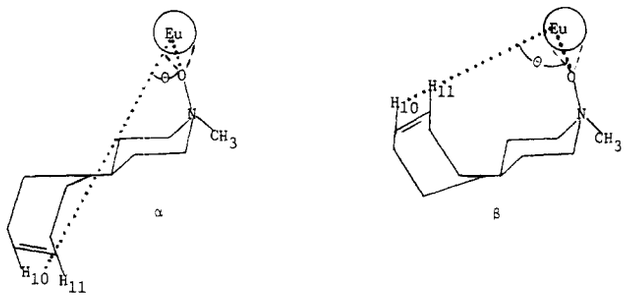

Figure 1. Stereochemical relationship between the N^+–O^- bond and the ethylene bridge protons in the europium complexed $\alpha + \beta$ isomers of cyproheptadine *N*-oxide.

so that a proton associated with a θ value greater than 50°, e.g., the β-C_{10} proton, would experience an upfield shift. These stereochemical relationships then may be represented diagrammatically for the two isomers as in Figure 1 and the α isomer assigned structure **1a**, the β isomer, structure **1b**.

Confirmation of these assignments was sought from calculations of the theoretical values for the $3(\cos^2\theta - 1)/r^3$ term for varied conformations of the isomeric europium complexes.[7] Because of the observed equivalence of H-10 and H-11, the europium atom must be positioned either (a) in a single conformation which is symmetrical with respect to the C_{10}–C_{11} double bond or (b) in two or more rapidly interconverting conformations such that on the average H-10 and H-11 are equivalent. For situation a, only two Eu–O–N–CH_3 dihedral angles, 0 and 180°, are acceptable. The calculations indicated that as long as the Eu–O–N angle was greater than 150°, the predicted direction for the lanthanide-induced shifts was as observed experimentally. In fact, owing to steric hindrance, no Eu–O–N dihedral angle of less than 150° would be expected. For situation b, the two most reasonable conformations are the staggered ones with Eu–O–N–CH_3 dihedral angles of 60 and 300°. In this case, the calculations indicated that the predicted direction of the shifts matched the experimental observations, provided the Eu–O–N angle exceeded 120°. Here also, no smaller Eu–O–N angle would be expected on either electronic or steric grounds.

Thus, the stereochemical relationships for the complexed isomers represented in Figure 1 appear valid and structure **1a** may be assigned to the α isomer and **1b** to the β isomer of cyproheptadine *N*-oxide.

Experimental Section[8]

4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine 1-Oxide (1a and 1b). A stirred solution of cyproheptadine (14.8 g, 0.0515 mol) in 150 ml of MeOH was treated portionwise with 30% H_2O_2 (18 g) and then held at room temperature for about 10 days. The cooled solution was stirred with a suspension of ca. 200 mg of 5% Pt/C in 1 ml of H_2O until the excess peroxide was destroyed. Evaporation of the filtered solution at 35 °C left a solid residue that was dried overnight at 20 mm over P_2O_5. The solid then was pulverized and dried at 0.2 mm over P_2O_5 for 24 h; yield, 15 g of the mixture of isomers.

A 10-g sample of the product was chromatographed on 700 g of SiO_2, eluting with 15 MeOH–85 $CHCl_3$. Fractions containing a single component of R_f 0.5 by TLC (20 MeOH–80 $CHCl_3$ development) were combined to afford the solvated crystalline α base **1a**. This was recrystallized from H_2O to give 5.2 g of the crystalline hemihydrate, mp 188–191 °C, after prolonged drying at room temperature at 0.2 mm.

The α-hydrochloride hemihydrate precipitated from a solution of the base in EtOH–HCl(g) and was recrystallized from EtOH, mp 205–211 °C dec.

Chromatographic fractions containing a single component of R_f 0.4 by TLC were combined to afford the crystalline β base **1b**, mp 194–199 °C dec. This base was not readily recrystallized and was converted to the hydrochloride salt with EtOH–HCl(g). The salt was recrystallized from EtOH to give 1.9 g, mp 223–228 °C dec, after prolonged drying at room temperature at 0.1 mm.

