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AN INVESTIGATION OF ALTERNATE SYNTHESIS FOR 2,2'-BIS(PHENYLETHYNYL)-5,5'-DIAMINOBENZIDINE

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Polymers Branch
Nonmetallic Materials Branch

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Several routes were investigated to develop an improved lower cost synthesis of the cited tetramine; a critical monomer used in forming the polyphenylquinoxaline polymer system with 2,2'-bis(phenylethynyl) moieties for intramolecular cyclization to the fused dibenzoanthracene structure. An immediate precursor to the tetramine 4-bromo-5-phenylethynyl-*o*-phenylenediamine was prepared in 43% overall crude yield from *o*-nitroamide. Activated coupling through the aryl bromide using the tris-(triphenylphosphine) Ni(0) species was unsuccessful. Substrate chelation of the Ni(0) via the o-diamine functionality was suggested as an inhibiting mechanism.

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18. (Continued) phenylethynylation
Chelation
acetamide
methanesulfonamide
p-toluene sulfonamide

FOREWORD

This research was conducted by the Polymer Branch, Nonmetallic Materials Division. This work was initiated under Project No. 2419, "Nonmetallic and Composite Materials," Task No. 241904, Work Unit Directive 24190415, "Structural Resins." It was administered under the direction of the Materials Laboratory, Air Force Wright Aeronautical Laboratories, Wright-Patterson Air Force Base, Ohio, with Dr. F. E. Arnold as the AFWAL/ML Work Unit Scientist. This report describes work conducted from September 1979 to September 1982.

The work described in this report was conducted by 1st Lt Patricia M. Lindley, Captain Alan A. Shaffer, and Dr. F. L. Hedberg. The manuscript was released by the authors in March 1983, for publication as a Technical Report.

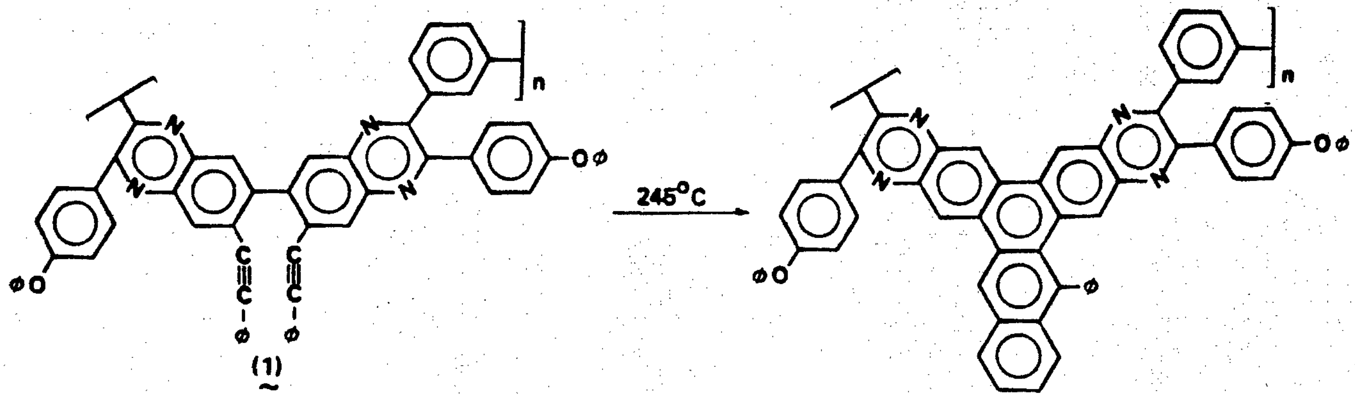
TABLE OF CONTENTS

TABLE OF CONTENTS (Concluded)

SECTION I

INTRODUCTION

One of the most significant breakthroughs in recent high temperature polymer technology was the demonstration of intramolecular cyclization (IMC) of the 2,2'-bis(phenylethynl) moiety within a polyphenylquinoxaline system.



(1)

Tg = 215°C

(2)

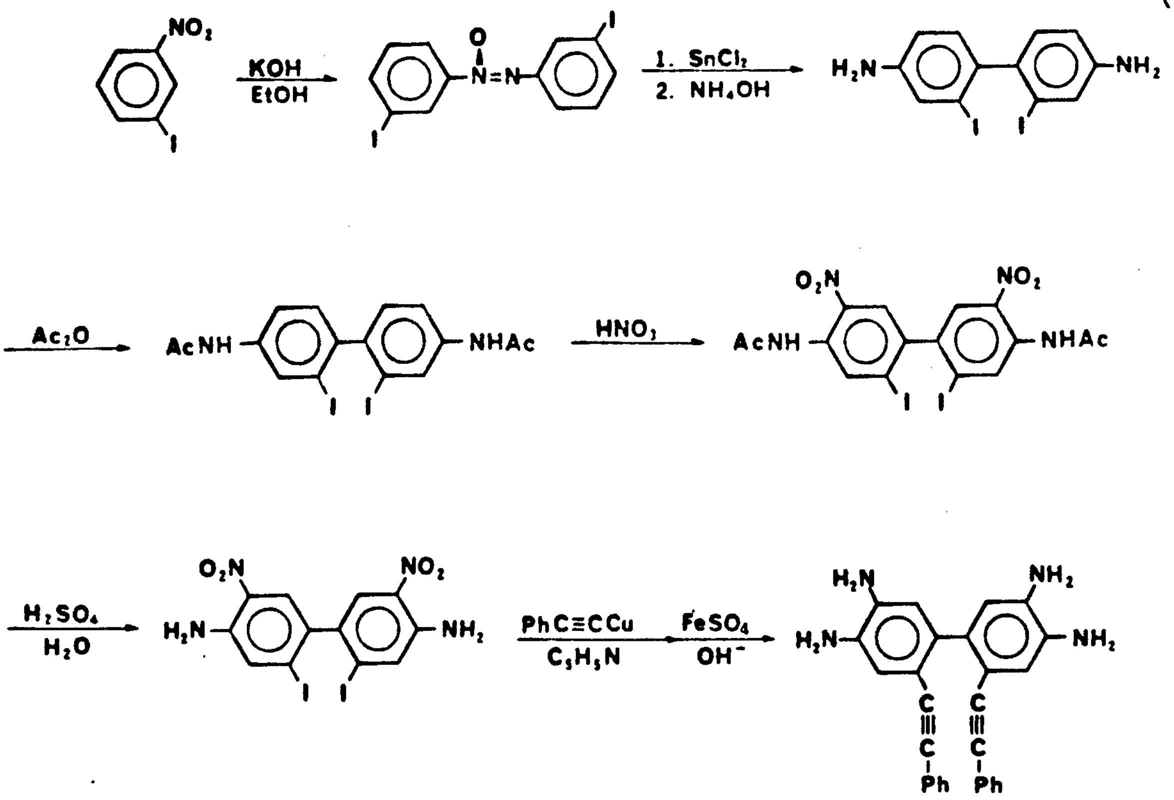
Tg = 365°C

Conversion to the fused aromatic dibenzoanthracene by heating at 246°C provided an increase in the polymer glass transition of about 150°C (Reference 1). "Cure" treatment of the polymer thus generated a modified substance with an end use application temperature capability greatly exceeding cure temperature. This development has crucial value to Air Force requirements for new lightweight high-temperature resistant composites.

Numerous model compounds have been prepared to investigate alternative intramolecular cyclizations that would yield as impressive an advancement in the glass transition temperature (T_g) (Reference 2). Unfortunately, no other systems to date have provided as clean or high yield a conversion or demonstrated a T_g advancement to warrant synthesis within a polymer. Also few other potential IMC systems are as readily incorporated into a polymer backbone as the 2,2'-bis-phenylethynyl moiety.

A major drawback of the polyphenylquinoxaline IMC system, particularly with respect to possible future scale-up and advanced development evaluation, is the seven step synthesis of the tetramine monomer, 2,2'-bis(phenylethynyl)-5,5'-diaminobenzidine (1). Isomer separation procedures proved tedious and were difficult to carry out on larger scales (25g) resulting in low single step yields; overall yield of the final product was only 8-10% (Reference 1).

(1)



I

In contrast, the bis-benzil monomer, m-bis(p-phenoxyphenyl glyoxaloyl) benzene (Reference 3) can be easily prepared in two steps from accessible starting materials. Treatment of the diacyl chloride of m-phenylene diacetic acid and diphenyl ether with aluminum chloride gave the diphenylaryl intermediate which was then converted to the bis-benzil by oxidation with selenium dioxide (Reference 4).

The development of a simpler synthesis of the tetramine monomer using low cost starting materials and fewer steps would enhance considerably the potential large-scale application of the IMC quinoxaline polymer in composite fabrication.

Two major synthetic approaches were used to deal with this problem. The first of these used di-halo, diamino compounds in a biaryl coupling reaction. The second approach involved a benzidine rearrangement with nitroanilines.

The coupling approach required preparation of symmetrical ortho diamine derivatives with para halogen substitution. Selective biaryl coupling through one aryl halide site would then give the tetramine analogue with proper 2,2'-dihalide functionality for subsequent phenylethynylation. 3,3'-Diaminobenzidine (DAB) was also used as a starting material in the event of its future commercialization, and to prepare reference 2,2'-diahalobiphenyl compounds for the coupling reactions.

Phenylethynylation was carried out on the 2,2'-diiodobiphenyl in the original IMC tetramine synthesis. The same general synthetic strategy was employed here, but steric and electronic factors would be expected to be more pronounced in the biphenyl structure than in the mono phenyl system. Work was thus also carried out on mono phenylethynylation of the dihalo-o-amides prior to biaryl coupling. The major synthetic difficulty here was limiting phenylethynylation to one Ar-X site, particularly when both halogens were the same.

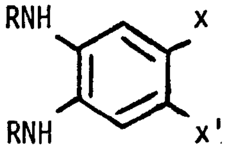
This research effort may be categorized into four reaction types: halogenation of the amine derivatives, coupling to diaryl, phenylthynylation, and regeneration of amine from amide derivatives. This report will discuss the synthetic effort using the above categories in order.

In addition, the report will deal with the second synthetic strategy, that involving the benzidine rearrangement reaction. This approach would somewhat resemble the state-of-the-art method; however, the presence of four nitrogen groups prior to rearrangement would eliminate the low yield nitration and reduction steps found in the current process. Discussion of this approach will follow the description of the biaryl coupling effort.

