Thus, $k_u = 2.6\ s^{-1}$. For the laser power and neutral gas pressures used, the unimolecular decomposition is favored over the laser-driven bimolecular reaction by a factor of 1.6:1.

Both the forward and backward reactions in equilibrium 1 proceed through a common intermediate, $(CH_3OH)_2H^+(OH_2)$.[11] The competitive dissocation of this species is evaluated using RRKM theory,[12-14] where the internal energy is taken as absorbed infrared energy added to a 300 K Boltzmann distribution of vibrational energy. At an added energy of 10.5 kcal/mol the *calculated* ratio of H_2O to CH_3OH loss is equal to the observed value of $k_f/k_r^{IR} = 19.8$. This implies $(CH_3OH)_2H^+$ absorbs an average of 3.9 infrared photons ($\bar{\nu} = 947\ cm^{-1}$) prior to bimolecular reaction with H_2O.

Selective excitation of reactants not only represents an interesting tool for experimental chemical dynamics, it offers the possibility of using measured changes in reaction rates as a spectroscopic probe. The use of infrared excitation to alter bimolecular reaction rates should provide a general technique for obtaining vibrational spectra of ions and transient molecules.

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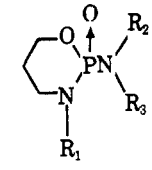
Resolution of Chiral Phosphamides

Sir:

The observation that the (−)-*S* isomer of cyclophosphamide {2-[bis(2-chloroethyl)amino]-2-oxo-1,3,2-oxazaphosphorinane, **1a**} is more effective against PC6 mouse tumors than the racemic mixture resulted in the development of a number of synthetic methods leading to the optically active forms of **1** and related compounds. Thus, the enantiomers of **1** were obtained by the separation of the diastereomers based on the additional optically active center introduced in the starting amino alcohol[2] or directly in **1**, using optically active naphthylphenylmethylsilyl chloride.[3] Following the resolution of isophosphamide[4] (**2**), an interesting synthesis of the enantiomers of triphosphamide (**3**) was recently published,[5] thus completing the picture. All of these methods except one[3] involve multistep



	R_1	R_2	R_3
1	H	$-CH_2CH_2Cl$	$-CH_2CH_2Cl$
2	$-CH_2CH_2Cl$	H	$-CH_2CH_2Cl$
3	$-CH_2CH_2Cl$	$-CH_2CH_2Cl$	$-CH_2CH_2Cl$

asymmetric synthetic processes and are not direct methods for resolution of **1–3.**

Possibly the simplest way to resolve **1** would involve separation of complexes formed with optically active H donors. Based on the observation that **1a** forms a stable crystalline monohydrate,[6] it was expected that crystalline complexes with other H-bonding agents (alcohols, phenols) would be formed. No crystalline complexes of the anhydrous **1** were, however, obtained under various conditions,[7] using (+)-ethyl lactate, (+)-phenylephrine, (+)-quinine, or the optically active 1-(dimethylamino)ethanol or its *N*-oxide, or with the more acidic 1-trichloromethylethanol and 2-(α-hydroxyethyl)-4-nitrophenol. It is interesting to note that neither the pure *S* nor the *R* forms of **1** form monohydrate,[8] only the racemic mixture.

Here we report the optical resolution of the chiral phosphamide of the type **1** via its diastereomers of *N*-acyloxyalkyl type, as outlined in Scheme I. Thus, cyclophosphamide, (±)-**1**, can be transformed to the alkylol derivative **4**, by dissolving anhydrous **1** in chloral. After reacting them at room temperature overnight, the chloral excess was evaporated. The oily product was purified by chromatography on silica gel ($CHCl_3$–acetone, 9:1) and recrystallized from cyclohexane to give **4** in 50% yield: mp 125–128 °C; ^1H NMR ($CDCl_3$) δ 7.5 (d, 1 H exchangeable in D_2O), 5.5 (m, 1 H), 4.3 (m, 2 H), 3.6 (m, 10 H), 2.1 (m, 2 H) ppm. The obtained racemic **4** was

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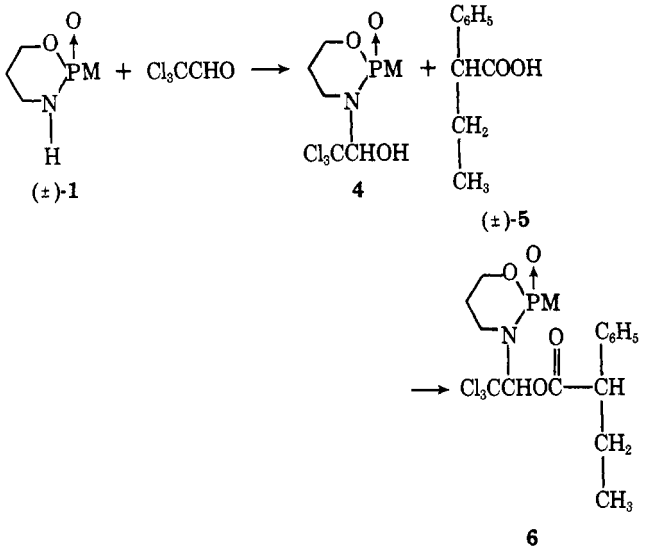
Scheme I



