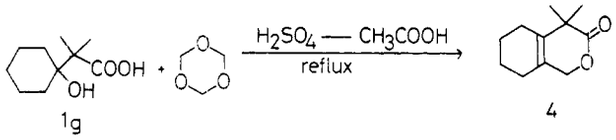
h, α,β-unsaturated δ-lactone **2b** was obtained in 88% yield; interestingly, at 25 °C for 8 h only spirolactone **3b** was obtained in 71% yield. The structures of compounds **2b** and **3b** were confirmed by spectral and elemental analyses. The same technique was used for the synthesis of **2b** and **3b** using several acidic materials. The results are listed in Table I. The reaction has also been extended to other 3-hydroxy acids. As shown in Table II, α,β-unsaturated δ-lactones **2** and spirolactones **3** are obtained in good yield. In the case of 2-(1′-hydroxycyclohexan-1′-yl)isobutyric acid (**1g**), β,γ-unsaturated δ-lactone **4** was obtained. These observations indicate that the reaction at lower temperature gives spirolactones **3**, but at higher temperature gives unsaturated δ-lactones **2**, respectively.



1g 4

Experimental Section

The reaction products were analyzed by GLC on a Shimadzu Model GC-3BF chromatograph using a 3 m × 3 mm column of 15% silicone DC 200 on 60–80 mesh Celite 545. NMR spectra were obtained using carbon tetrachloride as a solvent on a Hitachi Model R-24 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to a tetramethylsilane internal standard. IR spectra were obtained on a Jasco Model IR-G infrared spectrophotometer. UV spectra were obtained on a Hitachi Model EPS-3T spectrophotometer. Mass spectra were obtained on a Hitachi Model RMU-7M mass spectrometer.

Synthesis of Starting Materials. 3-Hydroxy acids **1** were prepared from carboxylic acids and cyclohexanone as reported previously.[6]

α,β-Unsaturated δ-Lactone 2b. A mixture of 2-(1′-hydroxycyclohexan-1′-yl)propionic acid (**1b**) (8.6 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), and 97% sulfuric acid (2.5 g) in 50 mL of acetic acid was refluxed for 0.5 h. To the reaction mixture, 200 mL of water was slowly added. It was then extracted with diisopropyl ether. The organic extract was washed with water and dried over sodium sulfate, the solvent was removed, and the residue was distilled in vacuo to give 7.3 g of **2b** (yield 88%): bp 124–125 °C (4 mm); IR (film) ν_{max} 1710 cm^{-1}; UV (CH_3OH) λ_{max} 232 nm (ϵ 10 000); NMR δ 1.1–1.7 [m, 6 H, $-(CH_2)_3-$], 1.8 (s, 3 H, CH_3C=C), 2.0 (m, 2 H, $-CH_2C$=C), 2.7 (m, 1 H, CHC=C), 3.2–4.4 (m, 2 H, $-COOCH_2-$); MS (*m/e*) M$^+$ 166.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.08; H, 8.50.

Spirolactone 3b. A mixture of 3-hydroxy acid **1b** (8.6 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), and 97% sulfuric acid (2.5 g) in 50 mL of acetic acid was stirred for 8 h at 25 °C. Workup in the usual fashion gave 6.5 g of **3b** (yield 71%): bp 117–119 °C (4 mm); IR (film) ν_{max} 1745 cm^{-1}; NMR δ 1.0 (d, J = 6 Hz, CH_3CH), 1.3–2.1 [m, 10 H, $-(CH_2)_5-$], 2.65 (q, J = 6 Hz, 1 H, CH_3CH), 5.3 (q, J = 6 Hz, $-OCH_2O-$); MS (m/e): M$^+$ = 184.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.21; H, 8.80.

β,γ-Unsaturated δ-Lactone 4. A mixture of 3-hydroxy acid **1g** (9.3 g, 50 mmol), 1,3,5-trioxane (2.7 g, 30 mmol), 97% sulfuric acid (2.5 g), and 50 mL of acetic acid was refluxed for 0.5 h. The mixture was treated in the usual way to give 7.5 g of β,γ-unsaturated δ-lactone **4** (yield 83%): bp 118–120 °C (5 mm); IR (film) ν_{max} 1735 cm^{-1}; NMR δ 1.2 [s, 6 H, $(CH_3)_2$], 1.65 (m, 4 H, $-CH_2CH_2-$), 1.9 (m, 4 H, $-CH_2C$=CCH_2-), 4.5 (s, 2 H, $-C$=CCH_2O-); MS (*m/e*) M$^+$ 180.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.19; H, 8.99.