SECTION II

RESULTS AND DISCUSSION

A. PREPARATION OF 4,5-DIHALO DERIVATIVES OF o-PHENYLENEDIAMINE



IIa. $R=CH_3C(O)-$, $x=x'=H$

IIb. $R=CH_3C(O)-$, $x=x'=Br$

IIc. $R=CH_3C(O)-$, $x=H$, $x'=Br$

IId. $R=CH_3C(O)-$, $x=x'=I$

IIe. $R=CH_3C(O)-$, $x=H$, $x'=Cl$

IIf. $R=CH_3C(O)-$, $x=H$, $x'=I$

IIg. $R=CH_3C(O)-$, $x=Br$, $x'=I$

IIh. $R=CH_3C(O)-$, $x=Br$, $x'=C_6H_5C\equiv C-$

IIIa. $R=CH_3S(O)_2-$, $x=x'=H$

IIIb. $R=CH_3S(O)_2-$, $x=x'=Br$

IIIc. $R=CH_3S(O)_2-$, $x=H$, $x'=Br$

IIId. $R=CH_3S(O)_2-$, $x=x'=I$

IIIe. $R=CH_3S(O)_2-$, $x=H$, $x'=Cl$

IVa. R=*p*-$CH_3C_6H_5S(O)_2$-, x=x'=H

IVb. R=*p*-$CH_3C_6H_5S(O)_2$-, x=x'=Br

IVc. R=*p*-$CH_3C_6H_5S(O)_2$-, x=H, x'=Br

IVd. R=*p*-$CH_3C_6H_5S(O)_2$-, x=x'=I

IVe. R=*p*-$CH_3C_6H_5S(O)_2$-, x=H, x'=Cl

Xa. R=H, x=x'=Br

Xb. R=H, x=Br, x'=ØC≡C-

Xc. R=H, x=x'=ØC≡C-

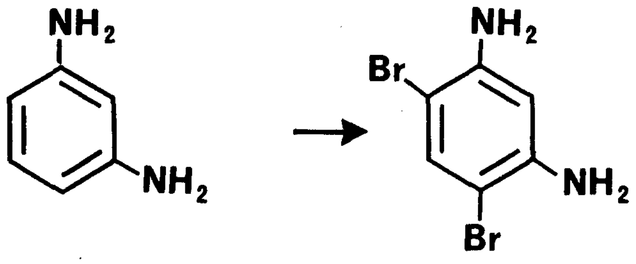
Xd. R=H, x=Br, x'=I

o-Phenylenediamine was the primary starting compound in the synthetic approaches because of its accessibility and low cost. Derivatization to the bisacetamide (IIa), bismethanesulfonamide (IIIa), and the bis-*p*-toluene sulfonamide (IVa) was accomplished with standard methodology.

Attempts to brominate compound IIa directly after acetylation caused precipitation of the substrate at the monobromo stage. Bromination of the compounds IIIa and IVa in acetic acid solution also gave only the mono brominated products. It was found that, by using N,N-dimethylacetamide (DMAC) as a co-solvent with acetic acid, dibromination with iron catalysis could be achieved clearly with compounds IIIa and IVa, but only in low yield with compound IIa. Overall yields from o-phenylenediamine for compounds IIIb, IVb, and IIb were 57%, 85%, and 15%, respectively. The strong *para* directing influence of the sulfonamide moieties in nuclear halogenation was verified by proton NMR spectroscopy, indicating equivalence of aromatic protons. (A europium shift reagent was used in the case of compound IVb.) As a result, compounds IIIb and IVb possessed the 1,2,4,5-substitution pattern critical for subsequent coupling to the 2,2'-dihalobiphenyl structure.

It has recently been reported that N,N-dimethyl-3-(trifluoromethyl) amiline was brominated in the <u>para</u> position in high yield with 2,4,4,6-tetrabromo-2,5-cyclohexadiene-1-one. (Reference 5).

This selective brominating agent was prepared by treating 2,4,6-tribromophenol with bromine in an acetic acid/sodium acetate mixture at ambient temperature. Although successfully applied to m-phenylenediamine to give the para dibromo product, is was not suitable for the ortho diamine analogue, generating tarry product.



Attempts were made to form the tetraiodo analogue from 3,4,6-triiodophenol for use as an iodinating agent for o-phenylenediamine and diaminobenzidine substrates. However, the dienone product could not be obtained presumably due to the steric crowding inherent in the product structure.

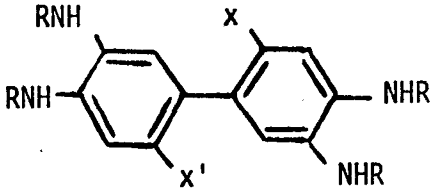
Numerous other attempts were made to iodinate the diamine derivatives IIa, IIIa and IVa or the o-phenylenediamine directly. Attempted iodination of the derivatives to IId, IIId, or IVd with elemental iodine in the presence of oxidizing agents such iodic acid, hydrogen peroxide-mercuric acetate, and silver acetate (employed to regenerate iodine from hydroiodic acid formed in reaction) only yielded trace or no iodinated product. Attempts to iodinate directly generally led to decomposition.

Iodinations were also attempted with iodine monochloride. Anomalous results were obtained in reactions of this reagent in acetic acid solution with compounds IIa, IIIa, and IVa. In all three cases, nuclear chlorination occurred preferentially to give the monochlorinated products IIe, IIIe, and IVe in moderate to near quantitative yields. Reaction at ambient temperature in dimethylacetamide also predominately gave chlorinated product. These products were confirmed by mass spectrometry and elemental analysis. Reaction of the compound IIa at 90°C overnight gave a small amount of iodinated product, but again the monochlorinated product was predominant. The full results of this work have been published separately (Reference 45).

In contrast, 2-nitroaniline proved of much greater utility as a substrate for iodination. Treatment with iodine monochloride in acetic acid gave 4-iodo-2-nitroaniline. Reduction with iron and hydrochloric acid (Reference 6) gave 2-amino-4-iodoaniline in 89% overall yield. Acetylation of 2-amino-4-iodoaniline gave compound IIf in near quantitative yield. Bromination with iron catalysis again using the acetic acid/DMAC co-solvent system gave compound IIg in high yield. 2-Nitroaniline was thus used exclusively as starting material when iodination appeared unsuitable as a starting material for carrying out straight forward iodinations, particularly in scale-up quantities.

Because of the low synthetic utility of biaryl coupling through aryl chloride sites, chlorination methods were not intentionally pursued.

B. PREPARATION OF 2,2'-DIHALO DERIVATIVES OF 3,3'-DIAMINOBENZIDINE



Va. R=p-$CH_3C_6H_5S(O)_2$-, x=x'=H

Vb. R=p-$CH_3C_6H_5S(O)_2$-, x=x'=Br

Vc. R=p-$CH_3C_6H_5S(O)_2$-, x=x'=I

VIa. R=$CH_3S(O)_2$-, x=x'=H

VIb. R=$CH_3S(O)_2$-, x=x'=Br

VIc. R=$CH_3S(O)_2$-, x=x'=I

VId. R=$CH_3S(O)_2$-, x=Br, x'=$C_6H_5C\equiv C$-

VIe. R=$CH_3S(O)_2$-, x=x'=C_6H_5C C-

VIIa. R=$CH_3C(O)$-, x=x'=H

VIIb. R=$CH_3C(O)$-, x=x'=Br

VIIc. R=$CH_3C(O)$-, x=x'=C_6H_5C C-

IX. R=H, x=x'=Br

3,3'-Diaminobenzidine (DAB) was, in like manner to o-phenylene-diamine, converted to the tetratosyl (Va), tetramesyl (VIa), and tetraacetamide (VIIa) derivatives. Bromination using the acetic acid/DMAC co-solvent system with iron catalysis gave the dibromo tetrasulfonamide products Vb and VIb in good yields. The desired specific 2,2'-bromination pattern was verified by C^{13} NMR, which displayed a singlet aryl C-Br peak indicating equivalence. This again was consistent with the strong para directing influence of the sulfonamide moieties. Compound VIIb was essentially insoluble in most organic solvents. High dilutions were required even with polar solvents such as N-methyl-2-pyrrolidinone, dimethyl sulfoxide, and hexafluoroisopropanol in conducting attempted brominations. No evidence of successful reaction was obtained.

Iodinations were also attempted on the compounds Va and VIa using a variety of conditions. Reactions with iodine in the presence of $CuCl_2/SnI_4$, $FeI_2\ 4H_2O/CuCl_2$, or Ag_2SO_4/H_2SO_4 to form compounds Vc and VIc were unsuccessful. Direct iodination of DAB was also attempted using I_2/Ag_2SO_4 in sulfonic acid solution, I_2/persulfate (Reference 8) and I_2/morpholine (Reference 9) without success. Reaction with iodine monochloride using acetic acid/DMAC gave only a low degree of iodination.

Attempts to prepare compounds Vc and VIc via metallation of the dibromo substrate with n-butyllithium followed by reaction with molecular iodine also failed (Reference 10), although somewhat higher levels of iodination were achieved than with other approaches. Presumably, the acidic sulfonamide proton interfered with the desired nuclear lithiation via acid-base interchange with the n-butyllithium.

C. BIARYL COUPLING OF 4,5-DIHALO DERIVATIVES OF o-PHENYLENEDIAMINE

The preparation of compounds IIIb and IVb with 1,2,4,5 substitution pattern provided proper configuration for biaryl coupling through one of the equivalent aryl bromide sites. Selective mono coupling would give compounds Vb and VIb. The synthetic utility of the sulfonamide moiety was perceived as three-fold: 1) easy to prepare and purify, 2) strongly para directing in halogenations via electrophilic aromatic substitution and 3) stable to biaryl coupling reaction conditions. The first two of these expectations were borne out; however, the third proved troublesome.

1. Via n-Butyllithium

Coupling was first attempted with n-butyllithium, based on the preparation of 2,2'-dibromobiphenyl in 50% yield from o-dibromobenzene (Reference 11). Using the stoichiometry of the literature preparation or an equimolar ratio in reaction with compounds IIb and IVb only regenerated starting compound, although a reaction exotherm was evident.

A probable explanation for these results involves the acidity of the tosylamide proton, which may cause an acid-base interchange with the n-butyllithium generating the di-lithiated salt. An aqueous work-up of the salt would regenerate starting material. When an excess of n-butyllithium was used in an effort to compensate for the acid-base interaction described above, dehalogenation occurred. The acidity of the amide proton clearly interfered prohibitively with the desired coupling reaction and this approach was thus abandoned.

2. Via Ullmann Coupling Methods

Reactions using n-butyllithium employed mild thermal conditions (-65°C up to ambient). The known stability of the sulfonamide moiety permitted synthetic attempts using forcing thermal conditions (90°C) with high-boiling aprotic solvents often required for aromatic nucleophilic substitutions. The familiar Ullman biaryl synthesis was examined in this regard (Reference 12). Earlier work had shown good biaryl coupling yield using the Ullmann reaction with 2-iodo-4-nitroacetamide (Reference 13), contrary to the general literature notion of the amide moiety inhibiting the reaction (Reference 14).

Attempted coupling of compound IIIb using N,N-dimethyl-formamide (DMF) as solvent at 136°C under nitrogen atmosphere overnight with a 9:1 stoichiometric excess of copper bronze to substrate (as used in the above reaction) led to decomposition of the starting material with generation of some free diamine presumably due to reduction of the substrate by DMF. Use of essentially the same conditions except DMAC as solvent gave clear evidence with thin layer chromatography (TLC) of desired coupling to compound Vb, although not in a yield of synthetic practicability. Starting material predominantly remained.

Ullmann reaction with compound IVb using comparable conditions gave quite different results: TLC (Silica gel/3:1 tetrahydrofuran:heptane) indicated debromination to be a serious competing reaction. By comparison with the known reference compounds, generation of the dimesylamide and biphenyl tetramesylamide was detected. Only scant evidence of the dibromo coupled product VIb existed. These results indicated that although some coupling occurred, debromination to arene both before and after the coupling step predominated. Also generated in the course of reaction was a significant quantity of black inorganic salts, presumably copper bromide, in quantities greater than would be expected for the desired reaction course. All starting material had been consumed.