M = $-N(CH_2CH_2Cl)_2$

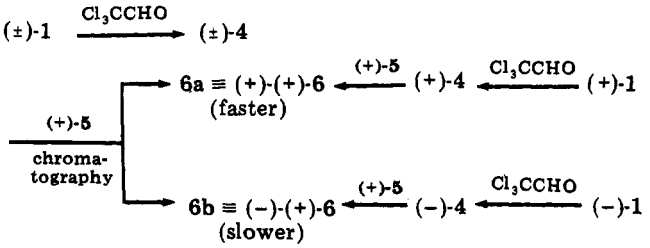
acylated with (±)-2-phenylbutyric acid (**5**) in pyridine using dicyclohexylcarbodiimide (DCCI) at room temperature. The oily product was chromatographed on silica gel ($CHCl_3$) and recrystallized from cyclohexane to yield in 35% the diastereomeric mixture of **6**: mp 77–79 °C; ^1H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 6.7 (m, 1 H), 3.5 (m, 13 H), 1.5 (m, 4 H), 0.9 (t, 3 H) ppm.

The alkylol derivative **4** was acylated under similar conditions with optically pure (+)-2-phenylbutyric acid, (+)-**5**. The white crystalline material obtained in 45% yield, mp 68–73 °C, had identical NMR and IR with those of **6**, but gave two spots on TLC (R_f 0.78 and 0.68, silica gel GF, $CHCl_3$–acetone 9:1, as eluant). Separation of the two products was achieved by column chromatography [silica gel GF, benzene–ethyl acetate (9:1, v/v)]. The first product was crystallized from petroleum ether to give **6a** (faster moving diastereomer): mp 122–123 °C; $[\alpha]^{24}_D$ −55.5° (*c* 1.03, CH_3OH); IR (KBr) 2930, 1750, 1250, 1090, 980, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 6.7 (d, 1 H), 3.6 (m, 13 H), 1.5 (m, 4 H), 0.9 (t, 3 H) ppm. The second product was crystallized from petroleum ether to give **6b** (slower moving diastereomer): mp 65–67 °C; $[\alpha]^{25}_D$ +17.4° (*c* 1.03, CH_3OH); IR and ^1H NMR identical with those of **6a**.

Since, besides the optically active carbon atom in the acid portion and the chiral phosphoramide, there is a third optically active center in the aldehyde portion, it was important to determine the exact nature of the diastereomers **6a** and **6b**, by starting with the enantiomers of **1**. Thus, (−)-**1**[9] was treated with chloral to give (−)-**4**[10] in 54% yield: mp 102–105 °C; IR (KBr) 3120, 1450, 1220, 1150, 1100, 920, 800 cm^{-1}; ^1H NMR identical with that of **4**. The alkylol (−)-**4** was coupled with (+)-**5**. The product was chromatographed on silica gel (benzene–ethyl acetate, 15:1) and crystallized from petroleum ether to give (−)-(+)-**6**: mp 68–70 °C; $[\alpha]^{25}_D$ +18.0° (*c* 1.06, CH_3OH); IR and ^1H NMR identical with those of **6**. Thus, **6b**, the slower moving diastereomer, can be identified as (−)-(+)-**6**. Similarly, (+)-**1** was reacted with chloral to give (+)-**4**, which upon coupling with (+)-**5** resulted in (+)-(+)-**6**: mp 122–128 °C; $[\alpha]^{23}_D$ −56.4° (*c* 2.06, CH_3OH); IR and ^1H NMR identical with those of **6**. Based on the optical rotation and other physical properties, the faster moving diastereomer **6a** can positively be identified as (+)-(+)-**6**. The above transformations are summarized in Scheme II.