When paraformaldehyde was used instead of 1,3,5-trioxane, 3.0 g of **4** was obtained (yield 33%).

Registry No.—**4**, 64884-59-9; 1,3,5-trioxane, 110-88-3; paraformaldehyde, 30525-89-4.

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Phosphorus Nuclear Magnetic Resonance Spectra of Complexes of Aluminum Chloride with Phosphorus(III) Chlorides: Structure of the Reaction Product from the Phenylphosphonous Dichloride Complex with Tetramethylethylene[1]

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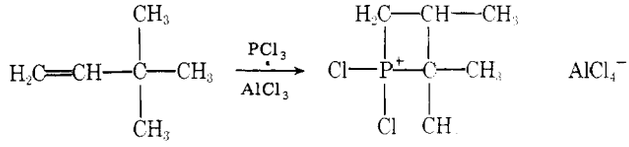
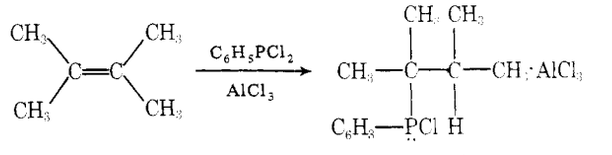
The use of aluminum chloride to activate phosphorus trichloride toward reaction with aromatic compounds dates back nearly one hundred years and has provided a standard method for the preparation of arylphosphonous dichlorides.[2] More recently, carbon–phosphorus bonds have been established by the reaction of olefins and mixtures of $AlCl_3$ and phosphorus(III) halides; the products are diverse and controlled by the structure of the olefin. The best known reaction of this type involves an olefin having a branched carbon attached to the double bond, which leads to the phosphetane system[3,4] via a skeletal rearrangement. A number of olefins have been used



in this process,[3,4] and other phosphorus halides that participate include $C_6H_5PCl_2$,[4] CH_3PCl_2,[4] and PBr_3.[5] Another course is followed with tetramethylethylene[6] and $C_6H_5PCl_2$; the product is noncyclic and alleged to have trivalent phosphorus in a complex with $AlCl_3$ (**1**). A reaction also occurs between



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ethylene and PCl_3[7] or PBr_3[8] in the presence of the corresponding aluminum halide; the products are more complex but depend in part on addition of a PX_2 fragment and halogen to the double bond. Phenylphosphonous dichloride gives the product $C_6H_5P(Cl)CH_2CH_2Cl$ in this reaction.[9] Extension of the reaction to dienes[10,11] has provided novel heterocyclic systems from participation of the second double bond.

In some of the reports on these reactions,[3-6,10,11] it has been assumed that the $AlCl_3$–PCl_3 interaction forms an ionic complex ($Cl_2\ddot{P}^+$ $AlCl_4^-$) and that the cation is the species attacking the olefin. Similar structures are also sometimes assumed to be formed from phosphonous dichlorides. While formation of such ionic complexes seems reasonable, there is actually no experimental evidence in the literature that points to their existence. Indeed, there is evidence to the contrary in the case of PCl_3; it is explicitly stated[12,13] that no complex, ionic or molecular, is formed in detectable amount from $AlCl_3$ and PCl_3, and recent reviews[2,14] of the reaction of such mixtures with aromatics are careful to point out that the attacking