Reactions using less forcing conditions to inhibit competing debromination, including lower reaction temperature (115°C), shorter reaction periods (5 hours), and 1:1 ratios of Cu bronze to substrate generated some dibromo coupled product. However, debromination remained a competing reaction. The presence of starting material at reaction termination also indicated a lower efficiency of coupling.

Several techniques were attempted in conjunction with the Ullmann reaction to improve its efficiency. The dissolving metal reduction of copper iodide with potassium metal to give elemental copper and potassium iodide via the naphthalide radical anion generates a finely divided slurry of Cu° with reportedly much higher reactivity in the Ullmann reaction (Reference 15). In the case of compounds IIb and IVb, however, using dimethoxyethane directly as solvent, no evidence of coupling could be obtained. 4-N,N-Dimethyaminopyridine, reportedly an effective catalyst in some aromatic nucleophilic substitution reactions, did not appear to have any impact in our systems. It was concluded that the yield of the dibromo biphenyl product from the Ullmann reaction ws too low to be of synthetic value and the approach was thus abandoned.

Compound IIb was not subjected to Ullmann coupling because at the high temperatures used (130°C), the ortho diacetamide moieties would be expected to cyclize to the 2-methyl benzimidazole.

3. Via Mercuric Salts

4,4'-Diacetanilidobiphenyl has been prepared in good overall yield (69%) from acetanilide via mercuric salt formation followed by biaryl coupling with palladium chloride and copper (Reference 16):

An attempt was made to apply this synthesis to compounds IIc, IIIc and IVc. However, strong reflux overnight in ethanol or acetic acid failed to generate any mercuric acetate product.

The mechanism of amide mercuration involves formation of an intermediate in which the mercury salt adds to the amide group prior to rearrangement to the *para* substituted product (Reference 17). Attempts to form this mercuric chloride salt with our systems also failed. Presumably, steric crowding around the *ortho*-diacetamide substrate, could inhibit this mechanism.

4. Via Nickel (o) Reagents

Biaryl coupling attempts thus far had been unsuccessful due to functional group incompatibility (n-butyllithium); competing side reactions (Ullmann); or steric hindrance (mercuric salts). The first two approaches used rather forcing conditions: a) high reactivity in the case of n-butyl lithium, and b) high temperatures with the Ullmann. A synthetic approach, using moderate conditions compatible with a variety of functional groups was needed. The oxidative addition of aryl halides to zerovalent nickel complexes to yield biaryl products appeared to meet these criteria.

Semmelhack, *et al*. (Reference 18) first disclosed the use of a zerovalent nickel complex when bis(1,5-cyclooctadiene)nickel(0) was reacted with a variety of aryl halides at moderate temperatures in DMF to produce biaryls, nickel dihalide and 1,5-cyclooctadiene. The reagent, which can be regarded as highly reactive solvated nickel metal, is selective for reaction at the carbon-halogen bond, especially for bromides and iodides.

Because the reagent is so reactive, there are manipulative disadvantages associated with it which make it less attractive. Its high reactivity makes it extremely air sensitive and thus tedious to prepare and use in scale-up quantities. Coupling attempts with our systems made using this reagent (supplied by Midwest Research Corp) were unsuccessful. There was a possibility, however, that the reagent had become oxidized to nickel(II) by the time it arrived at our facility. Its appearance was dark green rather than the bright yellow described for the desired product in the literature preparation (Reference 19).

Another form of zerovalent nickel, nickel carbonyl, also reacts with aryl iodides, but no simple biaryl is formed due to carbon monoxide ligand insertion. In addition, the extreme toxicity of nickel carbonyl makes it unattractive for potential scale-up use.

The *in situ* generation of a solvated zerovalent nickel reagent was reported by Kende, *et al*. in 1975 (Reference 20). The reduction of bis(triphenylphosphine) nickel(II) dichloride with zinc in the presence of triphenylphosphine generated the coordinately unsaturated tris(triphenylphosphine) nickel(0) reagent. This zerovalent nickel reagent was then used directly to affect biaryl synthesis from aryl halides. All reagents for generation of the nickel(0) reagent are commercially available. Furthermore, generation of the tris(triphenylphosphine) nickel(0) can be followed visibly from changes due to reduction of nickel, the initial deep blue color of the nickel(II) species turns green, then light green-yellow, and finally the characteristic red-brown slurry of the tris(triphenylphosphine) nickel(0). Only moderate heating (50°C) can be used since higher

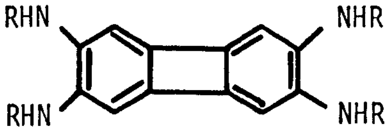
$$(\phi_3p)_2\ NiCl_2 + Zn + \phi_3p \rightarrow (\phi_3p)_3Ni^\circ + ZnCl_2$$

$$(\phi_3p)_3\ Ni^\circ + Ar\text{-}X \rightarrow Ar\text{-}Ar + NiX_2$$

temperatures cause decomposition of the nickel(0) reagent. The dibromodisulfonamide substrates IIIb and IVb were soluble in DMF, the only solvent found suitable for the *in situ* Ni(0) coupling reactions. The dibromodiacetamide compound IIb required high dilution for solvation.

Of particular importance to our system, was a literature reaction where the substrate possessed ortho substitution to the aryl halide, which for the bis-cyclooctadiene nickel(0) system greatly retarded reaction. Also, the overall 1,2,4,5 substitution pattern found in this reaction product paralleled that of compounds IIb, IIIb, and IVb.

Potential drawbacks did exist with the tris(triphenylphosphine) nickel(0) coupling scheme. The first of these was whether selective mono coupling would occur rather than competing dicoupling to give a biphenylene product:



Also, in the bis-(1,5-cyclooctadiene) nickel(0) system, phenol p-toluene-sulfonate esters were completely unreactive to coupling. No mention was made of compatibility with the sulfonamide moiety for this zerovalent nickel, although a parallel could be suspected.

Coupling attempts with the in situ generated tris(triphenylphosphine) nickel(0) were first carried out with compounds IIIb and IVb. Although prolonged reaction periods were used (ranging from overnight to one week), no evidence of coupling could be obtained. In fact, the red-brown color of the nickel(0) reagent persisted except for some darkening throughout the entire reaction period. Work-up gave essentially complete recovery of starting material, ruling out the possibility of carbon-halogen bond reduction because of the relative acidity of the sulfonamide proton. (This was reported as a competing reaction in the case of coupling with the bis(1,5-cyclooctadiene) nickel(0) when the substrate contained acidic functional groups such as phenol carboxylic acid.)

Inhibition of the coupling reaction in the case of the phenol and amine sulfonate esters may be due to bidentate chelation of these moieties with the Ni(0). Such complexation could prevent the oxidative addition of the aryl halide to the Ni(0) thus preventing subsequent biaryl coupling. Alternatively, steric hindrance imposed by the ortho bromine atom could have prevented reaction.

To determine if steric hindrance was the predominant factor preventing biaryl coupling of the dibromodisulfonamides using Ni(0), coupling reactions using identical conditions were performed with the mono-bromo bissulfonamide substrates IIIc and IVc. No evidence of coupling was detected after five days of reaction, implying that the sulfonamide moiety was primarily responsible for preventing reaction.

To remove both constraints noted above, nickel(0) coupling was performed with the mono-bromo bisacetamide substrate IIc. After a two-day reaction period, the reaction mixture had become green, indicating generation of Ni(II) consistent with biaryl formation. Furthermore, TLC indicated essentially complete reaction of starting material to give cleanly the biphenyl tetraacetamide compound VIIa. After work-up, the product melting point (280-290°C) compared with that of VIIa.

Nickel(0) coupling was next performed with the dibromo bisacetamide substrate IIb. Two-day reaction generated a yellow-green color, but TLC analysis indicated generation of the mono-bromo and unbrominated bisacetamide compounds IIc and IIa, with little or no evidence of coupling to compound VIIb. Mass spectral analysis of the crude product showed no characteristic triplet expected for two bromines (either from starting material or desired coupled product).

Arene formation is known (Reference 21) to be a potential competing reaction to biaryl formation. The appearance of the arene is explained by reference to two competing mechanistic pathways which exist for the in situ generated Ni(0). One of these paths leads to an Ni(0) moiety which can form both Ni(II) and Ni(I) after reaction. The Ni(II) intermediate proceeds to generate the coupled biphenyl product. The Ni(I) species, however, generates an aryl radical which can react rapidly by hydrogen abstraction from the solvent to form a dehalogenated product.

The relative amounts of Ni(I) formed are known to be dependent on: (1) the halide; (2) the solvent; and (3) the polar substituent. Aryl iodides show the greatest tendency to generate the deleterious Ni(I) species, but aryl bromides demonstrate the most pronounced variations in Ni(I) formation resulting from substituents on the phenyl ring. In particular, positively charged moieties (i.e., trimethylammonium) strongly promote Ni (I) formation, whereas negatively charged groups hinder it. The specific effect of the acetamide moiety has not been determined. Finally, more polar solvents promote formation of Ni(I). Kochi et al. reported relative yields of the halonickel(I) species from interaction of the tetra(triethylphosphine) nickel(0) with p-carbomethoxyphenyl iodide to be 46%, 76%, and 91%, using hexane, toluene, and tetrahydrofuran as solvent, respectively (Reference 21). In the case of the dibromo bisacetamide substrate IIb, high dilution in DMF was required for solvation; this could have promoted formation of the Ni(I) intermediate.

Electronic and possibly steric factors appeared to prevent successful biaryl coupling with the Ni(0) reagent using o-dibromo substrates. These results led to investigations of a final class of compounds, the o-bromophenylethynyl diamine derivatives, which could both eliminate the problems associated with selective coupling of an o-dihalo compound to a 2,2'-dihalobiphenyl and also the anticipated problems in converting a 2,2'-dihalobiphenyl compound to a 2,2'bis-(phenylethynyl) compound. The synthetic route to these derivatives was acetylation of 4-iodo-o-phenylenediamine followed by bromination at the 5 position to afford compound IIg and selective replacement of iodine by phenylacetylene to form 4-bromo-5-phenylethynyl-N,N'-diacetyl-o-phenylenediamine (IIh).

Reaction of substrate IIb with the Ni(0) reagent even after a one-month period did not show significant evidence of biaryl coupling. Mass spectrometry of the crude product did not indicate the coupled tetraacetamide product VIIc, but only starting material and the 2-methylbenzimidazole, XIb. The latter product was evidently generated from cyclization-dehydration of the o-diacetamide functionality. The free diamine analog of IIh prepared by hydrolysis of compound IIh also failed to couple directly to compound I as revealed in TLC comparison with the reference compound previously prepared (Reference 1).

D. PHENYLETHYNYLATION REACTIONS

Up to this point, the only halogenation method of general applicability to the derivatives of o-phenylenediamine and diaminobenzidine used as starting materials was bromination, with para orientation verified in the case of the sulfonamides. Iodination could only be obtained with o-nitroaniline. Because of the limited synthetic versatility of iodination approaches, and the lower cost of bromine over iodine, phenylethynylation methods applicable to bromine substitution were first examined.

