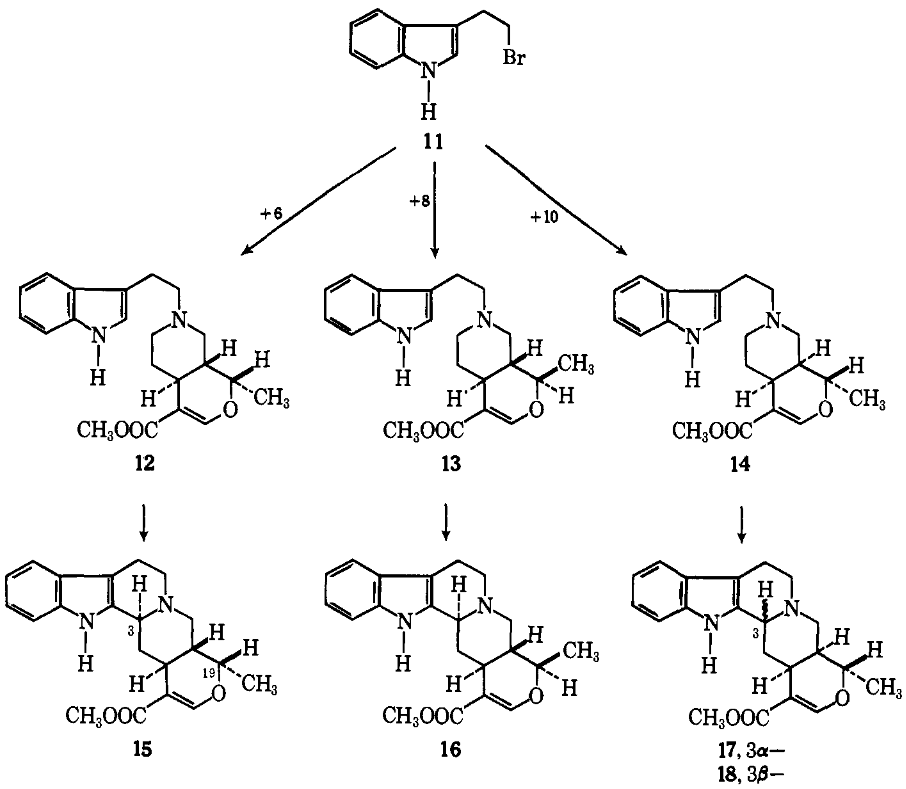
**Scheme II**



Hz, 2-*H*), 7.51 (d, 1 H, $J \sim 1$ Hz, $OC\mathit{H}{=}$); mass *m/e* 354 ($M^+$)], and **14** [mp 156–158°; nmr ($CDCl_3$) $\delta$ 1.30 (d, 3 H, $J = 6$ Hz, $C\mathit{H}_3$), 4.47 (doublet of quartets, 1 H, $J = 10$ and 6 Hz, $OC\mathit{H}CH_3$), 6.96 (d, 1 H, $J \sim 2$ Hz, 2-*H*), 7.49 (s, 1 H, $OC\mathit{H}{=}$); mass *m/e* 354 ($M^+$)] (see Scheme II).

Oxidative cyclization to the pentacyclic alkaloids was achieved using excess 1:1 mercuric acetate–ethylenediaminetetraacetic acid disodio salt followed by reduction of the iminium intermediates with sodium borohydride. The resulting mixtures were separated by preparative thin-layer chromatography, and all pentacyclic products were identified on the basis of their spectral and microanalytical data. Thus, oxidative cyclization of **12** in 2.5% aqueous acetic acid afforded racemic ajmalicine [**15**; 28%; hemihydrate from methanol, mp 216–219° dec, loss of water with darkening at 110–120°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 1700 (C=O), 1620 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 1.12 (d, 3 H, $J = 6.5$ Hz, $C\mathit{H}_3$), 3.66 (s, 3 H, $OC\mathit{H}_3$), 4.33 (m, 1 H, largest $J = 6.5$ Hz, $OC\mathit{H}CH_3$), *ca.* 7.0–7.6 (4 aromatic), 7.48 (d, 1 H, $J \sim 1$ Hz, $OC\mathit{H}{=}$), 8.21 (b, 1, N*H*); mass *m/e* 352 ($M^+$), 351 (M − 1), 184, 169, 156 (base peak)].[5,6] Under similar reaction conditions in aqueous ethanol **13** gave racemic 19-epiajmalicine [**16**; 20%; monohydrate after crystallization from methanol; mp 111–115°; ir ($CHCl_3$) 2850–2750 (Bohlmann bands), 1700 (C=O), 1620 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 1.33 (d, 3 H, $J = 6.5$ Hz, $C\mathit{H}_3$), 3.69 (s, 3 H, $OC\mathit{H}_3$), 3.81 (m, 1 H, largest $J = 10$ Hz, $OC\mathit{H}CH_3$) *ca.* 7.0–7.5 (4 H aromatic), 7.53 (d, 1 H, $J \sim 1$ Hz, $OC\mathit{H}{=}$), 8.1 (b, 1 H, N*H*); mass *m/e* 352 ($M^+$ and base peak), 351 (M − 1), 184, 170, 169, 156].[6] Analogous treatment of the cis compound **14** gave 43% of racemic 3,4,5,6-tetrahydroalstonine [**17**; mp 199.5–200.5°, crystallized from ethanol; ir ($CHCl_3$) 2850–2750, (Bohlmann bands), 1700 (C=O), 1635 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 1.35 (d, 3 H, $J = 6$ Hz, $C\mathit{H}_3$), 3.69 (s, 3 H, $OC\mathit{H}_3$), 4.46 (doublet of quartets, 1 H, $J = 10$ and 6 Hz, $OC\mathit{H}CH_3$), *ca.* 7.0–7.4 (4 H aromatic), 7.54 (s, 1, H, $OC\mathit{H}{=}$), 7.96 (b, 1 H, N*H*); mass *m/e* 352 ($M^+$ and base peak), 351 (M − 1), 337, 156],[7] 10% of the C-3 epimer, racemic akuammigine [**18**; hydrate from ethanol, mp 125–126°; ir ($CHCl_3$) no Bohlmann bands, 1690 (C=O), 1620 $cm^{-1}$ (C=C); nmr ($CDCl_3$) $\delta$ 1.31 (d, 3 H, $J = 6$ Hz, $C\mathit{H}_3$), 4.39 (m, 1 H, $OC\mathit{H}CH_3$), 7.55 (s, 1 H, $OC\mathit{H}{=}$); mass *m/e* 352 ($M^+$ and base peak), 351 (M − 1), 337, 156].[7,8]