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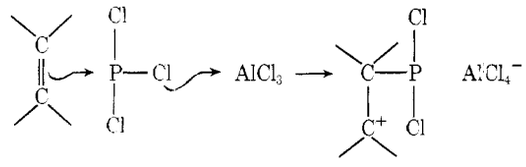
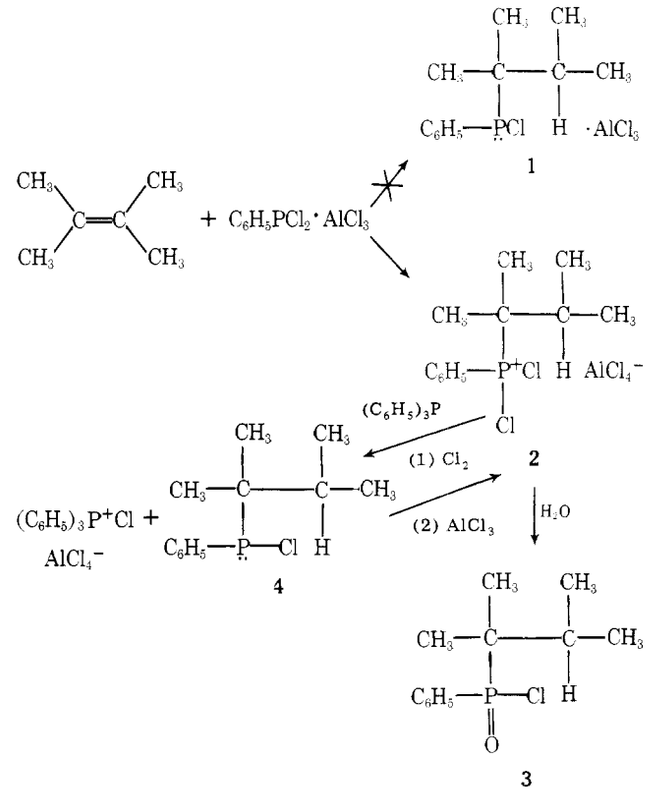
electrophilic species is of unknown structure. A new textbook[15] also refrains from showing the positive ion as the attacking species in reactions with aromatics or olefins. On the other hand, several papers have presented convincing evidence that amino-substituted phosphorus halides can be converted to cationic species with Lewis acids such as PCl_5,[16] $AlCl_3$,[17,18] and PF_5.[19] The nitrogen electrons are presumed to stabilize the positive charge in these products. The ^{31}P NMR chemical shifts are particularly indicative of the positive charge developing on phosphorus; very large downfield shifts occur relative to the neutral trivalent species (e.g.,[13] $(Me_2N)_2PCl$ δ +160, $(Me_2N)_2P^+$ δ +264; chemical shifts are referenced to 85% H_3PO_4, with positive values downfield). However, when nonionic complexes are formed from Lewis acids, chemical shift effects are small[18] and sometimes in the upfield direction, as with tertiary phosphines interacting with $AlCl_3$.[20]

We have now used ^{31}P NMR to examine the species formed between $AlCl_3$ and those phosphorus(III) halides so useful in the establishment of bonds to carbon. When $C_6H_5PCl_2$ or CH_3PCl_2 was mixed with 1 equiv of $AlCl_3$ in CH_2Cl_2 at 0 °C, clear solutions resulted. In both cases, the original ^{31}P NMR signal of the phosphonous dichloride vanished and was replaced by two strong signals at substantially higher field: CH_3PCl_2 δ +192.1, CH_3PCl_2·$AlCl_3$ δ +131.9 and +97.5; $C_6H_5PCl_2$ δ +161.2, $C_6H_5PCl_2$·$AlCl_3$ δ +112.1 and +84.3). A careful search for a phosphorus cation was made in the remote downfield region, but no measurable amount of such an ion was observed. It is clear that these *phosphonous dichlorides form molecular and not ionic complexes with $AlCl_3$*. The existence of two signals simply implies that complexes with varying ratios of reactants are formed, a phenomenon already observed for tertiary phosphine complexes.[20] This was confirmed by observing the effect of reactant ratio on the ^{31}P spectrum of $C_6H_5PCl_2$ complexes. With a 2:1 ratio of phosphonous dichloride to $AlCl_3$ only one ^{31}P signal was present (δ +110.9); the reverse ratio also gave only one signal but at much higher field (δ +69.1). Diphenylphosphinous chloride (δ +79.2 in CH_2Cl_2) was also included in our study and likewise formed two molecular complexes (δ +68.3 and +41.3) when mixed with 1 equiv of $AlCl_3$. On the other hand, PCl_3 failed to dissolve a noticeable amount of $AlCl_3$ in CH_2Cl_2, and the solution showed only the ^{31}P signal for PCl_3 (δ +219.2). This, of course, is consistent with the conclusions of others derived from different experimental approaches.[12,13]

These observations cast much doubt on the validity of the reaction mechanisms that employ divalent phosphorus cations as an electrophilic species. While the possibility cannot be excluded that a tiny, spectroscopically undetectable amount of such a species could serve as a relay to effect a reaction between the molecular complex or free phosphorus halide, it seems far more plausible to use as the electrophile that species which does exist in the medium. With this view, we assume that $AlCl_3$ serves to increase the electrophilic character of phosphonous dichlorides through complexation; for PCl_3, where no complex is formed, $AlCl_3$ may serve to assist in the removal of chloride as the C–P bond is forming.