Isomeric purity of the hydrochloride salts was determined to be >95% by both NMR and TLC (10 benzene–80 dioxane–10 concentrated NH_4OH development).

A solution of the α base **1a** (6.0 g, 0.02 mol) in 175 ml of toluene was stirred at reflux for 24 h. After 2 h, a white solid had begun to precipitate. The solid was collected from the cooled mixture by filtration and triturated with hot toluene (50 ml). The remaining solid (4.3 g) was dissolved in EtOH–HCl(g). The hydrochloride salt precipitated and was recrystallized from EtOH to give 4.1 g, mp 228–231 °C dec. This material was identical in all respects with the hydrochloride of the β isomer **1b**.

Acknowledgment. The authors wish to thank Dr. Laurance D. Hall of the University of British Columbia, Vancouver, Canada, for valuable advice and discussion, as well as for the calculations of the configurations of the lanthanide complexes.

Registry No.—**1a,** 54381-42-9; **1a** HCl, 60304-94-1; **1b,** 60251-34-5; **1b** HCl, 60268-34-0; cyproheptadine, 129-03-3.

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(7) These calculations were carried out by Victoria C. Gibb, using a computer program developed in the laboratory of Dr. Laurance D. Hall at the University of British Columbia, Vancouver, Canada. Standard values for all bond lengths and angles were used. Values for $\theta_{O,Eu,H}$ and $r_{Eu,H}$ were measured from Dreiding models, assuming no rotation of the europium atom around the N–O bond and the same relative position and binding constant of the metal for both isomers. Variations in the isomeric binding constants would effect only the magnitude but not the direction of the induced shifts.
(8) Melting points were determined with a calibrated thermometer in a Thomas-Hoover apparatus. ^1H NMR spectra were recorded on a Varian HA-100D spectrometer; ^{13}C NMR on a Varian CFT-20. Thin layer chromatography was done on precoated silica gel plates with UV indicator supplied by Analtech, Inc. Evaporations were carried out in a rotary evaporator at reduced pressure. Satisfactory analytical data (±0.4% for C, H, N) for **1a** and **1b** were submitted for review.

A Convenient Synthesis of Diaryl Methylphosphonates and Transesterification Products Therefrom

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Diaryl methylphosphonates have been useful as both enzyme model substrates[1] and reactive intermediates.[2] The literature describes two basic routes for their preparation. One involves the condensation of methylphosphonic dichloride with the appropriately substituted phenol.[3] However, methylphosphonic dichloride is not readily available and low yields have been reported in some of the aryl ester syntheses using this reagent. The second procedure[4] consists of reacting a triaryl phosphite with 1 equiv of methyl iodide. This Michaelis–Arbuzov rearrangement gives only modest yields, for instance, less than 70% in the case of 1. Moreover, it requires methyl iodide, an expensive reagent. We report, herein, an improved version of the latter rearrangement.

Our procedure involves addition of 1 molar equiv of methanol containing a catalytic amount of methyl iodide to a triaryl phosphite at 200–250 °C. The reaction, on a five molar scale,

Table I. Diaryl Methylphosphonates
$(ArO)_2P(O)Me$

Compd	Phenyl substituent	Yield, %	Bp, °C (mm) Obsd	Bp, °C (mm) Lit.	Mp, °C Obsd	Mp, °C Lit.
1	H	92	138 (0.15)	190–195 (11)[a]	35–36	36–37[a]
2	*p*-Me	56	171 (0.20)	220–225 (12)[a]	Viscous liquid	Viscous liquid
3	*m*-Me	53	145–147 (0.15)	200–205 (7)[a]	Viscous liquid	Viscous liquid
4	*p*-Cl	34	157–160 (0.03)	245 (20)[a]	Viscous liquid	Viscous liquid
5	*p*-*t*-Bu	61	174 (0.07)		65–67	
6	*p*-MeO	72	177–179 (0.03)		Viscous liquid	

[a] See ref 4a.