While the last reaction was fairly unselective, the shortness of the synthesis allowed us to prepare these pharmacologically interesting alkaloids in quantity.

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(5) E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *J. Amer. Chem. Soc.*, **91**, 7359 (1969).

(6) E. Winterfeldt, A. J. Gaskell, T. Korth, H. E. Radunz, and M. Walkowiak, *Chem. Ber.*, **102**, 3558 (1969).

(7) E. Winterfeldt, H. Radunz, and T. Korth, *ibid.*, **101**, 3172 (1968).

(8) Correct analytical figures have been obtained for all compounds for which physical and spectral data are given.

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## Synthesis with Zerovalent Nickel. Coupling of Aryl Halides with Bis(1,5-cyclooctadiene)nickel(0)

*Sir:*

Biaryls are commonly prepared by metal-promoted coupling of aryl halides, either directly with copper metal as in the Ullmann reaction[1] or by a two-step procedure involving the reaction of intermediate

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(1) P. E. Fanta, *Chem. Rev.*, **38**, 139 (1946); **64**, 613 (1964).

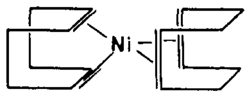
**Table I.** Coupling of Aryl Halides with Bis(1,5-cyclooctadiene) nickel in DMF

| Entry no. | Aryl halide | Coupling product | Yield, % |
|---|---|---|---|
| 1 | Chlorobenzene | Biphenyl (50°, 29 hr) | 14 |
| 2 | Bromobenzene | Biphenyl (52°, 25 hr) | 82 |
| 3 | Iodobenzene | Biphenyl (40°, 21 hr) | 71 |
| 4 | 4-Iodotoluene | 4,4′-Dimethylbiphenyl (40°, 20 hr) | 63 |
| 5 | 4-Bromoacetophenone | 4,4′-Diacetylbiphenyl (45°, 36 hr) | 93 |
| 6 | 4-Bromoanisole | 4,4′-Dimethoxybiphenyl (40°, 23 hr) | 83 |
| 7 | 4-Bromobenzonitrile | 4,4′-Dicyanobiphenyl (36°, 11 hr) | 81 |
| 8 | 4-Bromophenylacetonitrile | 4,4′-Bis(cyanomethyl)biphenyl (33°, 26 hr) | 79 |
| 9 | 4-Bromobenzaldehyde | 4,4′-Diformylbiphenyl (35°, 20 hr) | 79 |
| 10 | 4-Bromoaniline | Benzidine (35–45°, 90 hr) | 54 |
| 11 | Ethyl 4-bromobenzoate | 4,4′-Di(carboethoxy)biphenyl (40–60°, 19 hr) | 81 |
| 12 | 6-Bromopiperonyl methyl ether | 2,2′-Dimethoxy-3,3′,4,4′-bis(methylenedioxo)biphenyl (40–60°, 34 hr) | 67 |
| 13 | 6-Bromopiperonyl alcohol | None (33–35°, 24 hr) | 0 |
| 14 | 2-Bromothiophene | 2,2′-Bithiophene (42°, 22 hr) | 30[a] |
| 15 | 2-Bromotoluene | 2,2′-Dimethylbiphenyl (34°, 131 hr) | 41[a] |
| 16 | 2-Bromo-*m*-xylene | None (54°, 9.5 hr) | 0 |
| 17 | 2-Bromonitrobenzene | None (36°, 24 hr) | 0 |
| 18 | 4-Bromonitrobenzene | None (40°, 17 hr) | 0 |
| 19 | 4-Bromobenzoic acid | None (40–60°, 22 hr) | 0 |
| 20 | 4-Bromophenol | None (40°, 29 hr) | 0 |
| 21 | Sodium 4-bromobenzoate | None (30–65°, 22 hr) | 0 |
| 22 | Sodium 4-bromophenolate | 4,4′-Biphenol (37–60°, 28 hr) | 3 |

