both the experimentally determined ionization constants and the calculated substituent constants are summarized in Table I.

The values listed in Table I indicate that the  $-\text{CH}_2\text{P}(\text{O})(\text{OC}_2\text{H}_5)_2$ ,  $-\text{CH}_2\text{P}(\text{O})(\text{O}-n\text{-C}_4\text{H}_9)_2$ , and  $-\text{CH}_2\text{P}(\text{O})(\text{C}_6\text{H}_5)_2$  groups are moderately strong electron acceptors and are comparable in inductive effect with  $-\text{C}_6\text{H}_5$ ,  $-\text{CH}_2\text{COOC}_2\text{H}_5$ , and  $-\text{CH}_2\text{OC}_6\text{H}_5$  ( $\sigma^* = 0.60, 0.71$ , and  $0.85$ , respectively). Owing to the similarity in the ionization constants of **6** and **14** in 50% ethanol, it is probable that the electron-acceptor capacity of

(5) D. J. Martin and C. E. Griffin, *J. Organometal. Chem.*, **1**, 292 (1964).

(6) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

(7) B. J. Magerlein and F. Kagan, *J. Am. Chem. Soc.*, **82**, 593 (1960).

(8) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955).

(9) A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948).

(10) J. J. Richards and C. V. Banks, *J. Org. Chem.*, **28**, 123 (1963).

(11) D. B. Denney and L. C. Smith, *ibid.*, **27**, 3404 (1962).

(12) C. E. Griffin and M. Gordon, *J. Organometal. Chem.*, **3**, 414 (1965).

(13) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

TABLE I  
ACIDITIES OF PHOSPHORUS-SUBSTITUTED CARBOXYLIC ACIDS  
(RCOOH)<sup>a</sup>

Substituent (R)	pK <sub>a</sub>	σ*
-CH <sub>2</sub> P(O)(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	3.30 ± 0.05	+0.78
-CH <sub>2</sub> P(O)(O- <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub>	3.58 ± 0.05	+0.62
-CH <sub>2</sub> P(O)(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	3.62 ± 0.03	+0.60
	4.45 ± 0.05 <sup>b</sup>	...
-CH <sub>2</sub> P(S)(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	4.76 ± 0.06 <sup>b</sup>	...
-[CH <sub>2</sub> P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> ] <sup>+</sup>	1.77 ± 0.10	+1.68
-[CH <sub>2</sub> P( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> ] <sup>+</sup>	2.34 ± 0.10	+1.34

<sup>a</sup> Determined in water at 25° unless otherwise noted. <sup>b</sup> Determined in 50% aqueous ethanol at 25°.

TABLE II  
APPROXIMATE POLAR SUBSTITUENT CONSTANTS

Substituent	σ*
-P(O)(OC <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	+2.18
-P(O)(O- <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>2</sub>	+1.74
-P(O)(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	+1.68
-[P(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> ] <sup>+</sup>	+4.70
-[P( <i>n</i> -C <sub>4</sub> H <sub>9</sub> ) <sub>3</sub> ] <sup>+</sup>	+3.75

there are ample citations of reactions which illustrate the electron-acceptor capacity of these substituents.<sup>17</sup>

### Experimental Section<sup>18</sup>

the -CH<sub>2</sub>P(S)(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub> group is comparable with that of its oxy analog. As would be anticipated, the -CH<sub>2</sub>-P(*n*-C<sub>4</sub>H<sub>9</sub>)<sub>3</sub><sup>+</sup> and -CH<sub>2</sub>P(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub><sup>+</sup> groups are much stronger electron acceptors and approach the -CH<sub>2</sub>CN (σ\* = 1.30), -COCH<sub>3</sub> (σ\* = 1.65), and -CH<sub>2</sub>N(CH<sub>3</sub>)<sub>3</sub><sup>+</sup> (σ\* = 1.90) groups in electron affinity. The presence of the positive center close to the carboxyl group would be expected to facilitate the departure of a proton from that group. These data further indicate the triarylphosphonium group to be a stronger electron acceptor than the trialkylphosphonium group, a result supported by the observations of Bestmann regarding the acidities of α-methylene protons in trialkyl- and triarylphosphonium salts.<sup>14</sup>