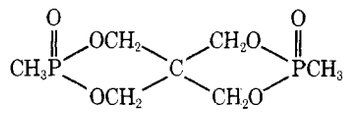
$$(ArO)_3P + MeOH \xrightarrow{0.5\%\ MeI} (ArO)_2P(O)Me + ArOH$$

requires only about 3 h. With triphenyl phosphite, **1** is obtained in 92% yield. The scope of this synthesis is detailed in Table I.

The process can best be rationalized in terms of a two-step mechanism. Initially, methanol transesterifies with the triaryl phosphite to produce diaryl methyl phosphite. Subsequently, this intermediate undergoes rearrangement to the phosphonate with regeneration of the methyl iodide.

Long-chain (C_8 and higher) alcohols have been reported[5] to undergo a similar reaction with triphenyl phosphite. The same report indicated that the lower alcohols would probably require elevated pressure. In our examination of short-chain alcohols under our atmospheric pressure process we noted that ethanol and 2-propanol afforded only diphenyl phosphite. Under these conditions, 1-propanol and 1-butanol transesterified with triphenyl phosphite but the products did not readily rearrange. However, benzyl alcohol did react to form diphenyl benzylphosphonate.

Exemplifying the utility of **1** as a reactive intermediate, various aliphatic alcohols were found capable of displacing phenol from **1**. For example, pentaerythritol and neopentyl glycol afforded **8** and **9** in 52 and 33% yields, respectively.



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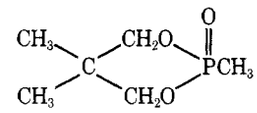

9

Experimental Section

NMR spectra were obtained with Varian Associates A-60A (^1H) and Bruker 90 (^{31}P) nuclear magnetic resonance spectrophotometers operating at ambient temperature. Chemical shifts are in parts per million relative to internal Me_4Si (τ units) and external 85% orthophosphoric acid for the ^1H and ^{31}P resonances, respectively. Except where otherwise noted, deuteriochloroform was employed as the NMR solvent. A Hewlett-Packard 5750 instrument was employed for the GLC analysis. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Diphenyl Methylphosphonate (1). A reactor fitted with an efficient condenser, thermometer, mechanical stirrer, and side-arm addition funnel was charged with 1552 g (5.0 mol) of triphenyl phosphite. The reactant was placed under a nitrogen blanket and heated to reflux. A solution of 5.0 g of methyl iodide in 160 g (5.0 mol) of methanol was then slowly added over a 2-h period. Throughout the addition, the temperature of the reactor contents was maintained within the 200–250 °C range. A further 1 h at 215 °C proved sufficient for the reaction to reach completion. Subsequently, an aspirator vacuum distillation removed 468 g (5.0 mol) of phenol containing a small amount of anisole. Thereafter, a high vacuum distillation recovered 1150 g (4.6 mol, 92% yield) of diphenyl methylphosphonate. GLC analysis using a 6-ft column packed with 10% OV-101 on Chromosorb W was employed to monitor the progress of both the reaction and distillation. The ^{31}P signal for compound **1** appeared at −24.0 ppm. ^1H NMR signals were seen at τ 8.36 (3 H, doublet, J = 18 Hz, CH_3P) and 2.9–2.5 (10 H, multiplet, phenyl).

General Procedure. The method as outlined for **1** was that employed for synthesis of the other analogues. Preparation of compounds **2–5** began from PCl_3 and the appropriate phenol. These were run on a 0.5 molar scale. The resultant phosphites were then purged of HCl and further reacted with methanol. Reported yields are based on starting PCl_3.

Bis(*p*-tolyl) Methylphosphonate (2). ^1H NMR signals were observed at τ 8.37 (3 H, doublet, J = 16.5 Hz, CH_3P), 7.77 (6 H, singlet, CH_3Ar), and 2.89 (8 H, broad singlet, phenyl), The ^{31}P NMR signal appeared at −23.6 ppm.

