anhydride–sodium acetate) into the corresponding enol lactone m.p. 196–197° (C, 73.55; H, 8.45) which readily gave the pentacyclic enone XIII, m.p. 142–143° (150°) (C, 77.45; H, 9.20 infrared identical with XIII *ex* natural conessine) on treatment with ethereal methylmagnesium iodide. Formation of the N,N-dimethylenamine with methanolic dimethylamine and *p*-toluenesulfonic acid was followed by its reduction with sodium borohydride–diglyme in a mixture of aqueous ethanol, acetic acid and sodium acetate,[4] and the resulting 3β-dimethylamino compound was then deacetylated (calcium in liquid ammonia) and methylated by the usual formic acid-formaldehyde procedure to give *dl*-conessine (XIV), m.p. 127.5–128.5° (Kofler). The identity of the infrared spectrum ($CCl_4$) with that of an authentic sample of the natural material establishes the suggested stereochemical course of the various synthetic steps.[5]

(4) This procedure is adapted from that first described by W. S. Johnson, *et al.* (*Tetrahedron Letters*, No. 2, 72 (1961)).

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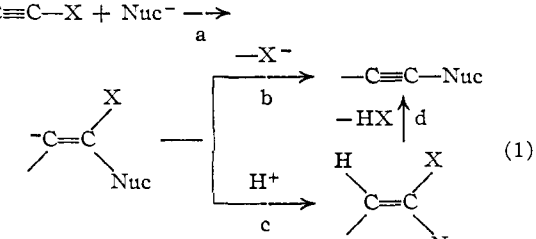
## NUCLEOPHILIC SUBSTITUTION AT AN ACETYLENIC CARBON

*Sir:*

Analogs of the ordinary displacement reaction are now known in the benzene[1] and ethylene series.[2] Based on several negative reports, it is generally considered that haloalkynes are inert to nucleophilic displacement.[3,4] Otherwise, the formation of —C≡C—Nuc in the presence of a proton donor often has been the over-all result of the now familiar addition elimination sequence, a–c–d in eq. 1[2,5]; indeed, the presence of a proton donor often renders the substitution mechanism uncertain.[6] Ott and Dittus do describe what appears to be close to an authentic displacement, *e.g.*, dichloroethyne with diethyl sodioethylmalonate in ether.[4,7]




(1)

We have observed that sodium thiolates react with haloalkynes in dimethylformamide (DMF) according to a–b in eq. 1. Thus we have obtained 1-phenyl-2-phenylthioethyne, 1-phenyl-2-pentachlorophenylthioethyne, and 1-phenyl-2-*p*-*tert*-butylphenylthioethyne. Of course, all of the products mentioned in this paper have given satisfactory elemental analyses. Of these, only the 1-phenyl-2-phenylthioethyne appears to be known; its properties and those of the derived sulfone check with those previously reported.[3b] Provided that the parent acetylene is available, the displacement path compares favorably with standard routes to thioethers.[8]

Typical of these preparations was that of 1-phenyl-2-*p*-toluenethioethyne. Sodium toluenethiolate was prepared by treatment of the thiol with sodium in refluxing toluene. The salt was filtered, washed with toluene and vacuum dried. A solution of the sodium toluenethiolate and phenylbromacetylene in DMF was stirred for 1 hr. and then worked up. Chromatography over alumina yielded white crystals, m.p. 45.5–46.5°, in 65% yield (*Anal.* Calcd. for $C_{15}H_{12}S$: C, 80.31; H, 5.39. Found: C, 80.46; H, 5.50). The sulfone was prepared by oxidation of the thioether with hydrogen peroxide to give a solid, m.p. 80–81° (*Anal.* Calcd. for $C_{15}H_{12}SO_2$: C, 70.29; H, 4.72. Found: C, 70.0; H, 4.78). The infrared triple bond absorption in the thioether and in the sulfone was at 4.72 μ and 4.74 μ, respectively, in agreement with data for similar compounds.

The proposed mechanism of eq. 1 is of some interest. Nucleophilic displacements at other unsaturated centers, *e.g.*, aromatic,[1] ethylenic,[2] and carbonyl[9] presumably have similar intermediates. Such carbanions have been suggested for base-catalyzed alcohol additions to alkynes,[10] and presumably occur in base-catalyzed deuteration of alkenes.[11]

Arens, *et al.*, use scheme 1 as a matter of course in the reactions of haloalkynes with nucleophiles in liquid ammonia.[6a] While this mechanism appears to be plausible and useful, it can only be considered as tentative.

The preceding examples taken together with our experience with other nucleophiles, *e.g.*, cyanide and amines, as well as with comparative kinetic data[12] suggest that any preconceived notions of the low nucleophilic reactivity at an acetylenic carbon must be revised. It is true that nucleophilic attack on haloalkynes, even under forcing conditions, has

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(7) Barring free radical initiation and catalysis, it seems reasonable to regard the couplings of haloalkynes with Grignard organo-copper or -lithium reagents as related processes involving polar aggregates: H. G. Viehe, *Ber.*, **92**, 3064 (1959); F. Bohlmann, P. Herbst, and H. Gleinig *ibid.*, **94**, 948 (1961).