Taft has shown that the inductive effect of a substituent is attenuated by a factor of 2.8 by the interposition of a methylene group. Thus, the σ\* value for a substituent R is taken as 2.8 times that of RCH<sub>2</sub>-. Applying this treatment to the -CH<sub>2</sub>P(O)(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub> group, an approximate value (2.18) for the diethoxyphosphono group is obtained. This indicates that the -P(O)(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub> substituent is a slightly better electron acceptor than a carbomethoxy group (σ\* = 2.00). This treatment can be extended to the other substituents of Table I to give the approximate polar substituent constants listed in Table II. Thus, the σ\* values of the two dialkoxyphosphono groups and the diphenylphosphono group are found essentially to flank that of the carbomethoxy group. The same implication of approximately equivalent electron-acceptor capacity is also given by a comparison of the σ<sub>p</sub> values for the diethoxyphosphono (0.60)<sup>3</sup> and the carbomethoxy (0.52)<sup>6</sup> groups. Thus, the results of σ and σ\* determinations are in good qualitative agreement.<sup>15</sup> The calculated σ\* values for the phosphonium substituents indicate them to fall in the same category of strong inductive electron acceptors as do trimethylammonium and cyano groups (σ\* = 5.32 and 3.64, respectively).<sup>16</sup>

The conclusions regarding the inductive effects of phosphono and phosphonium substituents reached in this study are in qualitative accord with much of the published data regarding the reactivity of organophosphorus compounds, particularly those studies concerning inductive activation of α positions by these substituents. Although little quantitative data exist,

(14) H. J. Bestmann, private communication cited in R. F. Hudson, *Pure Appl. Chem.*, **9**, 380 (1964).

(15) A recent determination of σ\* values for the dialkoxyphosphono and diphenylphosphono groups shows a similar correspondence with σ values (R. B. Davison and C. E. Griffin, unpublished results).

(16) These values are calculated from the corresponding σ\* values for the -CH<sub>2</sub>N(CH<sub>3</sub>)<sub>3</sub><sup>+</sup> (1.90) and -CH<sub>2</sub>CN (1.30) groups.<sup>6</sup>

**Diethyl Carboxymethylphosphonate (3).**—A solution of 18.5 g. (0.10 mole) of benzyl chloroacetate and 18.3 g. (0.11 mole) of triethyl phosphite was heated to 175° to give an exothermic reaction which raised the temperature slightly. During the reaction, a distillate of ethyl chloride was removed. After the initial reaction had subsided, the reaction mixture was heated at 200° for 1 hr. The crude residue (30.0 g.) was distilled at 1 mm. to give 25.1 g. (87%) of diethyl carbobenzyloxymethylphosphonate (2), b.p. 148–169°. Redistillation gave an analytical sample: b.p. 174–179° (1.5 mm.); *n*<sub>D</sub><sup>24</sup> 1.4932; infrared spectrum: 2985 (s), 1739 (s), 1502 (w), 1456 (w), 1399 (m), 1377 (m), 1266 (s), 1212 (m), 1176 (m), 1115 (s), 1054 (s), 1029 (s), and 969 (s) cm.<sup>-1</sup>; p.m.r. spectrum (CCl<sub>4</sub> solution): τ = 8.75 (CH<sub>3</sub>-C, (3), 7.13 (-CH<sub>2</sub>-P, 2, J<sub>PCN</sub> = 21.9 c.p.s.), 5.97 (-CH<sub>2</sub>-O, 5), 4.90 (-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub>, 1), 2.69 p.p.m. (C<sub>6</sub>H<sub>5</sub>-c).<sup>19</sup>

*Anal.* Calcd. for C<sub>13</sub>H<sub>19</sub>O<sub>6</sub>P: C, 54.54; H, 6.69; P, 10.82. Found: C, 54.37, 54.31; H, 6.80, 6.81; P, 11.13, 11.09.