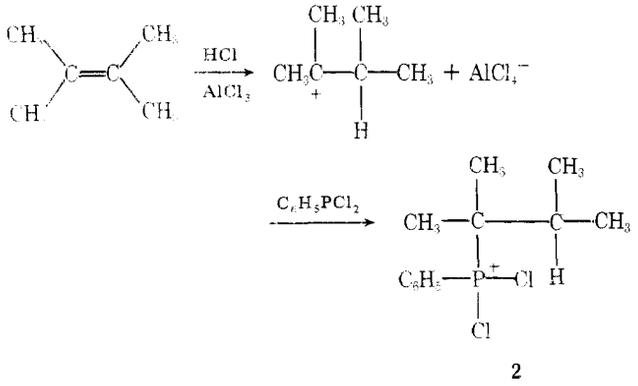


In examining the literature on $AlCl_3$-promoted reactions with olefins, we noticed one case that seemed explainable by a quite different mechanism; furthermore, the report showed a structure for a product that did not entirely satisfy the observed properties. The case is that of reaction of the $C_6H_5PCl_2$–$AlCl_3$ complex in CH_2Cl_2 with tetramethylethylene.[6] The product of this reaction has been assigned structure **1**. While the carbon fragment of the product seemed correctly assigned as depicted in **1**, with the hydrogen on the β-carbon introduced with the $AlCl_3$, it appeared more likely that the phosphorus functionality had the form $RC_6H_5P^+Cl_2$ $AlCl_4^-$ as in **2** rather than the form $RC_6H_5\ddot{P}Cl$·$AlCl_3$ of **1**. Thus, it was reported that a phosphinic chloride (**3**) was formed on water treatment of **1**; this would require that air oxidation accompany the process. However, the phosphinic chloride would be the expected product from partial hydrolysis of **2**. Also, the two methyls on the α-carbon were equivalent in their NMR spectra, a fact accommodated by **2** but not by **1**, where phosphorus is a chiral center. If **2** is indeed the correct structure, then the product obtained with $(C_6H_5)_3P$ would be **4**, as assigned,[6] but formed by the well-known halogen exchange reaction and not by decomplexation of **1** as proposed.



We therefore repeated this reaction and observed the same ^1H and ^{13}C NMR spectral properties as reported for the initial product.[6] We also obtained the ^{31}P NMR spectrum, which was not done in the original work, and observed a signal at δ +126.2. No other signals were present, implying complete conversion of the $C_6H_5PCl_2$–$AlCl_3$ complex to the product. This shift is consistent with ionic representation **2**, but does not prove its existence. This proof was then obtained by repeating the synthesis of phosphinous chloride **4** (^{31}P NMR δ +109.2) and treating it with 1 equiv each of chlorine and $AlCl_3$. The product, of necessity having structure **2**, was identical in NMR properties to the initial reaction product from the olefin.

With this revised structure the tentative mechanism[6] needs reconsideration since it cannot account for the formation of **2**. We see special mechanistic significance in the formation of the new carbon–hydrogen bond in **2**. The original work[6] showed conclusively that HCl or H_2O in the $AlCl_3$[21] was the source of this hydrogen, and we propose, as one possible mechanism, that protonation of tetramethylethylene is the initial step in the process leading to **2**. This would form a carbonium ion that could then alkylate the phosphonous dichloride. That a potent alkylating species is formed by in-



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reaction of the olefin and the $AlCl_3$ reagent is indicated by our observation that the olefin itself is alkylated, rapidly forming a polymer, when the phosphorus compound is omitted from the reaction medium. It is a known property of trivalent phosphorous compounds that they undergo alkylation by carbonium ions; the well-known reaction of Kinnear and Perren[22] employs this principle for C–P bond formation, using alkyl halides as the source of carbonium ions. Other mechanisms are not excluded, however, and one that is attractive involves a phosphirane intermediate, as proposed earlier.[6] If a phosphirane or any other type of intermediate is involved, it must have an extremely short lifetime; on conducting the reaction at −80 °C and examining the product by ^{31}P NMR after only 15 min, we found **2** to be the only species present.

