

- (9) Synthesized according to ref 2. All new compounds reported gave satisfactory C, H, and N elementary analysis.
 (10) The conformation of the newly introduced optically active center is not known; the (-)-4 notation refers to the chiral phosphoramidate only.
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 (12) Bodor, N.; Higuchi, T.; Sato, T.; Ueda, M.; Nakagawa, K., unpublished work.
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 (14) On leave of absence from Otsuka Pharmaceutical Co.

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

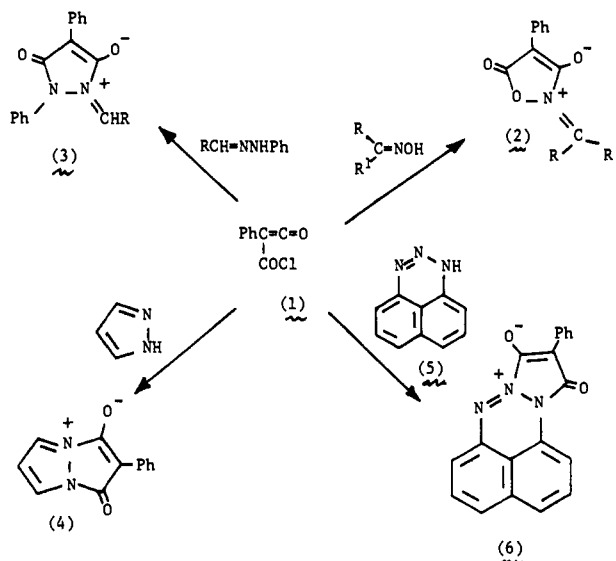
Sir:

(Chlorocarbonyl)phenylketene has been found¹ to be a very effective bielectrophile reacting with a variety of nucleophiles under mild conditions; e.g., with a monosubstituted thioamide under mild conditions; e.g., with a monosubstituted thioamide, ring closure occurs to a heteroaromatic, 6π -electron *4H*-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.

Aryldoximes 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' = Ph) was obtained as deep-red prisms [70%; mp 146-147 °C; ν_{CO} (KBr) 1795 (w), 1720 (s) cm^{-1}], and from 4-nitrobenzylidenehydroxylamine, 2 (R = 4-NO₂C₆H₄; R' = 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 obtained³ previously from 4-phenyl-3,5-dihydroxyisoxazole and aldehydes.

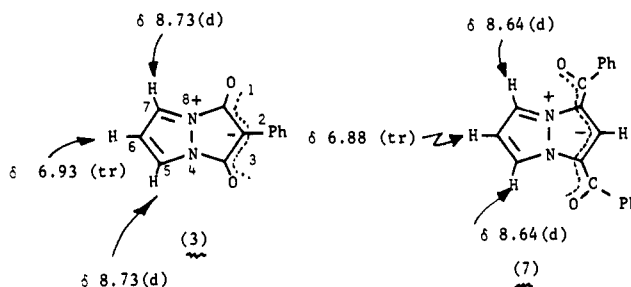
Representatives containing the pyrazole nucleus were as equally readily available by reaction of the ketene with arylaldehyde hydrazones. 1-(4-Dimethylaminobenzylidene)-2-phenylhydrazine gave *anhydro*-2-(4-dimethylaminophenylmethylene)-1,4-diphenyl-3-hydroxy-5-oxopyrazolium hydroxide [3, R = 4-(CH₃)₂NC₆H₄] 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-CH₃OC₆H₄) 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 H₂SO₄. 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 data⁵ 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 ¹³C NMR



spectrum (Me₂SO-*d*₆) of 3 with the C₂ chemical shift at 80.11 ppm and those of the C₁-C₃ carbonyl carbon atoms at 157.82 ppm is also consistent with the assigned structure. The length of the C₁-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-established

lished mesoionic compounds¹² and heteroaromatic betaines.^{2,9,10,13}

Work is currently underway in this laboratory defining the scope and limitations of these unique compounds, as well as studying their physical and chemical properties.

References and Notes

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- (4) Satisfactory analytical data were obtained for all compounds reported.
- (5) Determined by Professor Alan White, University of Western Australia. These data and those of related systems will be reported in full elsewhere. Bond lengths: C₁-C₂, 1.41; C₆-C₇, 1.38; C₇-N₈, 1.34; N₈-C₁₁, 1.49; N₄-N₈, 1.34; C₁-O, 1.22; C₂-phenyl, 1.47 Å.
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- (11) Derived from the Greek meaning "along side". This name was first suggested in a group discussion by Professor H. Herbrandson and we are indebted to him for his interest.
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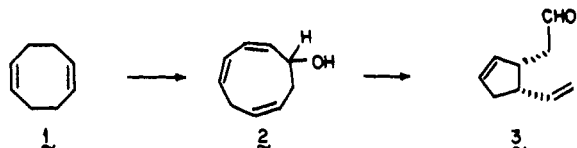
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A Stereocontrolled Synthetic Entry to the Primary Prostaglandins from Butadiene. Oxy Anionic Substituent Effects on [1,5]-Hydrogen Sigmatropy

Sir:

Many of the elegant schemes devised to gain access to the prostaglandins have capitalized on the availability of starting materials which contain a suitably functionalized five-membered ring.¹ Herein we describe a new direct approach to this challenging problem which (1) enjoys the economic advantage of being based on butadiene as raw material, (2) provides access to all of the primary prostaglandins and a number of analogues from a single precursor, and (3) allows for optical resolution at a pivotal early stage. The crux of the present strategy lies in efficient overriding by anionic [3,3]-carbon sigmatropy of the normal predilection of a polyunsaturated medium-sized ring for thermal [1,5]-hydrogen sigmatropy.