A solution of 4.58 g. (16 mmoles) of 2 in 50 ml. of absolute ethanol was reduced at atmospheric pressure over 200 mg. of 10% palladium on charcoal. The theoretical amount of hydrogen was absorbed within 20 min. The reaction mixture was filtered through a bed of Celite and the solvent was removed under reduced pressure to yield 2.99 g. (95%) of 3 as a colorless liquid: b.p. 160–163° (0.5 mm.); infrared spectrum: 2985 (s), 1727 (s), 1481 (w), 1449 (w), 1397 (m), 1376 (w), 1222 (s), 1164 (s), 1115 (s), 1054 (s), 1028 (s), 970 (s), and 899 (m) cm.<sup>-1</sup>; p.m.r. spectrum (neat): τ = 8.70 (CH<sub>3</sub>-C, 3); 6.99 (-CH<sub>2</sub>-P, 2, J<sub>PCN</sub> = 21.7 c.p.s.), 5.85 p.p.m. (-CH<sub>2</sub>-O, 5).

*Anal.* Calcd. for C<sub>6</sub>H<sub>13</sub>O<sub>6</sub>P: C, 36.74; H, 6.68; P, 15.79. Found: C, 36.92, 36.70; H, 6.77, 6.81; P, 15.94, 16.02.

**Di-*n*-butyl Carboxymethylphosphonate (5).**—Reaction of tri-*n*-butyl phosphite (70.0 g., 0.28 mole) and benzyl chloroacetate (48.0 g., 0.26 mole) was carried out in the same manner as the reaction with triethyl phosphite. Distillation of the reaction mixture gave 37.0 g. (83%) of di-*n*-butyl carbobenzyloxymethylphosphonate (4), b.p. 152–174° (0.015 mm.). Redistillation at 0.003 mm. gave 4 in an analytically pure state: 4.44 g., b.p. 149–165°, and 30.62 g., b.p. 156–165°, *n*<sub>D</sub><sup>25</sup> 1.4850. The two temperature ranges observed arose from a slight pressure fluctuation.

*Anal.* Calcd. for C<sub>17</sub>H<sub>27</sub>O<sub>6</sub>P: C, 59.63; H, 7.95; P, 9.05. Found: C, 59.38, 59.41; H, 8.03, 8.04; P, 8.91, 8.97.

The infrared spectrum had bands at 2890 (s), 1742 (s), 1506 (w), 1466 (m), 1404 (w), 1379 (w), 1271 (s), 1214 (s), 1116 (s), 1064 (s), 1027 (s), 988 (s), and 905 (w) cm.<sup>-1</sup>. The p.m.r. spectrum (CCl<sub>4</sub> solution) had τ = 9.08 (CH<sub>3</sub>-C, c), 8.92–8.25

(17) For pertinent reviews, see R. F. Hudson, *Pure Appl. Chem.*, **9**, 371 (1964); H. J. Bestmann, *ibid.*, **9**, 285 (1964); R. F. Hudson, *Advan. Inorg. Chem. Radiochem.*, **5**, 347 (1963); P. C. Crofts, *Quart. Rev. (London)*, **12**, 341 (1958).

(18) All infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer using chloroform solutions. The instrument was calibrated at 6.24 μ using a polystyrene film and all spectra are corrected. P.m.r. spectra were determined at 27° (probe temperature) with a Varian Associates Model A-60 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the τ scale in parts per million relative to TMS (τ 10.00). All melting points are uncorrected. Microanalyses were performed by Galbraith Microanalytical Laboratories. Column chromatography was carried out on 50-g. silicic acid columns (2.5 × 18 cm.).