Of several possible routes of phenylethynylation, only those using phenylacetylene with palladium catalysts were suitable for reaction with bromo substrates. Reaction with copper(I) arylacetylenes is only feasible in useful synthetic yield for iodo substrates (Reference 23). Furthermore, its preparation on a large scale is particularly tedious. Phenylethynylation catalysis with bis-(triphenylphosphine) palladium(II) dichloride and copper(I) iodide, first disclosed by Sonogashira et al. in 1975 (Reference 24), was described as specifically applicable to iodoarenes, bromoalkenes, and bromopyridines. The dibromo disulfonamide compounds IIIb and IVb were used as model systems to determine optimum reaction conditions. The <u>ortho</u> positioning of the bromine atoms could be expected to approximate the steric constraints present in the 2,2'-dibromobiphenyl systems Vb and VIb. Attempts to phenylethynylate the bromoamide substrates IIIb and IVb using this system failed. Effort thus focused on phenylethynylation using palladium(II) acetate/triarylphosphine catalyst, described by Heck et al. (Reference 25) to be applicable to both bromo and iodo arenes, although more forcing reaction conditions are necessary.

Phenylethynylation by the Heck method, using palladium(II) acetate/triphenylphosphine catalyst was unsuccessful with compounds IIIb and IVb. The desired reaction was inhibited apparently by phosphonium salt formation, evidenced by precipitate formations soon after mixing. Salt formation (known to be catalyzed by palladium) is believed to prevent ligand dissociation required for coordination of the acetylenic moiety with the palladium (Reference 26). Furthermore, the rate of phosphonium salt formation is accelerated by electron donating substituents in the aryl halide, as is the case with sulfonamide moieties.

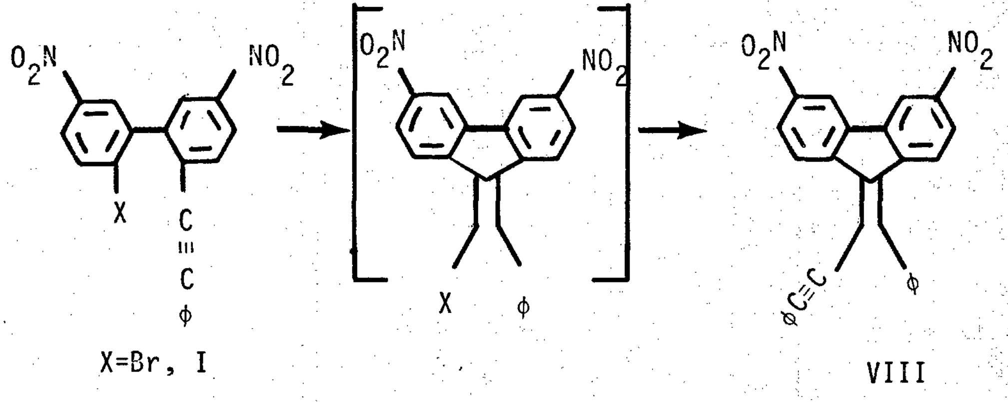
A useful variant of this synthetic method entailed use of tri-<u>o</u>-tolylphosphine rather than triphenylphosphine (Reference 27). The steric crowding imparted by the <u>o</u>-methyl groups apparently inhibits quaternization of the phosphonium salt.

Also, the larger tri-o-tolylphosphine ligands dissociate more readily promoting coordination of the acetylene and thus desired substitution. Using this modification with the dibromo dimesylamide substrate IIIb, clear evidence of reaction could be obtained with TLC due to fluorescene of the phenylethynylted products.

Optimum reaction conditions for forming the disubstituted product entailed a four-fold excess of phenylacetylene, 20 mole% and 10 mole% tri-o-tolylphosphine and $Pd(OAc)_2$ respectively, and a 1:1 pyridine/triethylamine solvent system under nitrogen atmosphere at 95°C overnight. Predominant formation of the disubstituted product was verified by C^{13} and proton NMR, and elemental analysis. However, the yield of product after chromatography ranged only from 20-40%.

The reaction conditions used for compound IIIb were applied to the biphenyl dibromo tetramesylamide compound VIb. The only variation was the necessity of using dimethylsulfoxide as a co-solvent with the pyridine triethylamine to dissolve the substrate. Chromatography gave low yields (15-25%) of product eluting as a broad fluorescent band with long retention time. Recrystallization from isopropanol gave a yellow amorphous solid which according to proton NMR and elemental analysis was predominantly the mono substituted product VId instead of the bis(phenylethynylated) product VIe. Even using a five-fold stoichiometric excess of phenylacetylene, TLC indicated predominantly compound VId as product. Differential scanning calorimetry showed a reaction exotherm for this material beginning at 225°C and reaching a maximum at 278°C. This exotherm behavior was comparable to that found for the 2,2'-bis(phenylethynyl)biphenyl intramolecular cyclization to 9-phenyldibenz[a,c] anthracene (Reference 1) but the intensity of this exotherm was very low, indicating only a small amount of compound VIe present.

Difficulty in obtaining the desired bis-(phenylethynylation) of 2,2'-dihalobiphenyl substrates using both the triphenylphosphine/palladium dichloride/CuI and palladium acetate/tri-o-tolylphosphine catalyst systems has been reported by other investigators (Reference 28). Attempted phenylethynylation of 2,2'-dibromo-5,5'-dinitrobiphenyl gave a high melting solid which was not the expected product, but was believed to be the result of an in situ intramolecular cyclization rearrangement.



VIII

C^{13} NMR analysis of the product from attempted bis(phenylethynylation) of the dibromo tetramesylamide substrate VIb revealed it to be a mixture predominantly composed of the monosubstituted product VId with smaller quantities of disubstituted product VIe and a compound containing 13 quaternary carbons (carbons not attached to hydrogen). A product analogous to II above could account for unknown material if the biphenyl carbons could be considered to have such similar environments that their chemical shifts overlap and appear as one, thus revealing 13 rather than 14 quaternary carbons.

The general difficulties encountered in attempting to double phenylethynylate the biphenyl system, particularly at the relatively hindered 2 and 2' sites, has some precedent. The vinylic substitution reaction of 1-bromo-2,5-diisopropylbenzene with methyl acylate using the palladium acetate catalyst gave a much better yield of substituted product using triphenylphosphine (79%) than tri-o-tolylphosphine (6%) (Reference 26). Evidently, because of steric crowding around the palladium atom, large aryl groups and large phosphines cannot both be utilized to give a high yield of product. The steric constraints inherent in the 2,2'-dibromobiphenyl structure would be expected to be as significant, or more so, than in the example above. Unfortunately, use of the less hindered triphenylphosphine, in our case, generated phosphonium salt preventing desired reaction.

Using the tri-o-tolylphosphine evidently suppressed phosphonium salt formation and allowed, to some extent, the first acetylenic substitution to occur. At this point, however, the additional steric crowding imparted by the mono-phenylethynyl moiety could have prohibited the second reaction of the palladium catalyst complex with the remaining aryl bromide site, particularly with the tri-o-tolylphosphine ligands. Thermolytic rearrangement of the bromo-phenylethynyl intermediate (perhaps promoted by the loss of steric strain in the process) could generate the vinyl bromide from the intramolecular cyclization postulated earlier. The dibenzofulvene structure now would have the bromine in a position more accessible to substitution. A second substitution would give the mesylamide analog of the aforementioned postulated side product (VIII). Low yields support the observation that, largely due to the steric constraints throughout, none of these processes could be favored.

Other considerations also led us to believe that compounds Vb and VIb were unsuitable as intermediates toward ultimate synthesis of the bis-phenylethynyl tetramine. Reaction conditions necessary to bring about cleavage of the sulfonamide moieties to free amine (including phenol/hydrobromic acid, sulfuric acid/water, and sulfuric acid/acetic acid) were incompatible with the internal triple bond, based on model reactions with diphenylacetylene, causing oxidative degradation of the acetylenic moiety. The biphenyl dibromo tetraacetamide compound VIIb, which we expected would be more easily cleaved to amine, using conditions compatible with the triple bond, could not be synthesized due to the insolubility of the tetraacetamide precursor VIIa, precluding bromination and subsequent phenylethynylation.

These results dictated a change in synthetic strategy to include two new approaches: (1) bis-phenylethynylation of the biphenyl dibromo tetramine directly, and (2) perform selective monophenylethynylation of a dihalo diacetamide/diamine substrate prior to biaryl coupling.

The free amine, IX, was obtained in 60-70% crude yield from compound VIb by cleavage with concentrated sulfuric acid and water. Although the compound was analogous to the mesyl derivative, the altered electronic environment (moderately electron donating mesylamide versus strongly electron donating amine) and steric environment (one could expect a somewhat greater degree of free rotation about the biaryl bond with the tetramine) warranted investigation. Also, the difficulty of bis-phenylethynylation of dihalo biphenyl substrates reported by other investigators only involved substrates having electron withdrawing groups (carbonyl, nitro) perhaps having a strong influence on reaction mechanism.

A variety of reaction conditions were used to attempt bis-phenylethynylation of compound IX. Reaction with copper phenylacetylide in pyridine at 100°C overnight led to decomposition of starting material. Reaction with phenylacetylene and the bis-triphenylphosphine palladium(II)dichloride/copper iodide catalyst in pyridine/diethylamine at 65°C for six hours gave no evidence of reaction, although starting material remained intact. Finally, reaction with phenylacetylene and the palladium(II)acetate/phosphine catalyst using both triphenylphosphine and tri-o-tolylphosphine (pyridine/triethylamine 100°C overnight) led to debromination via arene formation to diaminobenzidine.

Earlier cases of sterically hindered aryl halides being reduced to the corresponding arene have been reported. 2-Bromobiphenyl was largely converted to biphenyl during reaction with methyl acrylate using the Heck conditions (Reference 29). The reducing agent responsible has not been identified. Another possible competing reaction was phosphonium salt formation (precipitate formation was noted soon after mixing all reactants which then redissolved upon heating). Apparently, compound IX presented two worst-case scenarios for attempted phenylethynylation; steric hindrance prevented complete reaction and promoted reduction, and strongly electron donating groups prevented an electronic environment conducive to phosphonium salt formation.

To circumvent the difficulty in obtaining double phenylethynylation of the Vb, VIb, or IX 2,2'-dibromobiphenyl substrates selective monophenylethynylation of a dihalo diamine or diacetamide substrate was pursued. The desired intermediate product would have ortho positioning of the phenylacetylene and halogen moieties with para positioning of the amine functions. Coupling through the aryl halide would then give the bis(phenylethynyl) biphenyl product with proper functional group positionings.