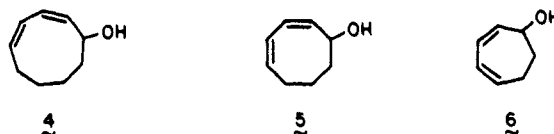
A product of butadiene cyclodimerization,² the commercially plentiful *cis*-2-1,5-cyclooctadiene (**1**) was efficiently transformed into *cis*-3-2,4,7-cyclononatrienol (**2**) by a previously described procedure.³ When solutions of **2** in benzene were heated at 160 °C for 3 h in sealed tubes, smooth conversion into a mixture of *cis*-2-3,7-cyclononadienone (80%) and aldehyde **3** (20%) was observed. The undesirable dominant formation of the dienone, which is in accord with kinetically favored [1,5]-hydrogen shift within **2**, was totally overcome



by alternate treatment with 1.2 equiv of oil-free potassium hydride in anhydrous tetrahydrofuran at room temperature.⁴ Under these conditions, quantitative conversion into **3**, homogeneous by TLC and VPC analysis, materialized. A noteworthy feature of this reaction is that it represents the first example where the process favored upon thermal activation does not continue to dominate under anionic conditions. Unanswered, however, is the question of whether [1,5]-hydrogen sigmatropy is affected by a substituent change from R = H to R = K. Since this reaction class had not previously been given attention, we have carried out quantitative kinetic studies on **2** and several additional prototypical dienols. *The present findings indicate that the general effect of oxy substitution on neighboring center chemistry remains substantial, although appreciably less so for [1,5]-H than for [3,3]-C sigma-tropy.*

The energetics of thermal [1,5]-H migration in neutral **2**, including the activation parameters (Table I), are seen to be slightly more elevated than those associated with comparable processes in unsaturated seven-⁵ and eight-membered rings.⁶ This somewhat heightened barrier to rearrangement is likely the end result of a less than ideal stereoelectronic alignment between the C-H bond and the p π components of the flanking diene moiety. Conversion into the lithium alkoxide did not appear to result in marked acceleration of either rearrangement. The situation for the oxy-Cope process improved when M = Na⁺; however, the behavior of the potassium alkoxide was truly spectacular (Table I). The rate enhancement for [3,3]-C shift proved to be very large (10¹⁰ at 25 °C), in agreement with precedent.⁴

The systems chosen for assessment of counterion-controlled [1,5]-H sigmatropy were the cyclic dienols **4**-**6**, prepared by photooxygenation of *cis*-2-1,4-cyclononadiene^{6c} and 1,4-cyclooctadiene,⁷ as well as diisobutylaluminum hydride reduction of 2,4-cycloheptadienone,⁸ respectively. In each of the three



examples, thermal activation proceeded smoothly to provide the corresponding β,γ -unsaturated ketone exclusively. First-order rate constants for the formation of 3-cyclononone,⁹ 3-cyclooctenone,⁹ and 3-cycloheptenone⁹ afforded linear Arrhenius plots and the activation parameters shown in Table II. From these rate data, it can be seen that the ease of [1,5]-H shift increases as the ring is decreased in size, as expected from the stereoelectronic considerations mentioned earlier.

When **4** was treated with 1.1 equiv of potassium hydride in dry tetrahydrofuran at room temperature, clean, high yield conversion into 3-cyclononone (post quench) occurred in a short time. The behavior of **5** was entirely analogous. An exception to this trend was found in the case of **6** which rearranged to mixtures of 3-cycloheptenone (major) and 3,5-cycloheptadienol (minor) in ratios which proved to be temperature dependent. Quantitative kinetic examination of these reactions at three temperatures confirmed that the potassium alkoxides were experiencing [1,5]-H migration at significantly enhanced rates (Table II). Important observations are the 10⁵-10⁶ rate accelerations common to all three systems, irrespective of their ring size, and the overcoming of substantially more negative ΔS^\ddagger values by appreciable decreases in ΔH^\ddagger (9-14 kcal/mol). In the presence of 5 equiv of 18-crown-6, a limiting ninefold additional rate acceleration was seen. For [3,3]-C migration, this factor is 180.⁴ Under these conditions, 6-O⁻K⁺ is converted *only* into 3,5-cycloheptadienol. This may arise from an enhanced predilection on the part of the increasingly "naked" alkoxide anion to experience intramolec-