(19) For each compound, chemical shifts cited are the centers of the multiplets. Numbers in parentheses refer to the multiplicity of the observed resonance (c = complex multiplet).

( $-\text{CH}_2-\text{C}$ , c), 7.13 ( $-\text{CH}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 22.0$  c.p.s.), 6.03 ( $-\text{C}-\text{H}_2-\text{O}$ , 4), 4.90 ( $-\text{CH}_2-\text{C}_6\text{H}_5$ , 1), and 2.69 p.p.m. ( $\text{C}_6\text{H}_5$ , c).

A solution of 3.34 g. (9.5 mmole) of **4** in 15 ml. of absolute ethanol was reduced over 200 mg. of 10% palladium on charcoal at atmospheric pressure; the theoretical amount of hydrogen was absorbed in 2 hr. The reaction mixture was filtered through a bed of Celite and the solvent was removed under reduced pressure to yield 2.34 g. (92%) of a colorless oil. This oil was chromatographed on silicic acid with chloroform-methanol (95:5) as eluent to give **5** as a colorless oil: infrared spectrum: 2967 (s), 1727 (s), 1466 (m), 1387 (m), 1233 (s), 1116 (s), 1064 (s), 1027 (s), 990 (s), and 902 (m)  $\text{cm}^{-1}$ ; p.m.r. spectrum ( $\text{CCl}_4$  solution):  $\tau = 9.28-8.23$  ( $\text{CH}_3-\text{C}$  and  $-\text{CH}_2-\text{C}$ , c), 7.12 ( $-\text{CH}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 21.8$  c.p.s.), and 5.88 p.p.m. ( $-\text{CH}_2-\text{O}$ , 4).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{21}\text{O}_5\text{P}$ : C, 47.61; H, 8.39; P, 12.28. Found: C, 47.38, 47.40; H, 8.42, 8.33; P, 12.35, 12.21.

**Diphenyl(carboxymethyl)phosphine Oxide (6).** A. By Carbonation of the Anion of Diphenylmethylphosphine Oxide.—Using the general procedure of Richards and Bands,<sup>10</sup> a solution of *n*-butyllithium (10 mmoles) in hexane was added to 2.16 g. (10 mmoles) of diphenylmethylphosphine oxide suspended in 40 ml. of anhydrous ether; the reaction mixture was refluxed for 3 hr. The suspension of lithium salt was poured with stirring onto a slurry of Dry Ice and ether. The ether was evaporated and the residue was treated with 50 ml. of 5% hydrochloric acid. The acidic solution was extracted three times with chloroform and the extracts were dried over sodium sulfate and concentrated under reduced pressure to give 2.76 g. of a waxy material which could not be crystallized. Chromatography of this material on silicic acid with chloroform-methanol (75:25) gave 1.45 g. (55%) of **6** as an oil which crystallized readily. The solid was recrystallized three times from aqueous ethanol and dried over phosphorus pentoxide under vacuum at room temperature to give colorless needles: m.p. 144–146° (lit. m.p. 145–146°,<sup>10</sup> 142–144°<sup>20</sup>); infrared spectrum: 1724 (s), 1592 (w), 1493 (w), 1437 (s), 1266 (m), 1167 (s), 1124 (s), 1099 (s), 996 (w), 897 (w), and 844 (w)  $\text{cm}^{-1}$ ; p.m.r. spectrum ( $\text{CDCl}_3$  solution):  $\tau = 6.51$  ( $-\text{CH}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 14.4$  c.p.s.), 2.53–2.22 ( $\text{C}_6\text{H}_5$ , c), and  $-1.87$  p.p.m. ( $-\text{OH}$ , 1).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{15}\text{O}_3\text{P}$ : C, 64.61; H, 5.00; P, 11.92. Found: C, 64.66, 64.60; H, 5.03, 5.10; P, 12.11, 12.08.