4,5-Dibromo-o-phenylenediamine (Xa) was prepared in moderate yield from the dimesyl precursor (IIIb) by cleavage with con. H_2SO_4/H_2O. The product was relatively air stable and did not require unusual precautionary handling, other than that routinely used for diamines. Optimum reaction conditions for preparation of the monophenylethynylated product Xb from this starting material employed a $Pd(OAc)_2$/tri-o-tolyphosphine catalyst, 1.5 equivalents phenylacetylene and piperidine solvent. Mass spectrometry confirmed the monosubstituted compound Xb to be the predominant crude product component, but significant amounts of the disubstituted product Xc and starting material existed. Chromatography using a wide variety of elutants failed to give appreciable separation of these three components. Other work-up procedures failed to isolate the desired mono substituted product.

The difficulty of selective mono-phenylethynylation of an ortho dibromo substrate, plus the added task of separating the resultant product mixture made this approach synthetically unattractive. Use of one equivalent of phenylacetylene in an attempt to avoid distribution resulted in a low yield of monosubstituted product, presumably due to mass loss of phenylacetylene caused by the known competing reactions of coupling to 1,4-diphenyl-1,3-butadiyne and acetylene polymerization. Use of too great an excess of phenylacetylene gave disubstituted product.

The synthetic difficulties just described accentuated the importance of preparing the ortho bromo-iodo diacetamide compound IIg. With the hetero halogen atoms located in equivalent positions relative to the diacetamide group, selective monophenylethynylation at either site would generate the same isomer for subsequent biaryl coupling. Advantage could be taken of the substantially greater reactivity of the aryl iodide moiety over aryl bromide to substitution with phenylacetylene using the bis-triphenylphosphine palladium(II)dichloride, cuprous iodide catalyst system. Reaction with 1.5 equivalent of phenylacetylene in DMF/diethylamine at ambient temperature overnight gave clean monophenylethynyltion to IIh with the bromine intact for subsequent coupling attempts as described previously.

E. HYDROLYSIS OF ACYL, MESYL, AND TOSYL AMINE DERIVATIVES

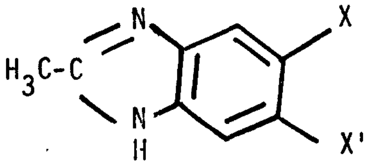
The regeneration of amine from the amide derivatives proved to be of greater synthetic difficulty than at first anticipted. Conditions necessary to cleave the sulfonamides to amines were incompatible with the triple bond moiety. This finding required major changes in the synthetic approaches pursued as described earlier.

Focus was aimed at cleavage of both the aryl and biaryl dibromosulfonamides prior to phenylethynylation. The reductive cleavage of methane sulfonamides has been obtained with 40% hydrobromic acid and phenol (Reference 30). The phenol is used to react with any bromine liberated to prevent bromination of the amine. Reaction with the o-dimesylamide model compound gave o-phenylenediamine; however, when applied to the bromo sulfonamides IIIb and IVb numerous complications arose. TLC indicated a complicated chromatograph suggesting competing side reactions. When diphenylacetylene was subjected to these conditions, it was completely consumed giving presumably the vinyl bromide addition product.

A mild and selective method for the cleavage of aryl sulfonamides employs a mixture of 40% (by volume) of sulfuric acid in glacial acetic acid (Reference 31). The reagent is described to be generally applicable to aryl sulfonamides. Even very hindered acyclic tosylamides have been converted to the amine in 90% yield. Other attempts to remove the tosyl group from these hindered systems resulted in numerous complications. The reactive component of the medium, presumably the protonated form of acetic acid which has an acidity on the order of 10^3 greater than H_3O^+, accounts for the milder conditions generally employed. When applied to the ortho disulfonamides IIb and IVb, however, a very different outcome prevailed. NMR, IR, and mass spectrometry revealed that 2-methyl-benzimidazole formation of compound XIa was occurring in situ, presumably via initial amine (or amine salt) generation, followed by acetylation and subsequent condensation cyclization promoted by heat and the acidic conditions. The same process occurred with the dibromo biphenyl analogs Vb and VIb giving dibromo-bis(2-methyl-benzimidazole) XII. Such action on ortho diamine derivatives has been described in the literature. Attempted hydrolysis of N-methyl-N,N', N'-tritoluene-p-sulfonyl-o-phenylene diamine using sulfuric acid/acetic acid gave, presumably through the same process, 1,2-dimethyl-benzimidazole (Reference 32).

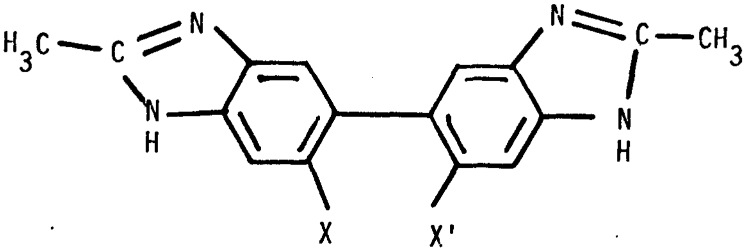
Best results were achieved by using a 3.5/1 sulfuric acid/water mixture (Reference 33). To obtain solution, high initial temperatures (120-130°C) had to be used. Subsequent heating at 110°C overnight under nitrogen gave moderate yields (50-70%) of free amine products after alkaline work-up. No evidence of sulfonation was observed and the bromines remained intact. The high reaction temperatures required for the sulfuric acid cleavage reactions, however, also rendered these methods incompatible with the triple bond, where model reactions with tolane indicated decomposition.

The ortho diacetamide functionality also proved troublesome to transform cleanly to the diamine. Focus centered on the bromo-phenylethynyl diacetamide compound IIh since hydrolysis to the diamine would give the immediate precursor



XIa X = X' = Br

XIb X = Br, X' = ϕC ≡ C-



XII X = X' = Br

to the bis-phenylethynyl tetramine product I via biaryl coupling. Although the bromo iodo diacetamide IIg was converted in moderate yield to the bromo iodo diamine Xd using concentrated sulfuric acid at 80°C, treatment in like manner at room temperature of the bromo phenylethynyl analogue IIh afforded immediate decomposition, generating a black tar. Because of the mineral acid sensitivity of the acetylenic moiety, basic conditions were examined. Treatment of compound IIh with ethanolic potassium hydroxide at ambient temperature gave no reaction. Two-hour reflux generated principally the aminoamide half product and a small quantity of compound Xb, according to mass spectrometry.

Overnight reflux of compound IIh in ethanolic potassium hydroxide with and without diethanolamine catalysis (Reference 34) gave a product with a high melting point (258-264°C) which, according to mass spectrometry, was principally the 2-methylbenzimidazole derivative XIb, presumably formed by the intramolecular dehydration condensation of the intermediate aminoamide catalyzed by the basic conditions. This reaction would also be promoted thermally due to the driving force of forming the stable five-membered ring promulgated by the reactive centers adjacently located. No peaks were observed corresponding to the aminoamide or diamine products.

Although mineral acid treatment of the substrate in question was not feasible, reaction with the Lewis acid boron trifluoride in alcoholic solution appeared promising. Deacylation of various phenyl substituted acetanilides, including the sterically hindered 2,6-dimethyl analogue was obtained with BF_3/methanol in near quantitive yield (Reference 35). Treatment of the bromo-phenylethynyl diacetamide substrate IIh with this reagent using a four-hour reflux period generated what was presumed to be a polar amine-boron trifluoride intermediate complex (no movement from origin in TLC using silica gel/THF). Based on later evidence obtained of final product identity, this complex may have been the aminoamide where the free amine corrdinated with BF_3. After treating the acidic solution with ammonium hydroxide to liberate the BF_3 by forming the ammonium complex, a precipitate immediately developed which displayed a very strong broad absorption in the infrared form 3 to 4 microns, characteristic of benzimidazole. Mass spectrometry confirmed this suspicion; molecular ions detected at m/e 310 and 312 were indicative of the bromo phenylethynyl-2-methylbenzimidazole product XIb.

It was evident at this point that acid or base catalyzed cleavage of the ortho diacetamide function was complicated by benzimidazole formation presumably via intromolecular cyclization of the aminoamide intermediate. The key difficulty appeared to relate to the ortho positioning of the acetamide moieties. Strongly basic or acidic conditions promoted cyclization to the benzimidazole; an alternate method was needed for specific transformation of the o-diacetamide to the diamine product.

Hydrazine has been shown to be an effective mild N-decylating reagent in reaction with various N-acetylamino sugars (Reference 36). Hydrazinolysis of methyl-N-acetyl-4,6-o-ethylidone-x-D-glucosaminide was obtained in 97.5% yield. Hydrazine hydrate (90% conc) gave a much better yield than anhydrous hydrazine (60.3% yield). In scale-up quantities, hydrazine hydrate would provide greater safety and convenience. Also, the gylcosidic linkage remained intact in all hydrazinolyses of the N-acetyl amino sugars, alluding to the possibility of triple bond compatibility.

Hydrazine hydrate (64% conc Eastman) was reacted with the bromo phenylethynyl diacetamide substrate IIh at 100°C overnight under nitrogen atmosphere. Aqueous work-up gave a white precipitate which quickly agglomerated to form a tan-colored, taffy-like product. Thorough vacuum drying gave the product as a light tan semi-crystalline solid. Mass spectrometry indicated it to be the desired diamine Xb (m/e 286,288). No peaks were observed corresponding to starting material or aminoamide. However, a small quantity of benzimidazole XIb was evident from TLC evaluation of the crude product. The infrared spectrum showed the acetylenic absorption at 2200 cm^{-1}, indicating compatibility of the triple bond.

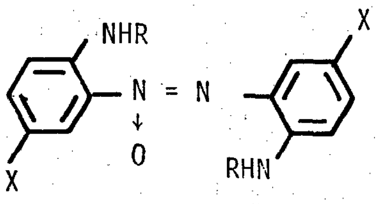
F. BENZIDINE REARRANGEMENT APPROACHES

Attempts to use the benzidine rearrangement to get the biphenyl tetramine system, involved two separate problems. The first of these was the synthesis of an azoxy or azo precursor from readily available starting materials. The second difficulty, one which was never overcome, dealt with the benzidine rearrangement itself.

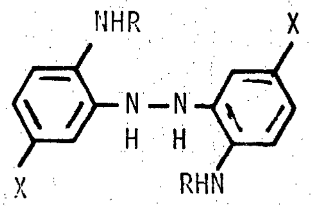
To deal with the synthesis of the azoxy materials, a variety of approaches were tried, but the starting material in all cases was an ortho-nitroaniline substrate. This material was chosen because it was readily available and was less expensive. The presence of a nitro group also allowed for easily controlled halogenation reactions where substitution would occur preferentially para to the amine functionality. This was important to assure the 2,2' positioning of the halogens in the final biphenyl product.

A number of different substituted nitroanilines were used in the course of the work. The most desirable starting material was 4-iodo-2-nitroaniline, synthesized by the method described previously. In addition, the analogous 4-chloro and 4-bromo materials were used in some model reactions. Another interesting starting compound was obtained by the phenylethynylation of 4-iodo-2-nitroaniline. If this material, a deep red crystalline solid, would couple and then rearrange, the desired tetramine would be complete. Finally, the acetamide derivative of nitroaniline was prepared in the event difficulties were encountered with the stability of free amine groups.