The uniqueness of the behavior of tetramethylethylene to the $C_6H_5PCl_2$–$AlCl_3$ complex needs to be emphasized. No other example is known of a structure where there is net addition of hydrogen and a phosphorus function to the double bond. Tetramethylethylene represents the only tetrasubstituted olefin among the several compounds that have been exposed to the $AlCl_3$–phosphorus halide complexes, and the well-known higher order of nucleophilicity of such olefins may be responsible for its different behavior and postulated sensitivity to protonation. Its failure to form a phosphetane has also been attributed[6] to the high energy requirement for the 1,2-hydride shift (in essence forming a primary carbonium ion) that would have to occur as a prelude to cyclization. The specificity of the differing reaction paths is remarkable; we prepared the reaction mixture from the phosphetane-forming[4] olefin 3,3-dimethyl-1-butene and $C_6H_5PCl_2$ and found only the two ^{31}P NMR signals expected for the *cis*- and *trans*-1-chlorophosphetanium ions (δ +98.6 and +86.5). No trace of a product from hydrogen incorporation was present. If a common intermediate, such as a phosphirane, were involved in the olefin reactions, it would seem quite unlikely that two different pathways, each to the total exclusion of the other, should be followed. We believe this attests further to the unique behavior of tetramethylene and supports the concept of the first step being its protonation.

Experimental Section

General. All manipulations of trivalent phosphorus compounds were conducted under nitrogen in a glove bag. ^{31}P NMR spectra were obtained by the Fourier transform technique on a Bruker HFX-10 system at 36.43 MHz with proton decoupling; chemical shifts are referenced to 85% H_3PO_4, with downfield shifts positive.

Phenylphosphonous Dichloride–Aluminum Chloride Complex. To a slurry of 1.33 g (0.01 mol) of commercial anhydrous aluminum chloride in 7 mL of dried methylene chloride was added 1.79 g (0.01 mol) of $C_6H_5PCl_2$. The mixture was protected with nitrogen and stirred at room temperature for 3 h. A slightly green solution containing a trace of solid was obtained. The ^{31}P NMR spectrum of the solution had strong signals at δ +112.1 and +84.3.

When the complex was prepared from 2.66 g (0.02 mol) of $AlCl_3$ and 1.79 g (0.01 mol) of $C_6H_5PCl_2$, the ^{31}P spectrum had one signal at δ +69.1. A mixture of 1.33 g (0.01 mol) of $AlCl_3$ and 3.58 g (0.02 mol) of $C_6H_5PCl_2$ had one signal at δ +110.9.

Methylphosphonous Dichloride–Aluminum Chloride Complex. The complex was prepared as above from 1.17 g (0.01 mol) of CH_3PCl_2 and 1.33 g (0.01 mol) of $AlCl_3$ in 7 mL of CH_2Cl_2. The ^{31}P NMR spectrum consisted of two strong signals at δ +131.9 and +97.5.

Diphenylphosphinous Chloride–Aluminum Chloride Complex. The complex was prepared from 0.01 mol of each reagent in 20 mL of CH_2Cl_2. The ^{31}P NMR spectrum of the resulting solution had two strong signals, δ +68.3 and +41.3.

Reaction of the Phenylphosphonous Dichloride–$AlCl_3$ Complex with Tetramethylethylene. To the preformed 1:1 complex described previously was added 1.18 mL (0.01 mol) of tetramethylethylene. The heat of the reaction induced reflux. After being stirred for 1 h with no temperature control, the mixture was stripped of solvent and the residue taken up in $CDCl_3$ for NMR studies. The ^{31}P NMR spectrum consisted of one signal at δ +126 for **2**; the ^{13}C and ^1H NMR spectra matched those previously reported.[6] The same NMR results were obtained when complexes formed with the varying reactant ratios were used. The use of freshly sublimed $AlCl_3$ caused no change in the product.