B. By Oxidation of Diphenylallylphosphine Oxide (7).—The phosphine oxide **7** was prepared using the procedure of Arbuzov and Nikonorov.<sup>9</sup> A solution of 2.9 g. (50 mmoles) of allyl alcohol in 25 ml. of anhydrous ether containing 4.0 g. (50 mmoles) of pyridine was cooled to 0°. Addition of 11.0 g. (50 mmoles) of diphenylchlorophosphine caused immediate reaction and the precipitation of pyridine hydrochloride; after addition was completed, the reaction mixture was stirred for 40 min. The mixture was filtered and the solvent was removed from the filtrate to yield 12.5 g. of an oil. The oil was heated and, at 180°, a violent reaction occurred to give a red oil which crystallized on cooling to give a colorless solid. This solid was washed repeatedly with ether to give 7.9 g. (65%) of **7** which was chromatographed on silicic acid using chloroform as eluent to give colorless crystals: m.p. 99–100° (lit.<sup>9</sup> m.p. 94–95°); p.m.r. spectrum:  $\tau = 6.88$  ( $-\text{CH}_2-\text{P}$ , two doublets,  $J_{\text{PCH}} = 14.5$  c.p.s.), 5.13–3.83 ( $=\text{CH}$ , c), 2.58, and 2.15 p.p.m. ( $\text{C}_6\text{H}_5$ , c).

A mixture of 242 mg. (1 mmole) of **7**, 21 mg. (0.134 mmole) of potassium permanganate, 1.712 g. (8 mmoles) of sodium iodate, and 414 mg. (3 mmoles) of potassium carbonate in 700 ml. of aqueous *t*-butyl alcohol was allowed to stir at room temperature for 20 hr. Ethylene glycol (1 ml.) was added to destroy the excess oxidant. The reaction mixture was extracted six times with chloroform and the chloroform extracts were dried over magnesium sulfate and filtered. Removal of solvent gave 0.312 g. of material which was chromatographed on a 3-g. silicic acid column. Elution with chloroform gave 147 mg. of unreacted **7**. Elution with chloroform-methanol (95:5) gave 66 mg. (25%) of **6** as an oil which crystallized on seeding. This material was identical in all respects with the sample prepared by the preceding method.

**Triphenyl(carboxymethyl)phosphonium Chloride (9).** A. By Reaction of Chloroacetic Acid and Triphenylphosphine.—The

procedure described by Denney and Smith<sup>11</sup> was followed to give **9** (38%), m.p. 218–219° (lit.<sup>10</sup> m.p. 221–223°). This sample had the reported infrared characteristics<sup>11</sup>; p.m.r. spectrum ( $\text{CF}_3\text{COOH}$  solution):  $\tau = 5.43$  ( $-\text{CH}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 14.1$  c.p.s.) and 2.23 p.p.m. ( $\text{C}_6\text{H}_5$ , c).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{18}\text{ClO}_2\text{P}$ : C, 67.32; H, 5.08; Cl, 9.94; P, 8.68. Found: C, 67.31, 67.40; H, 5.03, 5.12; Cl, 9.98, 10.03; P, 8.59, 8.74.

B. By Hydrogenolysis of Triphenyl(carboxymethyl)phosphonium Chloride (10).—A solution of 6.55 g. (25 mmoles) of triphenylphosphine and 4.62 g. (25 mmoles) of benzyl chloroacetate in 25 ml. of dry benzene was allowed to stand for 1 week at room temperature. The colorless crystalline material which precipitated was collected by filtration and washed three times with benzene to give 5.17 g. (46%) of **10**: m.p. 133–135°; p.m.r. spectrum ( $\text{ODCl}_3$  solution):  $\tau = 5.00$  ( $-\text{CH}_2-\text{O}$ , 1), 4.21 ( $-\text{C}-\text{H}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 14.0$  c.p.s.), and 3.00–1.92 p.p.m. ( $\text{C}_6\text{H}_5$ , c).