When all of these materials had been made, a variety of reactions to get the azo compounds were attempted. In many literature reactions, oxidation of amines to azo compounds is documented, but in this case, it was necessary to reduce the nitro groups in order to obtain the desired substitution pattern. Several techniques were not compatible with the presence of an amine group; however, a method was found which did seem to be efficient (Reference 37). It involved treating the nitroaniline with zinc dust, sodium hydroxide, ethanol, and water to give a 35% yield of 2,2'-diamino-5,5'-diiodoazoxybenzene (XIII, X=I, R=H).



XIII



XIV

By the same method, azoxy products were also prepared with X=Cl, R=H; X=I, R=C(O)CH_3; X=-C C , R=H.

When the various substituted azoxy compounds were synthesized, the second problem, the benzidine rearrangement, was attacked. In this case, a solution to the problem could not be found, and most of the attempted reactions led to cleavage of the azoxy linkage and diamine formation.

Historically, there is some basis for these results. Some of the earliest and most extensive work on the peculiarities of the benzidine rearrangement was done by Jacobson in 1922 (Reference 38). He found that azo compounds with meta amine substitutions would rearrange to the tetramine while ortho amine substituents led only to cleavage and diamine formation. Para substitution patterns will not rearrange at all either, but this is because the rearrangement site is blocked and we can not make analogies to the problems with our systems.

Jacobson's work involved reduction of an azoxy substrate to the hydrazo followed by rearrangement. This was done in a single step through the use of a $SnCl_2$-HCl system. This concerted reaction is the most desirable way to achieve the biphenyl product, but reduction to the hydrazo can be done as a separate step, followed by rearrangement of the isolated hydrazo. In fact, this is probably the most common way to run the benzidine rearrangement reaction, but was unsuccessful with all of our azoxy derivatives (XIII). Since it was possible that the $SnCl_2$-HCl system was simply too forcing, affording amine in all cases, some other methods were explored.

Among the reagents used in an attempt to reduce the azoxy derivatives (XIII) to their hydrazo analogs (XIV) were: formamidinesulfinic acid (Reference 39); hydrazine and palladium on charcoal (Reference 40) or copper (Reference 41); zinc dust and NH_4OH (Reference 42). All of these conditions led to diamine formation and recovery of small quantities of starting material. In addition, the Pd-C, hydrazine conditions led to dehalogenation as well. The reduction conditions used in the state-of-the-art preparation led to the same results.

Perhaps the most interesting approach to the hydrazo problem involved the method of Brown, et al. (Reference 43) which used lithium aluminum hydride and THF at 0°C. Though the end result was still diamine formation, along with some dehalogenation, the progress of the reaction was easy to follow by thin layer chromatography (reversed phase TLC plates, 5:1 methanol:water elutant). The TLC revealed successive reduction from azoxy to azo followed by cleavage to the diamine. Perhaps most interestingly, when the iodonitroaniline substrate was used in the reaction, the azoxy and azo compounds also formed before the cleavage took place. These results seem to indicate that the desired hydrazo compound is particularly unstable. While the reaction in LiAlHy is slow enough to indicate formation of azo and azoxy products in the uncoupled nitroaniline, no evidence of hydrazo, even as an intermediate, is found at all.

This inability to form the hydrazo could result from steric effects due to the presence of *ortho* amine groups. Another possible explanation for the difficulty lies in the sensitivity of free amines to reactions which might compete with hydrazo formation. This possibility seems unlikely, however, because reactions run with acetamide derivatives still give the cleavage product. That leaves steric considerations as the most likely explanation, and this is a difficulty which is not easily overcome.

Unless a new technique for allowing a hindered substrate to rearrange is found, this approach to tetramine synthesis does not look promising. The presence of additional amine substitution, especially in the *ortho* position, is too great a problem at this point.

SECTION III

EXPERIMENTAL

A. N,N'-DIACETAMIDO-o-PHENYLENEDIAMINE (IIa)

o-Phenylenediamine (92.7 mmoles, 10g) was dissolved in 100 ml benzene in a 250 ml Erlenmeyer flask. Acetic anhydride (231.8 mmoles, 23.6g) was added to the flask. After 10-15 minutes, a light precipitate appeared in the benzene. The precipitate, off-white, was filtered after one hour. The precipitate was recrystallized from isopropanol and dried to give a 90% yield of white product, m.p. 185°C (lit. m.p. 185-186°C). Product confirmed by mass spectrometry.

B. 4,5'-DIBROMO-N,N'-DIACETAMIDO-o-PHENYLENEDIAMINE (IIb)

o-Phenylenediamine (46.3 mmoles, 5.0g) was placed in a three-necked, round bottom flask equipped with reflux condenser, N_2 inlet, and thermometer. Glacial acetic acid (50 ml) and dry DMAC (20 ml) were added to the flask, which was then heated to 70°C under nitrogen. A trace of iron filings was added, and then bromine (69.4 mmoles, 11.1g) in 50 ml glacial acetic acid was added rapidly, dropwise, to the solution. The reaction was heated overnight at 90°C.

Cooling to room temperature, pouring over ice/water and suction drying gave a low yield of product (2.44g, 15.1%). The product was recrystallized from isopropanol. Mass spectrometry indicated the desired dibrominatd product (m/e 349, 351, 353), but also showed a small amount of the monobrominted material (m/e 271, 273). Elemental analysis: C, 36.46 (34.29); H, 2.75 (2.82); N, 8.14 (8.00); Br 45.68 (45.71).

C. N,N'-DIMETHANESULFONYL-o-PHENYLENEDIAMINE (IIIa) AND N,N'-DITOLUENE-p-SULFONYL-o-PHENYLENEDIAMINE (IVa)

o-Phenylenediamine (92.7 mmoles, 10g) was dissolved in 50 ml pyridine in a 125ml Erlenmeyer flask. The corresponding sulfonyl chloride (232 mmoles) was added to the reaction vessel. A mixing exotherm was noted, and the reaction was stirred for one hour at room temperature after the exotherm subsided. The pyridine solution was poured into 300ml 10% HCl and the light precipitate which resulted was filtered, recrystallized from isopropanol, and dried to give compound IIIa, m.p. 213-214°C (lit. [Reference 46] m.p. 214°C) and compound IVa, m.p. 204-205°C (lit. [Reference 47] m.p. 204-205°C). Mass spectrometry confirmed desired product.

D. 4,5-DIBROMO-N,N'-DITOLUENE-p-SULFONYL-o-PHENYLENEDIAMINE (IVb)

Bromine (30.36 mmoles, 4.85g) was mixed with glacial acetic acid (125 ml) and charged to a 250 ml three-necked reaction vessel. A trace of iron filings was added to the mixture, a nitrogen blanket established, and the mixture heated to an internal temperature of 75-80°C.

At this point, the substrate (12.01 mmoles, 5.0g), dissolved in 15 ml dry DMAC, was added dropwise to the acetic acid/bromine solution. During the 10 minute addition period, the internal temperature gradually increased from 70°C to 85°C. Heating under nitrogen was continued overnight at 90°C.

After overnight reaction period, the mixture was cooled to ambient temperature. Pouring over ice/wter and filtering gave a light, tan-red product. The crude product was dissolved in hot ethanol (400 ml) and then water (200 ml) ws added in portions to precipitate the product. Another 200 ml of water was added to affect complete precipitation of product. Vacuum drying gave a 92% yield of the product, m.p. 196-204°C. Mass spectrum: 573, 575, 577 (2 Br, M+1) - Elemental analysis: C, 41.96 (41.83); H, 2.96 (3.14); N, 4.97 (4.88); S, 11.11 (11.15); Br, 27.69 (27.85) [theoretical values in parenthesis].

E. 4,5-DIBROMO-N,N'-DIMETHANESULFONYL-o-PHENYLENEDIAMINE (IIIb)

Bromine (47.88 mmoles, 7.65g) was mixed with glacial acetic acid (125 ml) and added to a 250 ml three-necked reaction vessel. A catalytic quantity of iron filings was added and the internal temperature was brought to 78°C under nitrogen atmosphere. At this point, the dimesylamide substrate (18.94 mmoles, 5.0g) dissolved in 15 ml dry dimethylacetamide was added dropwise to the bromination solution over a 15-minute period.

Heating under N_2 atmosphere was continued overnight at 95°C after which the mixture was cooled to ambient temperature. Upon cooling, a precipitate formed which was filtered and washed with fresh acetic acid to give white crystalline product. Vacuum drying gave 5.19g product, m.p. 235-237°C. The filtrate was poured into a kilogram of ice/water giving, after filtration and drying, 2.34g further product. Total yield was 94%. Mass spectrometry indicated the desired product with two bromines m/e 421, 423, 425. Proton NMR indicated a sharp singlet at 7.6 δ indicating equivalent aromatic protons. Elemental analysis: C, 22.87 (22.75); H, 2.27 (2.37); N, 6.84 (6.64); S, 15.52 (15.17); and Br, 37.66 (27.91).

F. MONOBROMO-NHR DIAMIDES

The monobromo diamide compounds were prepared in the same manner as the dibromo compounds; however, no dimethylacetamide was used as a cosolvent. The mono-bromo diacetamide compound (IIc) precipitated immediately upon formation in acetic acid. The mono-bromo ditosyl (IVc) and dimesylamides (IIIc) were obtained by aqueous work-up. These products were confirmed by mass spectrometry.

G. N,N',N",N'"-TETRA(TOLUENE-p-SULFONYL)-3,3'-DIAMINOBENZIDINE (Va)

Thoroughly dried and deaerated pyridine (200 ml) was added to a mixture of diaminobenzidine (20 mmoles, 4.3g) and tosyl chloride (120 mmoles, 22.9g). Nitrogen was bubbled through this mixture for a four-day reaction period. The clear black solution was then poured over two liters of water to give a white precipitate which was filtered, washed and dried at pump vacuum at 80°C overnight. The low melting crude product (m.p. 120-140°C) was stirred with hot acetic acid, filtered, washed with water, air dried, dissolved in dimethylacetamide and precipitated from water. Filtration, washing, and thorough vacuum drying gave the white product (11.7g) in 70% yield, m.p. 295-297°C with decomposition. Elemental analysis gave C, 57.06 (57.83); H, 4.42 (4.58); N, 6.88 (6.95); and S, 15.56 (15.42).

H. 2,2'-DIBROMO-N,N',N",N'"-TETRATOLUENE-p-SULFONYL-5,5'-DIAMINOBENZIDINE (Vb)

Bromine (2.4 mmoles, 0.6g) was mixed with glacial acetic acid (25 ml) and charged to a 50 ml three-necked flask. A nitrogen blanket was established and the mixture was heated to an internal temperature of 70°C. At this point, a trace of iron filings was added. The tetratosylamide of DAB (1.2 mmoles, 1.0g) dissolved in dimethylacetamide (5 ml) was added dropwise over a five-minute period. Heating at 70°C was continued for two hours. After cooling, aqueous work-up gave a precipitate, which after drying, displayed a low melting point (110-130°C).

The crude compound was purified by dissolution in a minimal quantity of hot ethanol. After treatment with decolorizing carbon and filtering, an equal volume of water was added to the ethanolic solution. A white suspension formed, which after cooling in the refrigerator overnight, filtered to give light-gray crystals with a m.p. of 252-256°C. C^{13} NMR of this compound supported the 2,2'-dibromo structure.