Synthesis and Chlorination of Phenyl(1,1,2-trimethylpropyl)phosphinous Chloride (4). To the reaction mixture of 4.0 g (0.03 mol) of $AlCl_3$, 5.37 g (0.03 mol) of $C_6H_5PCl_2$ and 2.5 g (0.03 mol) of tetramethylethylene in 70 mL of CH_2Cl_2 was added 7.9 g (0.031 mol) of triphenylphosphine. The mixture was stirred at room temperature for 30 min and then diluted with 130 mL of pentane. On cooling, a yellow oil separated; the supernatant liquid was removed and stripped of solvent. Distillation gave 3.0 g (44%) of **4**, bp 89–93 °C (0.05 mm). Its ^1H NMR spectrum agreed with that already reported;[6] ^{31}P NMR (CH_2Cl_2) δ +109.2.

To a solution of 1.7 g (0.0075 mol) of **4** in 25 mL of CH_2Cl_2 at −78 °C was added 5.4 mL of a 0.028 M solution of chlorine (0.0075 mol) in CH_2Cl_2 over a 5-min period. The solution was allowed to warm to room temperature. The ^{31}P NMR spectrum consisted of a single signal at δ +124.7; addition of 0.0075 mol of $AlCl_3$ caused only a small downfield shift to a value (δ +126) agreeing with **2**. The ^1H NMR spectrum also matched that of **2**.

Reaction of 3,3-Dimethyl-1-butene with $C_6H_5PCl_2$·$AlCl_3$. To 15 mL of CH_2Cl_2 and 2.0 g (0.015 mol) of $AlCl_3$ at 0 °C was added 2.7 g (0.015 mol) of phenylphosphonous dichloride. The homogeneous mixture was treated slowly at 0 °C with a solution of 1.26 g (0.015 mol) of 3,3-dimethyl-1-butene in 5 mL of CH_2Cl_2. After about 1 h from the start of the addition, an aliquot was removed and found to have ^{31}P NMR signals at δ +98.6 and +86.5. To confirm that both signals were associated with a 1-chlorophosphetanium ion the mixture was reduced with 3.03 g (0.015 mol) of tri-*n*-butylphosphine at 0 °C. The product was poured into pentane; the pentane layer was collected and distilled (60–65 °C at 0.01 mm) to give 1.6 g (56%) of a mixture of *cis*- and *trans*-2,2,3-trimethyl-1-phenylphosphetane,[4] having δ +3.3 and +27.9.

Registry No.—**2**, 64872-75-9; **4**, 54193-51-0; $PhPCl_2$·$AlCl_3$ complex, 22646-95-3; $AlCl_3$, 7446-70-0; $PhPCl_2$, 644-97-3; $MePCl_2$·$AlCl_3$ complex, 52375-16-3; $MePCl_2$, 676-83-5; Ph_2PCl·$AlCl_3$ complex, 22646-94-2; Ph_2PCl, 1079-66-9; tetramethylethylene, 563-79-1; triphenylphosphine, 603-35-0; 3,3-dimethyl-1-butene, 558-37-2; *cis*-2,2,3-trimethyl-1-phenylphosphetane, 64884-28-2; *trans*-2,2,3-trimethyl-1-phenylphosphetane, 64884-29-3.

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Neurotoxins of *Karwinskia humboldtiana*. Atropisomerism and Diastereomeric Oxidation Products