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(9) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

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(11) S. I. Miller and W. G. Lee, *ibid.*, **81**, 6313 (1959).

(12) A. K. Kuriakose and S. I. Miller, unpublished results.

often failed[3]; on the other hand there appear to be favorable nucleophiles and solvents which facilitate the steps a-b of eq. 1. For example, $C_6H_5C{\equiv}CP(C_6H_5)_3{}^+Br^-$ and $C_6H_5C{\equiv}CP(C_4H_9)_3{}^+Br^-$ have been prepared from reactions in ether at room temperature. We are investigating the scope and rationale of these displacements involving nucleophiles containing sulfur, nitrogen, phosphorus, oxygen, *etc.*, in detail.

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## NEUTRON ACTIVATION AS A METHOD FOR LABELLING THE PHOSPHORUS OF NUCLEOTIDES[1]

*Sir:*

Ribonucleotides and deoxyribonucleotides labelled with phosphorus-32 have been of great value in exploring the biochemistry of nucleic acids. The preparation of such compounds tends to be complex, however, involving as it does either biological methods or multi-step synthetic procedures with chromatographic purification of the final product.[2] These problems are particularly unfortunate, since the half-life of phosphorus-32 is comparatively short (14.3 days).

It was found recently that neutron activation could be used as a method for the preparation,[3] from "cold" selenium-containing organic compounds, of the corresponding substances labeled with selenium-75; under these conditions only negligible decomposition occurred. It was of interest, therefore, to determine whether neutron activation could be applied to the phosphorus of nucleotides.

Samples (100 to 200 mg.) of 5′-adenosine monophosphate (AMP), 5′ - adenosine diphosphate (ADP), 5′-adenosine triphosphate (ATP), 3′-adenosine monophosphate (3′-AMP), and 5′-deoxyadenosine monophosphate (dAMP) were irradiated in the water-cooled compartment of a graphite reactor at a neutron flux of $6.5 \times 10^{11}$ neutrons/cm.$^2$/sec. for 62 hours. After discharge, the samples were permitted to stand for 150 hours to permit decay of sodium-24 in those samples (ADP, ATP) that had been submitted as sodium salts. Gamma spectrometry showed traces of arsenic-76 and antimony-122 in dAMP, traces of antimony-122 in 3′-AMP, and traces of residual sodium-24 in ADP and ATP. All other radioactivity was attributable to phosphorus-32.

Seventeen days after discharge from the reactor, the radioactivity of the samples was determined using a low background automatic counter (Nuclear–Chicago) with a counting efficiency of 45%. Aliquots of sample solutions were plated on stainless steel planchettes. Recovery of samples after activation was quantitative; no purification was carried out prior to counting.

These results were obtained:

| Compound | Counts/μmole/min. |
|---|---|
| AMP | $2.4 \times 10^5$ |
| ADP | $4.9 \times 10^5$ |
| ATP | $8.0 \times 10^5$ |
| 3′-AMP | $2.0 \times 10^5$ |
| dAMP | $2.2 \times 10^5$ |

Chromatography of the activated compounds (isobutyric acid:concd. ammonium hydroxide: water; 66:1:33) yielded well-defined spots with $R_f$ values identical with those of control material. Neutron activation did not reduce the ability of the ATP sample (Pabst Laboratories, lot no. 131A) to induce luminescence in the luciferin–luciferase assay which specifically requires the triphosphate.[4] This assay was carried out in quadruplicate.

Use of a strip counter showed only negligible radioactivity outside the spots. On the basis of these findings, neutron activation appears to be a useful tool for the labelling of the phosphorus of nucleotides and presumably of other phosphorus-containing compounds.

(1) This work was supported, in part (H.G.M.), by grants from the National Science Foundation (G19329) and the U. S. Public Health Service (CY-3937).

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## THE QUESTION OF INTIMATE ION PAIRS[1]

*Sir:*

Ion pairs (I) are intermediates in substitution reactions of triphenylmethyl (trityl) or benzhydryl compounds with hydroxylic reagents (solvolysis, hydrolysis, alcoholysis or acetolysis) or salts.[3]

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{I}{R^+X^-} \xrightarrow[\text{or } M^+Z^-]{HOY} \underset{\text{or RZ}}{ROY}$$

(multistep)

Since certain rearrangement or racemization reactions of these compounds proceed even faster than substitution and also show a very large (but not identical) dependence of rate on solvent,[4] these

(1) Supported in part by the Atomic Energy Commission. We are grateful to Dr. W. v. E. Doering for information[2] in 1959 on trityl benzoate-*carbonyl*-$O^{18}$.

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