I. N,N',N",N'"-TETRAMETHANESULFONYL-3,3'-DIAMINOBENZIDINE (VIa)

Diaminobenzidine (23.4 mmoles, 5.0g) was added to a 500 ml three-necked flask equipped with reflux condenser, nitrogen inlet, and additional funnel. Dry pyridine (200 ml) was added; the system was placed under nitrogen blanket and stirred at ambient temperature until solution was obtained. Then, at ambient temperature, mesylchloride (140.40 mmoles, 16.1g) was added at such a rate that a mild exotherm was maintained up to 50°C (15-minute period).

After the reaction exotherm had subsided, the mixture was heated to reflux overnight. After cooling, the reaction mixture ws poured over 1500g ice/water, filtered, and vacuum dried to give the product (10.71g) in 82% yield, m.p. 294-297°C. Elemental analysis: C, 37.18 (36.50); H, 4.16 (4.18); N, 10.69 (10.65); S, 24.40 (24.33).

J. 2,2'-DIBROMO-N,N',N",N'"-TETRAMETHANESULFONYL-5,5'-DIAMINO BENZIDINE (VIb)

Bromine (41.13 mmoles, 6.6g) mixed with glacial acetic acid (180 ml) was added to a 250 ml three-necked flask fitted with a condenser, thermometer, nitrogen inlet and addition funnel. The solution was heated to 70°C under nitrogen. A trace of iron was added to the flask, and then a solution of the tetramesylamide substitute (13.71 mmoles, 7.21g) in 30 ml dry DMAC was added dropwise to the reaction. An 8°C exotherm was noted.

The reaction temperature was raised to 90°C and maintained there for four days. Shorter reaction times failed to give dibrominated product. Aqueous work-up gave a light precipitate which after drying weighed 7.32g (78%). Recrystallization from three liters of a 1:1 mixture of ethanol/water gave a white crystalline product, m.p. 255-257°C. C^{13} NMR gave a singlet for the aryl C-Br moiety indicating 2,2'-bromination. Elemental analysis: C, 28.61 (28.07); H, 2.82 (2.92); N, 8.13 (8.19); S, 18.62 (18.71); Br, 23.55 (23.39).

K. N,N',N",N'"-TETRAACETAMIDO-3,3'-DIAMINOBENZIDINE (VIIa)

This compound was prepared in essentially quantitative yield by mixing diaminobenzidine and five equivalents of acetic anhydride in acetic acid at room temperature for one hour. The product precipitate was collected, washed with water and vacuum dried, m.p. 300-308°C. Elemental analysis gave: C, 62.41 (62.81); H, 5.17 (5.80); N, 14.62 (14.65).

L. TRI-o-TOLYLPHOSPHINE (12)

This was prepared by the procedure reported in the literature (Reference 26).

M. ATTEMPTED PREPARATION OF 4,5-BIS(PHENYLETHYNYL)-N,N'-DIMETHANESULFONYL-o-PHENYLENEDIAMINE (VIe)

4,5-Dibromo-N,N'-dimethanesulfonyl-o-phenylenediamine (4.74 mmoles, 2.0g) was added to a 50 ml reaction flask equipped with a nitrogen inlet and reflux condenser. An equal volume mixture of dry pyridine/triethylamine (20 ml) was added, along with phenylacetylene (18.63 mmoles, 1.90g). The system was purged with nitrogen several minutes after which tri-o-tolylphosphine (0.987 mmoles, 0.30g) and palladium(II) acetate (0.446 mmoles, 0.10g) were added. The reaction ws heated at 95°C overnight under a N_2 blanket.

After cooling to ambient temperature, the dark brown-black reaction mixture was taken up in chloroform (150 ml). The chloroform solution was washed with 10% HCl (3x60 ml), with water (1x80 ml) and allowed to evaporate.

Dry column chromatography with silica gel and elution with a 1:1 mixture of ethyl acetate/heptane provided separation of the product as a broad fluorescent band.

The crude product after chromatography (0.42g, 19% yield) was recrystallized from 1:1 heptane/$MeCl_2$ to give a yellow crystalline solid, m.p. 213-217°C. Elemental analysis: C, 60.38 (62.07); H, 4.49 (4.31); N, 6.39 (6.03); S, 13.69 (13.79); Br 3.61, (0.00).

N. 2-BROMO-2'-PHENYLETHYNYL-N,N',N", N'"-TETRAMETHANESULFONYL-5,5'-DIAMINOBENZIDINE (VId)

The dibromo tetramesylamide substrate (0.731 mmoles, 0.5g), phenylacetylene (7.31 mmoles, 0.75g), tri-o-tolyphosphine (.146 mmoles, .045g) and palladium (II) acetate (.073 mmoles, .017g) were employed using procedure 13. A ternary solvent system composed of 5 mls each of pyridine, triethylmine, and dimethylsulfoxide was used.

After heating overnight at 88°C under nitrogen, the cooled reaction mixture was taken up in methylene chloride (125 ml), extracted with 10% HCl (3x30 ml) and water (1x30 ml) and allowed to evaporate. Dry silica gel column chromatography using heptane to remove the phosphine, followed by elution with a heptane/ethyl acetate mixture removed a fluorescent band. The crude yellow solid (.12g, 23% yield based on mono substituted product) was recrystallized from isopropanol. Elemental analysis and C^{13} NMR indicated predominance of the mono substituted product.

O. 2-AMINO-4-IODOANILINE

Concentrated hydrochloric acid (1200 ml) was added with mechanical stirring to 4-iodo-2-nitroaniline (.303 mmoles, 80g, prepared as described in Reference 44). Iron powder (3.14 mmoles, 175.4g) was added portionwise during a 35-minute period. The reaction mixture was stirred at ambient temperature for four hours.

The precipitate which developed in the reaction mixture was filtered, washed with hydrochloric acid (500 ml), refiltered, and suction dried. The crude product was washed with hot saturated sodium bicarbonate (1050 ml) and filtered. The filter cake was then dissolved in 800 ml methylene chloride and filtered through celite. The methylene chloride phase was evaporated to dryness and the product was recrystallized from 3:1 hexane/methylene chloride using decolorizing carbon to give the product (58.15g) in 82% yield, m.p. 74-76 (lit. m.p. 73°C).

P. 4-IODO-N,N'-DIACETAMIDO-o-PHENYLENEDIAMINE (IIf)

4-Ioso-o-phenylenediamine (8.55 mmoles, 2.0g) was dissolved in benzene (50 ml). After stirring under gentle nitrogen flow for several minutes, acetic anhydride (17.10 mmoles, 1.74g) was added in one portion to the reaction flask. In several minutes a precipitate developed which was filtered, washed with benzene and dried overnight to give 2.17g of product (96%). Recrystallization from isopropanol (120 ml) using a decolorizing carbon gave the pure product, m.p. 198-200°C. Mass spectrometry confirmed the desired product. Elemental analysis: C, 37.69 (37.74); H, 3.45 (3.46); N, 8.76 (8.81); I, 39.95 (39.94).

Q. 4-IODO-5-BROMO-N,N'-DIACETAMIDO-o-PHENYLENEDIAMINE (IIg)

Bromine was mixed with acetic acid (13 ml) and placed in a 25 ml, two-necked reaction flask equipped with reflux condenser, nitrogen inlet, and addition funnel. The mixture was heated to 70°C under nitrogen blanket. A trace of iron filings added.

4-Iodo-N,N'-diacetamido-o-phenylenediamine (1.57 mmoles, 0.5g) dissolved in 3 ml dimethylacetamide (heating was required to obtain solution) was added dropwise to the bromine solution at 70°C. After several minutes, a precipitate developed in the reaction mixture. After stirring for 30 minutes, the precipitate was filtered off and washed with distilled water to give a white solid. The filtrate was then poured into ice/water which generated further precipitate. This was also filtered, washed with water, and vacuum dried. The crude product (0.49g/79%) was recrystallized from ethanol to give the product with m.p. 285-287°C. Elemental analysis gave: C, 31.80 (30.23); H, 2.76 (2.52); N, 7.40 (7.05); Br 18.21, (20.15); I, 30.34 (31.99).

R. 4-BROMO-5-PHENYLETHYNYL-N,N'-DIACETAMIDO-o-PHENYLENEDIAMINE (IIh)

Bis-(triphenylphosphine)palladium(II)dichloride (0.055 mmoles, 0.04g) was placed in a 500 ml reaction flask equipped with a nitrogen inlet (all glassware dried in oven overnight). 4-Iodo-5-bromo-N,N'-diacetamido-o-phenylenediamine (9.95 mmoles, 3.95g) was dissolved with gentle heating in dimethylformamide (165 ml). Diethylamine (82 ml) was then added and the mixture was charged to the reaction vessel.

Phenylacetylene (14.93 mmoles, 1.52g) was added to the reaction mixture. After establishing a nitrogen atmosphere, copper(I)iodide (0.110 mmoles, 0.021g) was added. The solution became very deep purple.

Stirring under nitrogen atmosphere at ambient temperature was allowed to proceed two days. At this point, the reaction mixture had become clear yellow. Pouring over 3500 ml ice/water gave the crude product as a gray precipitate which, after vacuum drying, gave 3.19g crude product (87% yield). Recrystallization from ethyl acetate (1600 ml) gave 2.80g product (75.9% yield), m. p. 232-236°C. Mass spectrometry confirmed the desired product. Elemental analysis: C, 57.56 (58.22); H, 3.96 (4.04); N, 7.81 (7.55); Br, 21.08 (21.56).

S. 4,5-DIBROMO-*o*-PHENYLENEDIAMINE (Xa)

4,5-Dibromo-N,N'-dimethanesulfonyl-*o*-phenylenediamine (1.18 mmoles, 0.5g) was added to a mixture of concentrated sulfuric acid (15 ml) and water (6 ml). Under a nitrogen atmosphere, the slurry was heated up to 130°C at which point the substrate dissolved. The temperature was moderated to 113°C for overnight reaction. By the next morning, the reaction mixture had turned black. The solution was poured into 250 ml of water giving a small amount of red-brown precipitate which was filtered off. The filtrate was then made alkaline by addition of aqueous sodium hydroxide which generated a yellow precipitate. This was filtered and vacuum dried to give 0.10g product. The alkaline phase was extracted with chloroform (4x100ml) and allowed to evaporate giving an additional 0.08g of product. Total crude yield was 58%. Recrystallization from 1:1 methylene chloride/hexane gave white crystalline product, m.p. 148-150°C. Mass spectrometry confirmed the desired product. Elemental analysis: C, 27.17 (27.07); H, 2.12 (2.26); N, 10.04 (10.53); Br, 60.29 (60.15).

T. 2,2-DIBROMO-5,5'-DIAMINOBENZIDINE (IX)

2,2'-Dibromo-N,N',N",N'"-tetramethanesulfonyl-3,3'-diaminobenzidine (0.74 mmoles, 0.5g) was added to a mixture of 15 ml sulfuric acid and 6 ml water. Under nitrogen atmosphere the mixture was heated up to 120°C to dissolve the substrate. The temperature was moderated to 100°C for overnight reaction under nitrogen atmosphere.