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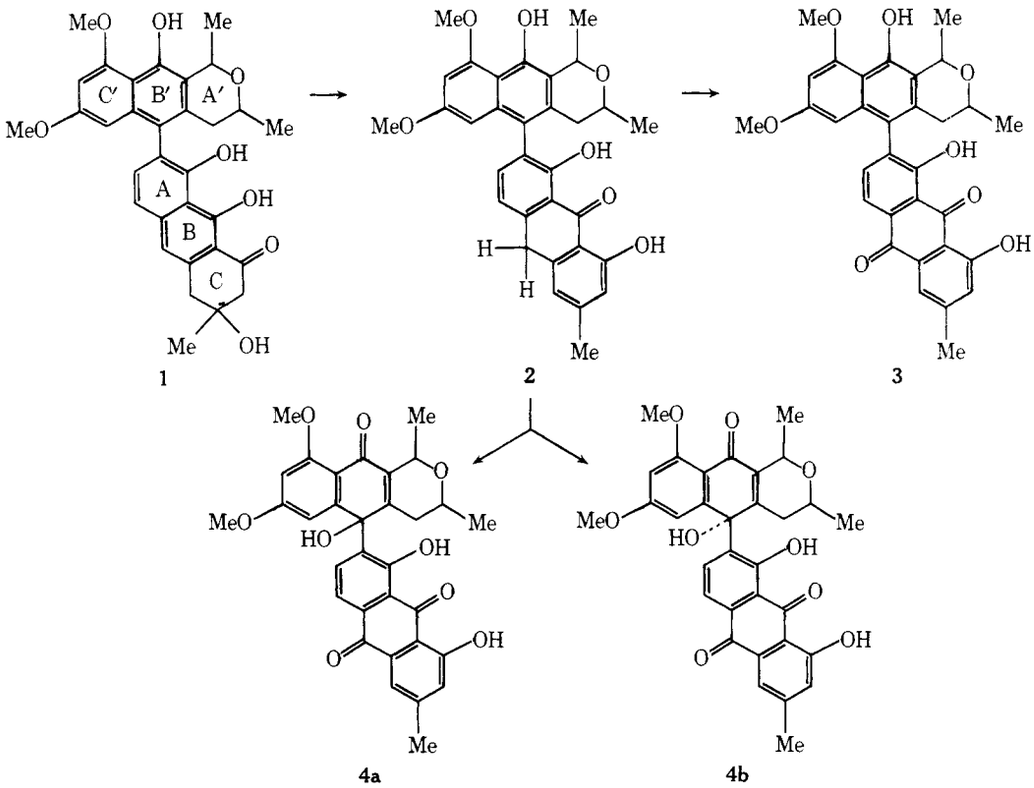
A previous report from this laboratory[2] described the isolation and structure elucidation of several polyphenolic components of the neurotoxic fruit of *Karwinskia humboldtiana*, Zucc. (Rhamnaceae). These polyphenolic neurotoxins include four C_{15} "dimers" which have since been isolated from the roots of the plant by Dominguez and students.[3] We now report evidence from proton nuclear magnetic resonance (^1H NMR) studies that, as isolated from seeds of *K. humboldtiana* following extensive fractionation,[2] one of the "dimeric" polyphenolic neurotoxins (1) exists as a mixture of two conformational isomers (i.e., atropicisomers) of the biphenyl type.[4-6] In addition, we report the formation of two oxidation products of **1** which are isomeric at a newly formed chiral center (C-5′, see structures **1**, **4a**, **4b**) and exhibit ^1H NMR spectra which are individually quite similar to the spectra of the respective conformational isomers of **1** (and its transformation products **2** and **3**).

The ^1H NMR spectrum of **1**, a major component of the neurotoxic extract of *K. humboldtiana*, exhibits a number of features which made initial interpretation difficult.[2] Thus, chromatographically homogeneous samples of **1** exhibited ^1H NMR spectra in which the number of hydrogen resonances exceeded the number of hydrogens (32) established by high resolution mass spectrometry. In these spectra, and in spectra of transformation products **2**, derived by dehydration of **1**,[2] and **3**, formed by oxidation of **2**[2] (see Figure 1A for the spectrum of **3**), several specific resonances failed to integrate for an integral number of hydrogens. It became clear that the nonintegral resonances occur in pairs, i.e., they arise from hydrogens which, owing to the existence of two conformational isomers, experience two different magnetic environments. For quinone **3**, this "doubling" of resonance signals was observed for the 1′-methyl, H-5, H-6, H-6′ and the 1- and 8-hydroxyl hydrogen resonances (see Figure 1A). The spectra of **1** and **2** are similar.[2]

When samples of **2** or **3** in $CDBr_3$ were heated, the equilibrium between the conformational isomers was altered. In each case, heating resulted in an increase in the intensity of signals owing to the minor conformational isomer. After heating solutions of **2** and **3** in $CDBr_3$ at 100 °C for ~1 h, the isomer concentrations were approximately equal in each case; heating beyond 1.5 h caused sample decomposition.

When a wet methanol solution of **2** was allowed to stand at room temperature in air for several months, two new products were formed. The products were shown by mass spectrometry to be isomers of empirical formula $C_{32}H_{28}O_9$. The spectral properties of the newly formed isomers were very similar to each other and showed many similarities to those of **3**. Thus, the ultraviolet–visable spectra of the isomers were essentially identical and assignable as an anthraquinone chromophore with a long wavelength band at 435 nm. The ^1H NMR spectrum of each (Figures 1B and 1C) showed typical anthraquinone 1,8-dihydroxy resonances at about δ 12, but the characteristic phenolic hydroxy signal associated with the 10′-



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