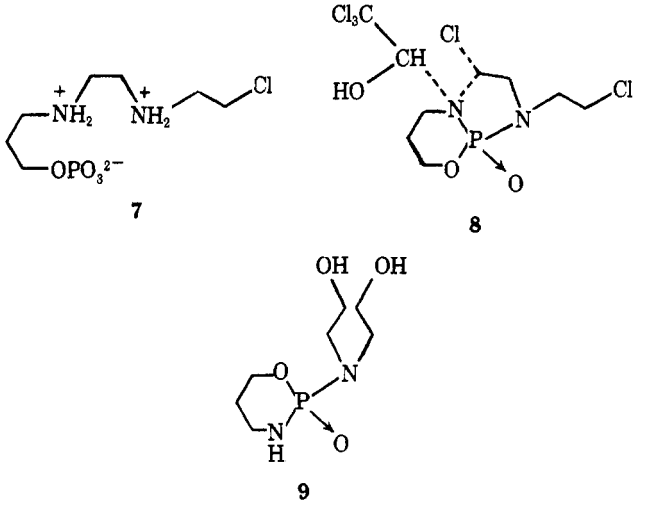
Although the configuration of the optically active carbon introduced from chloral is not known, it is clear that the procedure leads to resolution of the chiral phosphoramide. As

Scheme II



expected, the two diastereomers do not form in the same amount. When the (+)-acid was used, **6a**, corresponding to (+)-(*R*)-**1**, was obtained as the major and the more desired **6b**, containing the (−)-(*S*)-**1**, as the minor product. The situation should be different using (−)-**5** or other optically active acids.

The esters could be cleaved in methanolic HCl to the corresponding chloral adducts (+)-**4** and (−)-**4**. Acid-catalyzed cleavage of **4**, however, led to the known[11] hydrolysis product **7**, possibly formed via an intramolecular attack as indicated



by **8**. *N*-Alkylol derivatives containing aldehydes other than chloral are much less stable and easily revert to the original amides. The chloral adducts are also reversible in the case of stable phosphamides (or other amides), such as the compound **9**, closely related to **1** and useful in asymmetric synthesis of **1** and related compounds.[12] The *N*-acyloxyalkyl derivatives of **9** will also be obtained by direct coupling of a salt of **9** with an α-halo ester. In many other cases, the acyloxyalkyl derivatives of various amides can be obtained directly using α-halo esters.[13] Thus, optically active acyloxyalkyl esters should be useful for the resolution of a large number of optically active amides, otherwise obtained exclusively by asymmetric synthesis.

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Reactions of (Chlorocarbonyl)phenylketene. Formation of a New Class of Heterocyclic Zwitterion

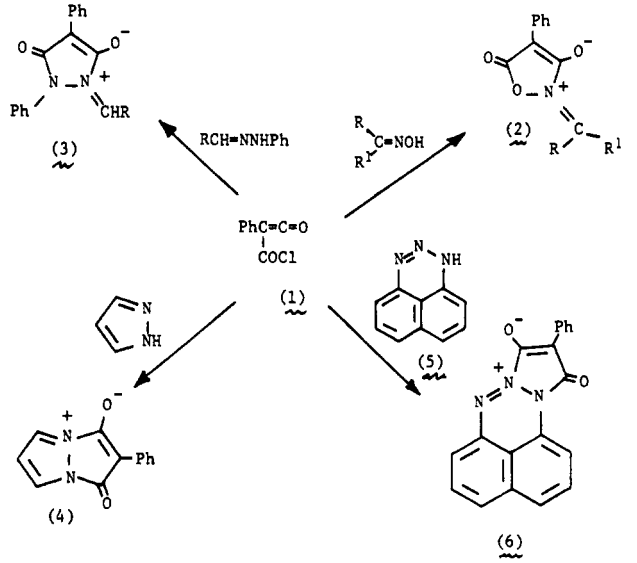
Sir:

(Chlorocarbonyl)phenylketene has been found[1] to be a very effective bielectrophile reacting with a variety of nucleophiles under mild conditions; e.g., with a monosubstituted thioamide, ring closure occurs to a heteroaromatic, 6π-electron 4*H*-1,3-thiazinium betaine.[2] We now report the formation of a new class of heterocyclic zwitterion obtained in the extremely facile reaction of a variety of substrates containing a monoprotonic 1,2-binucleophilic system with the ketene.

Arylaldoximes and ketoximes and (chlorocarbonyl)phenylketene (**1**) in anhydrous ether or THF gave a series of deeply colored products whose structures are represented by **2.** Thus, from (diphenylmethylene)hydroxylamine, *anhydro*-2-(diphenylmethylene)-3-hydroxy-5-oxo-4-phenylisoxazolium hydroxide (**2**, R = R^1 = Ph) was obtained as deep-red prisms [70%; mp 146–147 °C; ν_{CO} (KBr) 1795 (w), 1720 (s) cm^{-1}], and from 4-nitrobenzylidinehydroxylamine, **2** (R = 4-$NO_2C_6H_4$; R^1 = H) was obtained as deep purple needles [65%; mp 170 °C; ν_{CO} (KBr) 1790 (s), 1710 (s) cm^{-1}; M^+· 310 (6)]. A wide variety of arylaldoximes was thus converted into **2.** These products were identical with those obtained[3] previously from 4-phenyl-3,5-dihydroxyisoxazole and aldehydes.