A solution of 0.93 g. (2.1 mmoles) of **10** in 10 ml. of absolute ethanol was reduced over 100 mg. of 10% palladium on charcoal at atmospheric pressure. The theoretical amount of hydrogen was absorbed in 3 hr. The reaction mixture was filtered and the solvent was removed to yield an oil which crystallized on standing. Recrystallization from absolute ethanol-diethyl ether gave 0.66 g. (88%) of **9**, m.p. 217–218°. This material was identical in all respects with that prepared by the preceding method.

**Tri-*n*-butyl(carboxymethyl)phosphonium Chloride (12).** A. By Hydrolysis of Tri-*n*-butyl(carboxymethyl)phosphonium Chloride (13).—A solution of 10.1 g. (50 mmoles) of tri-*n*-butylphosphine in 100 ml. of ether was cooled to 0°. Ethyl chloroacetate (6.13 g., 50 mmoles) was added dropwise to this solution over a period of 5 min. The reaction mixture was allowed to warm to room temperature and allowed to stand for 48 hr. The colorless solid which precipitated was collected by filtration and washed several times with ether to give 8.7 g. (53%) of **13**: m.p. 85–87°; p.m.r. spectrum ( $\text{CCl}_4$  solution):  $\tau = 8.98$  [ $\text{CH}_3-\text{C}$  (butyl), c], 8.67 [ $\text{CH}_2-\text{C}$  (ethyl), 3], 8.38 [ $-\text{CH}_2-\text{C}$  (butyl), c], 7.45–6.75 [ $-\text{CH}_2-\text{P}$  (butyl), c], 5.77 ( $-\text{CH}_2-\text{O}$ , 4), and 5.58 p.p.m. ( $-\text{CH}_2-\text{P}$ , 2).

A solution of 3.24 g. (10 mmole) of **13** in 75 ml. of 3% hydrochloric acid was allowed to stand at room temperature until the reaction mixture had evaporated to dryness. The resulting viscous oil was chromatographed on a silicic acid column with chloroform-methanol (95:5) as eluent to give 2.6 g. (90%) of **12** as a viscous, colorless oil. Repeated chromatography on silicic acid gave an analytical sample: infrared spectrum: 3058 (s), 2469 (m), 1730 (s), 1473 (s), 1366 (s), 1316 (m), 1279 (m), 1235 (s), 1215 (s), 1183 (m), 1100 (s), 1005 (m), 963 (m), and 908 (s)  $\text{cm}^{-1}$ ; p.m.r. spectrum ( $\text{CDCl}_3$  solution):  $\tau = 9.08$  ( $\text{CH}_3-\text{C}$ , c), 8.45 ( $-\text{CH}_2-\text{C}$ , c), 7.48 [ $-\text{CH}_2-\text{P}$  (butyl), c], 6.12 ( $-\text{CH}_2-\text{P}$ , 2,  $J_{\text{PCH}} = 13.0$  c.p.s.), and  $-2.28$  p.p.m. ( $-\text{OH}$ , 1).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{30}\text{O}_2\text{P}$ : C, 56.65; H, 10.19; P, 10.44. Found: C, 56.42, 56.38; H, 10.21, 10.35; P, 10.34, 10.30.

B. By Reaction of Chloroacetic Acid and Tri-*n*-butylphosphine.—A solution of 20.2 g. (0.10 mole) of tri-*n*-butylphosphine and 11.3 g. (0.12 mole) of chloroacetic acid in 600 ml. of methanol was heated at 40° for 72 hr. Removal of the solvent at reduced pressure followed by extraction of the residue with ether gave 21.6 g. (73%) of a colorless, viscous oil. A sample of 2.86 g. of the oil was purified by chromatography as above to give 2.77 g. of **12**, which was identical in all respects with the sample prepared in the preceding experiment.