Bis(*m*-tolyl) Methylphosphonate (3). ^1H NMR signals were observed at τ 8.30 (3 H, doublet, J = 17.5 Hz, CH_3P), 7.72 (6 H, singlet, CH_3Ar), and 3.4–2.5 (8 H, multiplet, phenyl). The ^{31}P NMR signal appeared at −23.5 ppm.

Bis(*p*-chlorophenyl) Methylphosphonate (4). ^1H NMR signals were observed at τ 8.24 (3 H, doublet, J = 17.5 Hz, CH_3P) and 3.0–2.3 (8 H, multiplet, phenyl). The ^{31}P NMR signal appeared at −24.8 ppm.

Bis(*p*-*tert*-butylphenyl) Methylphosphonate (5). ^1H NMR signals were observed at τ 8.70 [18 H, singlet, $(CH_3)_3C$], 8.26 (3 H, doublet, J = 17.5 Hz, CH_3P), and 2.75 (8 H, A_2B_2 quartet, phenyl). The ^{31}P NMR signal appeared at −23.9 ppm.

Anal. Calcd for $C_{21}H_{29}O_3P$: C, 70.00; H, 8.06; P, 8.61. Found: C, 69.83; H, 8.21; P, 8.50.

Bis(*p*-methoxyphenyl) Methylphosphonate (6). ^1H NMR signals were observed at τ 8.35)3 H, doublet, J = 17.5 Hz, CH_3P), 6.32 (6 H, singlet, CH_3O), and 3.08 (8 H, A_2B_2 quartet, phenyl). The ^{31}P NMR signal appeared at −24.6 ppm.

Anal. Calcd for $C_{15}H_{17}O_5P$: C, 58.44; H, 5.52; P, 10.10. Found: C, 58.00; H, 5.74; P, 10.10.

Diphenyl Benzylphosphonate (7). To a flask containing 155 g (0.5 mol) of refluxing triphenyl phosphite was added over a 1.5-h period a mixture of 54 g (0.5 mol) of benzyl alcohol and 0.5 g of methyl iodide. The reaction temperature was maintained at 200–250 °C for a further 3.5 h. Thereafter, 43.9 g (0.47 mol) of phenol by-product was removed by distillation. The product (**7**) distilled at 186–187 °C (0.06 mm) and weighed 113 g (0.35 mol, 70% yield). Upon cooling **7** solidified. Recrystallization in ligroin gave white needles with mp 61–62 °C (lit.[4a] mp 60 °C). ^1H NMR signals (neat) were observed at τ 6.62 (2 H, doublet, J = 22 Hz, CH_2OP) and 3.2–2.6 (15 H, multiplet, phenyl). A ^{31}P NMR signal was observed at −19.5 ppm.

3,9-Dimethyl-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane 3,9-Dioxide (8). A mixture of 74.4 g (0.30 mol) of diphenyl methylphosphonate, 20.4 g (0.15 mol) of pentaerythritol, and 0.1 g of magnesium chloride was heated together at 192–205 °C for 6 h. Thereafter, 54.6 g (0.58 mol) of phenol was removed under a 26-mm vacuum and a pot temperature of 120–200 °C. Crude product (38.2 g) remained behind in the reactor. Sublimation at 210 °C (0.05 mm) afforded 20.1 g (0.078 mol, 52% yield) of **8**. The product was a hygroscopic, white, crystalline solid, mp 240–241 °C (lit.[6] mp 239–241 °C). ^1H NMR signals (Me_2SO-d_6 as solvent) were observed at τ 8.36 (6 H, doublet, J = 17 Hz, CH_3P) and 6.0–5.4 (8 H, multiplet, CH_2O). The ^{31}P NMR signal appeared at −27.2 ppm.