After cooling to ambient temperature, the reaction mixture was poured into 125 ml of water and made alkaline by gradual addition of aqueous sodium hydroxide. Upon alkalinity, a precipitate developed which was collected and dried to give 0.06 product. The alkaline filtrate was extracted with chloroform (4x100ml) which yielded after evaporation 0.11g further product, overall yield 63%, m.p. 176-180°C. Mass spectrum: base peak m/e's at 370, 372, 374, indicative of two bromines.

U. 4-BROMO-5-PHENYLETHYNYL-o-PHENYLENEDIAMINE (Xb)

4-Bromo-5-phenylethynyl-N,N'-diacetamido-o-phenylenediamine (5.96 mmoles, 2.21g) was mixed with 110 ml hydrazine hydrate (64% concentration/Eastman). Under a nitrogen atmosphere, the heterogeneous mixture was heated up to 100°C with stirring. The substrate gradually dissolved and heating was continued at 100°C overnight.

The clear yellow solution was cooled to ambient temperature. A slight turbidity developed. The reaction mixture was slowly poured into one liter of ice/water which generated a white precipitate that quickly agglomerated to a tan-colored, resinous material. The aqueous phase was decanted off. The crude product was thoroughly vacuum dried at 80°C for several days to give a light-tan, semi-crystalline solid, m.p. 90-100°C. IR was consistent with a phenylethynylated diamine. TLC analysis showed complete conversion of starting material although some benzimidazole had been formed. Crude yield was 1.52g, 89%.

V. 2,2'-DIAMINO-5,5'-DIIODOAZOXYBENZENE (XIII)

Ethanol (45 ml) was added to 4-iodo-2-nitroaniline (18.94 mmoles, 5.0g) in a round bottom flask to form an orange suspension. NaOH (3.7g) was dissolved in 11ml H_2O, and the hot base was added to the reaction. All substrate dissolved upon addition of base. Zinc dust (3.5g) was then added to the hot solution. After 10 minutes, a red precipitate appeared in the reaction mixture. When the reaction had stirred for one hour, the precipitate was filtered and recrystallized from ethanol to give 1.60g (35%) of a mixture of orange and red crystals with distinctly different structures. The orange (m.p. 168-172°C) and red (m.p. 169-172°C) crystals were separated and evaluated by mass spectrometry to confirm that both were the azoxy product.

W. 4-PHENYLETHYNYL-2-NITROANILINE

4-Iodo-2-nitroaniline (75.6 mmoles, 20.00g, prepared as described in Reference 44) was dissolved in 280 ml diethylamine and was placed in a round bottom flask. Bis(triphenylphosphine)palladium dichloride 0.40 mmoles, 0.28g) and phenylacetylene (113.6 mmoles, 11.6g) were added to the reaction flask, and the system was purged with nitrogen for 10 minutes. The nitrogen flow was reduced and CuI (0.80 mmoles, 0.16g) was added to the flask. After four hours at room temperature, the reaction was poured into 2L10% H_2SO_4/ice. A red precipitate was collected and recrystallized from MeOH/H_2O to give 15.86g (88%), m.p. 162-163°C. Product confirmed by mass spectrometry, NMR, and infrared. Elemental analysis: C, 70.50 (70.59); H, 4.21 (4.20); N, 11.50 (11.76).

SECTION IV

CONCLUSIONS

A total synthesis of the 2,2'-bis(phenylethynyl)-5,5'-diaminobenzidine target compound was not achieved since biaryl coupling of the bromo phenylethynyl diamine precursor could not be obtained with the Ni(0) reagent. Time did not allow investigation of other biaryl coupling methods with this substrate. The most significant contribution of this work provided a synthesis of the aforementioned bromo phenylethynyl diamine compound, an immediate precursor to the target tetramine provided that an efficient biaryl coupling scheme through the aryl bromide site can be found.

The multistep nature of the synthesis of this material is certainly a disadvantage, but all reactions are of high yield and can be done in a straight forward manner. Most of the reactions can be expected to be scaled-up successfully, with the possible exception of the conc HCl/Fe reduction of the iodo-nitroaniline. The yields at each step result in an overall yield of 43% of the bromo phenylethynyl diamine from o-nitroaniline. If a biaryl coupling scheme with an inherent yield of 50% or greater could be discovered, an optimum overall yield of the target tetramine of 21% would result, a significant improvement over the state-of-the-art synthesis.

Assuming chelate inhibition of the Ni(0) reaction, several investigative routes may be pursued. Protecting groups could be used for the o-diamine possessing steric bulk sufficient to prevent chelate formation (i.e., t-butyl). Of course appropriate cleavage methods would have to be established. Transformation of the o-diamine moiety to a cyclic structure, mimicking the benzimidazole, could provide parallel inhibition of chelation. Again, however, a major problem would be efficient regeneration of the diamine after biaryl coupling.

Alternatively, future advances in organometallic chemistry may provide new "solvated metal" species capable of promoting aryl coupling. Other transition metals less susceptable to amine chelation could hold promise. Furthermore, any improved stability of these reagents may allow higher reaction temperatures for carrying out the aryl coupling, possibly improving yields and reducing time requirements. Close scrutiny of the literature should be maintained to ascertain any methods that may be applicable to coupling of the bromo-phenylethynyl-diamine.

The benzidine rearrangement approach to synthesis of the desired tetramine also failed to give the tetramine. Here, the appropriate azo or azoxy derivatives could be made, but rearrangement to the tetramine failed. New reagents for the reaction may be introduced which would allow a stabilized hydrazo product to form thereby permitting the rearrangement; however, possibilities for this do not look particularly hopeful at present.

Further investigation should be made into these approaches, mainly through scrutiny of new research as it appears in the literature. While the possibility of a totally unique approach to the synthesis problem should not be overlooked, this work does provide some background and potential precursors to the desired tetramine system.

REFERENCES

1. a. F. L. Hedberg and F. E. Arnold, J. Polym. Sci. Polym. Chem. Ed., 14, 2607 (1976);
   b. F. L. Hedberg, P. M. Lindley, C.Y-C. Lee and I. J. GoldFarb, J. Polym. Sci. Polym. Chem. Ed., 20, 3069 (1982).

2. K. S. Y. Lau, F. E. Arnold, "Potential Chemical Systems for Intramolecular Cycloaddition Cures," AFML TR-79-4065, May 1979.

3. P. M. Hergenrother, Macromolecules, 7, 575 (1974).

4. W. Wrasidlo, J. M. Augl, J. Polymer Sci, Part A-1, 7, 3393 (1969); J. Polymer Sci, Part B, 7, 281 (1969).

5. G. L. Fox, G. Hallas, J. D. Hepworth, K. N. Paskins, Org Syn, 22, 20 (1942).

6. B. N. Feitelson, J. Chem Soc, 2389 (1952).

7. W. C. Baird, J. H. Surridge, J. Org Chem, 35, 3436 (1970).

8. K. Elbs, H. Volk, J. Prakt Chem, 99, 269 (1919).

9. P. Chabrier, J. Seyden-Penne, A. M. Fouace, Compt Rend, 245, 174 (1957).

10. S. A. Kandil, R. E. Dessy, J. Am Chem Soc, 88, 3027 (1966).

11. H. Gilman, B. Gaj, J. Am Chem Soc, 22, 447 (1957).

12. P. E. Fanta, Synthesis, 9 (1974).

13. F. L. Hedberg, F. E. Arnold, AFML TR-76-198, March 1977.

14. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Inc, 507 (1968).

15. R. D. Reike, L. D. Rhyne, J. Org Chem, 44, 3445 (1979).

16. R. A. Kretchner, R. Glowinski, J. Org Chem, 41, 2661 (1976).

17. L. G. Makarova, A. N. Nesmeyanov, "The Organic Compounds of Mercury," Methods of Elements-Organic Chemistry Series, Vol 4, A. N. Nesmeyanov, K. A. Kochesnkov, Ed, North-Holland Publishing Co, Amsterdam, 1967.

18. M. F. Semmelhack, P. M. Helquist, L. D. Jones, J. Am Chem Soc, 93, 5908 (1971).

19. B. Bogdanoivc, M. Kroner, G. Wilke, 699, 1 (1966).

20. A. S. Kende, L. S. Liebeskind, D. M. Briatsch, Tetrahedron Letters, 39, 3375 (1975).

REFERENCES (Continued)

21. T. T. Tsou, J. K. Kochi, J. Am Chem Soc, 101, 6319 (1979).

22. Mackenzie, Mellor, Mills, Chort, J. Proc Roy Soc N. S. Wales, 78, 70 (1944).

23. R. D. Stephens, C. E. Castro, J. Org Chem, 28, 3313 (1963).

24. K. Sonogashira, Y. Tohda, N. Hagihara, Tetrahedron Letters, 50, 4467 (1975).

25. H. A. Dieck, F. R. Heck, J. Organometallic Chem, 93, 259 (1975).

26. C. B. Ziegler, R. F. Heck, J. Org Chem, 43, 2941 (1978).

27. R. F. Heck, Accts Chem Res, 12, 146 (1979).

28. K. S. Y. Lau, AFWAL-TR-83-4063; T. K. Dougherty, K. S. Y. Lau, and F. L. Hedberg, J. Org. Chem., 48, 5273 (1983).

29. H. A. Dieck, R. F. Heck, J. Am Chem Soc, 96, 1133 (1974).

30. H. R. Snyder, R. E. Heckert, J. Am Chem Soc, 74, 2006 (1952).

31. P. D. Carpenter, M. Lennon, J. Chem Soc, 664 (1973).

32. G. W. H. Cheeseman, J. Chem Soc, 3308 (1955).

33. C. S. Marvel, M. D. Helfrick, J. P. Belsley, J. Am Chem Soc, 51, 1272 (1929).

34. S. O. Ericksson, L. Bratt, Acta Chem Scand, 21, 1812 (1967).

35. L. Sihlbonn, Acta Chem Scand, 8, 529 (1954).

36. M. Fujinaga, Y. Matsushima, Bull Chem Soc Japan, 39, 185 (1966).

37. L. S. Tul'chinskaya, N. B. Karlstedt, N. A. Polyaka, V. M. Berezovski, Zhrunal Obshchei, 38, 2457 (1968).

38. P. Jacobson, Ann, 428, 76 (1922).

39. H. Beyer, H.J. Haase, W. Wildgrube, Ber, 91, 247 (1958).

40. P. M. G. Bavin, Can J. Chem, 36, 238 (1958).

41. A. Furst, R. C. Berlo, S. Hooton, Chem Rev, 65, 51 (1965).

42. P. Ruggli, K. Holzle, Helv Chim Acta, 26, 1190 (1945).

43. H. C. Brown, P. M. Weissman, N. M. Yoon, J. Am Chem Soc, 88, 1458 (1966).

REFERENCES (Concluded)

44. F. L. Hedberg, M. R. Unroe and D. L. Bush, AFWAL-TR-85-4036.

45. P. M. Lindley, A. A. Shaffer and F. L. Hedberg, AFWAL-TR-85-4039.

46. H. Stetter, Chem. Ber., 86, 197 (1953).

47. J. Sawlewicz and J. Jasinska, Roczniki Chem., 38, 1073 (1964).

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