**Measurement of Ionization Constants.**—A solution of 0.5 mmole of the acid in 47.5 ml. of deionized water was titrated with 0.1 *N* carbonate-free potassium hydroxide (Anachemia Chemicals Ltd.). After the addition of each 0.5 ml. of alkali, the pH of the solution was determined with a Beckman Zeromatic pH meter in conjunction with a glass electrode and a saturated calomel electrode. Titrations were carried out in 50-ml. beakers which contained the electrodes, a nitrogen inlet, and a thermometer; stirring of the solution was accomplished by a slow stream of nitrogen bubbles. The beaker was suspended in an automatically controlled constant-temperature bath at  $25 \pm 0.1^\circ$ . The titrant was delivered from a buret (calibrated to 0.01 ml.) which was protected from the atmosphere with a soda lime tube. Each p*K* value was calculated by standard methods<sup>12</sup> from six to ten determinations covering the range of 10–90% neutralization. The p*K* values obtained in this manner agreed to  $\pm 0.10$  p*K* unit and were averaged. Duplicate titrations were made with an agreement of  $\pm 0.07$  unit. Activity corrections

and liquid junction potentials were neglected throughout, and hence the experimental values are nonthermodynamic dissociation constants.<sup>21</sup>

(21) Tables listing the potentiometric titration results and the calculated  $pK$  values over the titration range are given in ref. 4b.

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## Synthetic Nucleosides. LXV.<sup>1a</sup> Studies on the Synthesis of *cis*-2,3-Diamino Sugars. V.<sup>1b</sup> Neighboring Group Reactions with Derivatives of Methyl 2-Amino-4,6-*O*-benzylidene-2-deoxy- $\alpha$ -D-altropyranoside<sup>1c</sup>

B. R. BAKER AND T. L. HULLAR<sup>1d</sup>

Department of Medicinal Chemistry, School of Pharmacy,  
State University of New York at Buffalo, Buffalo, New York 14214

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Treatment of methyl 4,6-*O*-benzylidene-*N*-cyano-2-deoxy-2-(*p*-tolylsulfonamido)-3-*O*-(*p*-tolylsulfonyl)- $\alpha$ -D-altropyranoside (10a) with hydrogen sulfide gave the *N*-detosylated thioureido derivative, methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(*p*-tolylsulfonyl)-2-thioureido- $\alpha$ -D-altropyranoside (16). Cyclization of 16 in pyridine or ethanolic solution gave 2-amino-4',6'-*O*-benzylidene-1'-*O*-methyl- $\alpha$ -D-mannopyrano[2',3':4,5]-2-thiazoline (17). In contrast, anionic cyclization of the ureido derivative, methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-(*p*-tolylsulfonyl)-2-ureido- $\alpha$ -D-altropyranoside (25), gave the aziridine, methyl 4,6-*O*-benzylidene-*N*-carbamoyl-2,3-dideoxy-2,3-imino- $\alpha$ -D-mannopyranoside (26). These results further confirm the generality that formation of aziridines readily occurs when the requisite substituents are *trans*-diaxial to each other. Addition of benzylamine to 10a gave, after cyclization and hydrolysis, a derivative of 2,3-diamino-2,3-dideoxy-D-mannose.

Recent studies<sup>1b,2-4</sup> directed to the synthesis of *cis*-2,3-diamino sugars showed that a secondary sulfonate ester group could be displaced by a trifunctional neighboring group<sup>5</sup> to give three- or five-membered rings depending upon the conditions of the reactions. Thus, in pyridine solution the sulfonate ester in methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-methanesulfonyl-3-thioureido- $\alpha$ -D-altropyranoside (1) was displaced by the thioureido sulfur atom to give 2-amino-4',6'-*O*-benzylidene-1'-*O*-methyl- $\alpha$ -D-allopyrano[3',2':4,5]-2-thiazoline (2) (Scheme I).<sup>3</sup> However, under conditions sufficiently basic to form an anion (methanolic sodium methoxide), the sulfonate ion was displaced by the secondary nitrogen atom to give the aziridine derivative, methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-imino-*N*-thiocarbamoyl- $\alpha$ -D-allopyranoside (3).<sup>3</sup>