2,5,5-Trimethyl-2-oxo-1,3,2-dioxaphosphorinane (9). A reactor was charged with 74.4 g (0.30 mol) of diphenyl methylphosphonate, 31.2 g (0.30 mol) of dry neopentyl glycol, and 0.2 g of magnesium chloride. These reactants were heated at 210–250 °C for 4 h. Subsequently, phenol (36 g, 0.38 mol) was removed by distillation. Further distillation afforded a liquid with bp 128–130 °C (3.4 mm) that soon solidified. Recrystallization from benzene–heptane afforded white crystals, mp 119–121 °C (lit.[7] mp 119–121 °C), weighing 16.0 g (0.10 mol, 33% yield). The observed ^1H NMR spectrum of **9** was consistent with that reported by Edmundson.[8]

Registry No.—**1**, 7526-26-3; **2**, 60142-74-9; **3**, 60142-73-8; **4**, 6395-59-1; **5**, 60705-72-8; **6**, 60705-73-9; **7**, 10419-87-1; **8**, 3001-98-7;

9, 873-97-2; $(ArO)_3P$ (Ar = p-MeC_6H_4), 620-42-8; $(ArO)_3P$ (Ar = m-MeC_6H_4), 620-38-2; $(ArO)_3P$ (Ar = p-ClC_6H_4), 5679-61-8; $(ArO)_3P$ (Ar = p-t-BuC_6H_4), 4235-89-6; $(ArO)_3P$ (Ar = p-$MeOC_6H_4$), 19909-81-0; $(ArO)_3P$ (Ar = Ph), 101-02-0; methanol, 67-56-1; benzyl alcohol, 100-51-6; pentaerythritol, 115-77-5; neopentyl glycol, 126-30-7; phosphorus trichloride, 7719-12-2; p-methylphenol, 106-44-5; m-methylphenol, 108-39-4; p-chlorophenol, 106-48-9; p-$tert$-butylphenol, 98-54-4; p-methoxyphenol, 150-76-5; phenol, 108-95-2.

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A Convenient Determination of σ^+ Values

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The empirical σ^+ parameters devised by Brown and Okamoto[1] to account for the effect of substituents in aromatic electrophilic substitution reactions possess a much greater generality. For instance, Streitwieser et al.[2] have recently demonstrated their applicability to gas-phase protonation of benzenes.

We report here an easy and straightforward method for measurement of previously unavailable σ^+ values, from NMR chemical shifts in meta- or para-substituted benzylidene malononitriles[3] $XC_6H_4CH{=}C(CN)_2$. These are prepared according to standard procedures.[4] The singlet resonance for the olefinic proton is readily identified in the ^1H NMR spectrum. Relationship 1

$$\sigma^+ = 3.57\delta_H - 29.6 \qquad \text{(para substituents)} \quad (1)$$

holds for 5% w/v acetone-d_6 solutions,[5] with a correlation coefficient of 0.989 (11 points) (Figure 1). The σ^+ parameters are thus determined to ±0.3 at the 99% confidence level (three standard deviations). Use of the ^{13}C chemical shift for the cyano-bearing carbon, with a distinctive chemical shift of 80 ± 10 ppm,

$$\sigma^+ = 0.16\delta_C - 13.4 \qquad \text{(para substituents)} \quad (2)$$

leads to better accuracy also for deuteriochloroform solutions (25% w/v) with a correlation coefficient of 0.998 (seven points, including the substituents in the recommended[6] basis set) (Figure 2). Equation 2 is both more *sensitive* and more *accurate* than previous correlations between ^{13}C chemical shifts

Table I. Comparison with Published Correlations Between σ^+ and ^{13}C Chemical Shifts

Compd	Slope	Standard deviation	Ref
Triaryl carbocations	−0.06	0.23	7
Benzenes	0.12	0.19	8
Benzylidenemalononitriles	0.16	0.04	This work