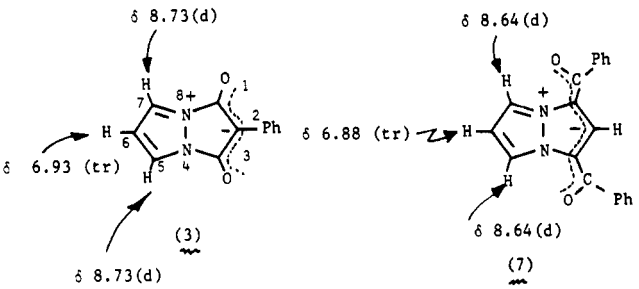
Representatives containing the pyrazole nucleus were as equally readily available by reaction of the ketene with arylaldehyde hydrazones. 1-(4-Dimethylaminobenzylidene)-2-phenylhydrazine gave *anhydro*-2-(4-dimethylaminophenylmethylene)-1,4-diphenyl-3-hydroxy-5-oxopyrazolium hydroxide [**3**, R = 4-$(CH_3)_2NC_6H_4$] as deep-maroon prisms [55%; mp 222–223 °C; ν_{CO} (KBr) 1650 (s), 1600 (s) cm^{-1}; M^+· 369 (69)], and 1-(4-methoxybenzylidene)-2-phenylhydrazine gave **3** (R = 4-$CH_3OC_6H_4$) as deep-purple prisms [74%; mp 188–190 °C; ν_{CO} (KBr) 1660 (s), 1580 (s) cm^{-1}; M^+· 370 (40)]. Both monocyclic ring systems **2** and **3** were relatively stable in the solid state but, on dissolution in a suitable solvent, underwent rapid hydrolysis to 3,5-dihydroxy-4-phenylisoxazole and 3,5-dihydroxy-1,4-diphenylpyrazole, respectively, consistent with the presence of the immonium salt moiety. In some cases the zwitterionic systems could be regenerated from these dihydroxy heterocycles and the appropriate aldehyde.

Several bi- and tricyclic representatives of this new type of zwitterion have also been prepared by incorporating the 1,2-binucleophilic system into a ring. Pyrazole gave *anhydro*-1-hydroxy-3-oxo-2-phenylpyrazolo[1,2-*a*]pyrazolium hydroxide (**4**) as violet prisms (77%) from methanol [mp 247–248 °C; ν_{CO} (KBr) 1680 (s), 1650 (vs), 1600 (m) cm^{-1}; M^+· 212



(100)] which was also prepared from 3,5-dihydroxy-4-phenylpyrazole and malonaldehyde diethyl acetal in the presence of a trace of H_2SO_4. A variety of methyl-, phenyl-, and methylthio-substituted pyrazoles and benzopyrazole derivatives gave the corresponding substituted derivatives of **4,** and analogous fused-ring systems were obtained from 1,2,4-triazole derivatives. Reaction of the triazine **5** with the ketene gave the tetracyclic system **6** as deep-violet prisms (93%) from benzene–petroleum ether: ν_{CO} (KBr) 1780 (m), 1680 (s) cm^{-1}. Other six-membered rings containing the "cyclic hydrazone" structural feature react in a similar fashion.

The spectral characteristics of the bicyclic system **3** are particularly informative. X-ray data[5] show the system to be planar and that it is best represented as a betaine comprising a pyrazolium cation and a delocalized β-diketone anion rather than having an 8π-electron-delocalized system. This structural representation is reinforced by the ^1H NMR data which are consistent with those reported for **7,** considered[6a] to be best represented as the betaine shown. The NMR data for the pyrazolium protons are also in good agreement with those reported[6b] for monocyclic pyrazolium cations. The ^{13}C NMR



spectrum (Me_2SO-d_6) of **3** with the C_2 chemical shift at 80.11 ppm and those of the C_1–C_3 carbonyl carbon atoms at 157.82 ppm is also consistent with the assigned structure. The length of the C_1–N_{7a} bond is slightly longer than normal and is suggestive of a significant contribution in the ground state from the open chain, ketene form such as has been proposed to account for similar long bonds in several other heterocyclic, zwitterionic systems.[7] The above compounds are representatives of a new class of unique, heterocyclic zwitterions containing stable 1,4 dipoles.[8] Heteroaromatic betaines containing the pyrimidine,[9] thiazine,[2] or selenazine ring systems have hitherto been the only ring systems prepared which contain 1,4 dipoles.[10] As these ring systems cannot be considered as ylides and because of the large number of conceptually available systems, we propose that they be called paraionic compounds,[11] providing a ready distinction between the already well-estab-

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