Ring closure of 1 to form the aziridine 3 can be attributed to the *trans*-diaxial disposition of the attacking and departing groups. The anion of the secondary nitrogen atom is thus ideally positioned to effect an intramolecular nucleophilic displacement of the mesylate; the anion of the primary nitrogen or of the sulfur are not so advantageously placed and furthermore would suffer hindrance by the axial C-1 methoxyl.<sup>7</sup> Under conditions insufficiently basic to form an anion, displacement by the most nucleophilic function, in

(1) (a) For the previous paper in this series, see B. R. Baker and D. H. Buss, *J. Org. Chem.*, **30**, 2308 (1965). (b) For the previous paper in this series, see B. R. Baker and T. Neilson, *ibid.*, **29**, 1063 (1964). (c) This work was supported in part by Grant CY-5845 of the National Cancer Institute, U. S. Public Health Service. (d) National Science Foundation Postdoctoral Fellow, 1963-1964. (e) Abbreviations used: Ac = acetyl; Bz = benzoyl; Ms = mesyl = methanesulfonyl; and Ts = tosyl = *p*-tolylsulfonyl.

(2) B. R. Baker and T. Neilson, *J. Org. Chem.*, **29**, 1047 (1964).

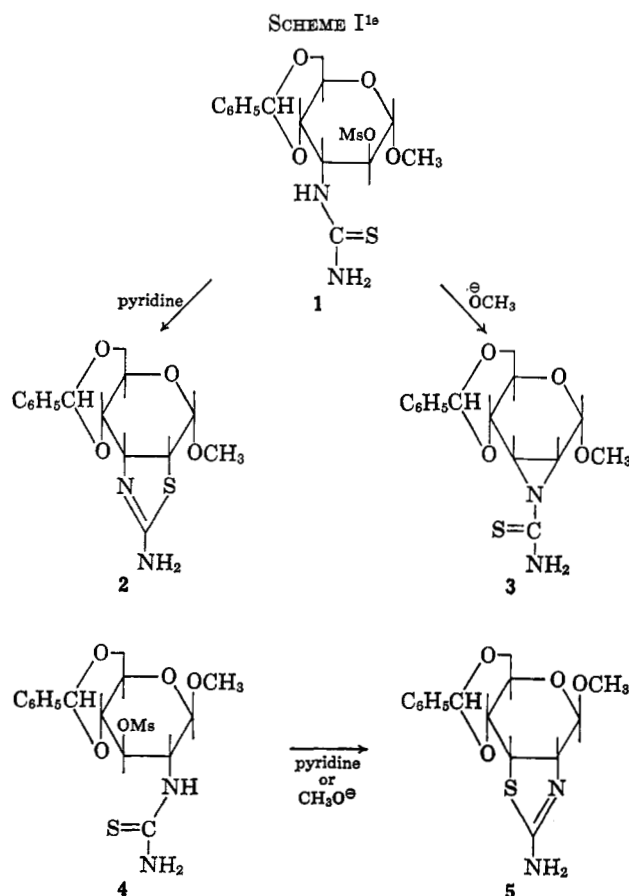
(3) B. R. Baker and T. Neilson, *ibid.*, **29**, 1051 (1964).

(4) B. R. Baker and T. Neilson, *ibid.*, **29**, 1057 (1964).

(5) Such groups may alternatively be termed tridentate neighboring groups to follow the terminology of Scott and Flynn.<sup>6</sup>

(6) F. L. Scott and E. Flynn, *Tetrahedron Letters*, 1675 (1964).

(7) D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 5295 (1963).



this case the thione group, is the expected course of reaction.

In methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methanesulfonyl-2-thioureido- $\beta$ -D-glucopyranoside (4) ring closure occurs in pyridine or sodium methoxide solution to give only the thiazoline 5.<sup>3</sup> The lack of aziridine formation from 4 undoubtedly results from the *trans*-