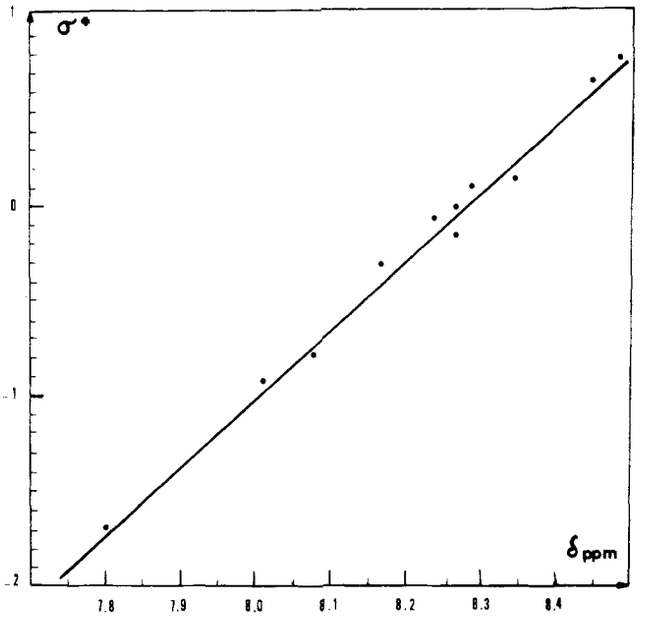

Figure 1. ^1H chemical shift for the olefinic proton vs. σ^+ in acetone-d_6 solution: $\sigma^+ = 3.574\delta - 29.579$.

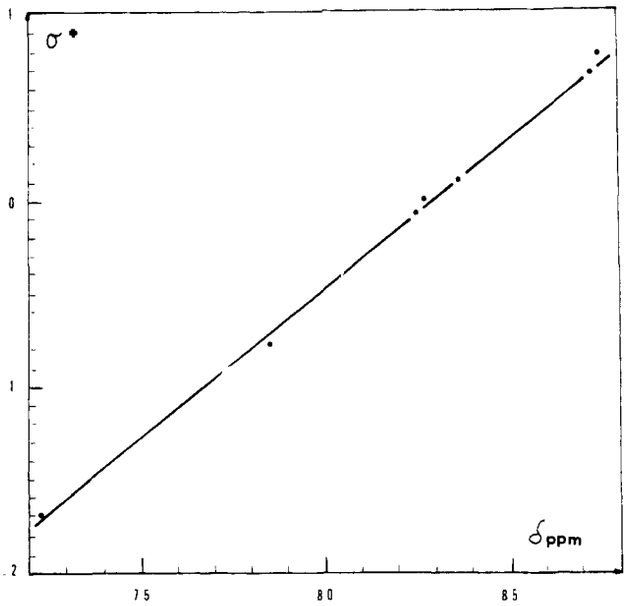

Figure 2. ^{13}C chemical shift for the cyano-bearing cation vs. σ^+ in chloroform-d solution: $\sigma^+ = 0.162\delta - 13.415$

and σ^+ parameters (Table I). Another advantage of our approach is the possibility of evaluating σ^+ for a meta substituent, since in acetone-d_6 solution a *single* relationship holds

$$\sigma^+ = 0.18\delta_C - 14.8 \qquad \text{(meta and para substituents)} \quad (3)$$

with a correlation coefficient of 0.993 (nine points) (Figure 3). This last relationship (3) yields σ^+ values to ±0.08 at the 99% confidence level.

As an application, we have used this method to determine unknown σ^+ values (Table II). Our values of σ^+ for the mesylate and tosylate groups, viz., 0.15 and 0.16, respectively, are of interest since they complement the σ_p, σ_I, and σ^* values just determined, using acidities or ^{19}F chemical shifts, by Stang and Anderson.[9] The σ^+ value for the dicyanomethylidene $HC{=}C(CN)_2$ substituent points to a powerful acceptor, in the same class as the cyano or nitro groups.

In summary, benzylidene malononitriles display strong polarization of the exocyclic double bond putting positive