[a] This yield was obtained by quantitative glpc analysis using an internal standard.

arylmagnesium halides[2] or aryllithium reagents[2c–e,3] with salts of metals such as Ni,[2a,3b] Co,[2a,c–g,3a] V,[2a,3c] Ti,[3a] Cu,[2a] Cr,[2c] Fe,[2c] U,[2e,g] Tl,[2b] etc. The Ullmann reaction is limited in scope by the high temperatures required (often higher than 200°);[1] the second method is limited to substrates with functional groups stable to arylmagnesium or -lithium intermediates, a serious restriction.

We wish to report that bis(1,5-cyclooctadiene)-nickel(0) reacts directly with a variety of aryl halides at moderate temperatures in dimethylformamide (DMF) to produce biaryls, nickel dihalide, and 1,5-cyclooctadiene (COD) according to eq 1. The yields are



$$+\ 2\,\text{Ar-X} \xrightarrow[25\text{–}40°]{\text{DMF}} \text{Ar-Ar} + \text{NiX}_2 + \text{COD} \qquad (1)$$

generally high (Table I) and functional groups which would not survive with arylmagnesium or aryllithium intermediates (*e.g.*, ketone, aldehyde, ester, nitrile) do not interfere with this reaction. The experimental procedure is illustrated by the conversion of 4-bromoacetophenone to 4,4′-diacetylbiphenyl.

A solution of 4-bromoacetophenone (1.35 g, 6.78 mmol) in 10 ml of dimethylformamide is added rapidly to a suspension of bis(1,5-cyclooctadiene)nickel[4] (1.026 g, 3.73 mmol) in 10 ml of dimethylformamide under inert gas (argon or nitrogen) at 25°. The mixture is stirred at 45° for 36 hr, then partitioned between 20 ml of 3% aqueous hydrochloric acid and 20 ml of methylene chloride. After being filtered to remove finely divided nickel, the organic layer is washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue is triturated with 5 ml of ethyl ether to leave a colorless residue (0.749 g, 93%) of pure 4,4′-diacetylbiphenyl, mp 193.5–194°; lit.[6] mp 192–193°.

Bis(1,5-cyclooctadiene)nickel has been used as a catalyst in diene oligomerization,[7] and one report shows that allylic halides react with the reagent to form π-allylnickel halides,[8] but no example of carbon–carbon bond formation from organic halides has appeared. It can be considered to be essentially solvated nickel metal, a very reactive form of the metal. The reagent is rather selective for reactions at the carbon–halogen bond, especially for bromides and iodides. Nickel carbonyl, another available form of zerovalent nickel, also reacts with aryl iodides, but insertion of the carbon monoxide ligand complicates the reaction; no simple biaryl is formed.[9]

The reaction in eq 1 has several limitations as indicated by entries 13–22 in Table I. The presence of ortho substituents in the aryl halides slows the reaction so that 2-bromotoluene fails to react completely even after 131 hr at 34°, and 2-bromo-*m*-xylene shows no sign of reaction after 9.5 hr at 54°. Raising the temperature accelerates the rate of decomposition of bis(1,5-cyclooctadiene)nickel and gives no increase in the extent of conversion of the aryl halide.

Acidic functional groups (hydroxyl, carboxylic acid) bring about reduction of the carbon–halogen bond at

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(2) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Constable and Co., Ltd., London, 1954, Chapter 5; (b) A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, **90**, 2423 (1968); (c) R. Pallaud and J. L. Zenou, *C.R. Acad. Sci., Ser. C*, **266**, 1608 (1968); *Chem. Abstr.*, **69**, 86666 (1968); (d) G. Adda and R. Pallaud, *C.R. Acad. Sci., Ser. C*, **266**, 35 (1968); *Chem. Abstr.*, **69**, 18720 (1968); (e) J. P. Morizur, *Bull. Soc. Chim. Fr.*, 1331 (1964); (f) W. B. Smith, *J. Org. Chem.*, **26**, 4206 (1961); (g) J. P. Morizur and R. Pallaud, *C.R. Acad. Sci.*, **252**, 3076 (1961).

(3) (a) R. Pallaud and J. M. Pleau, *ibid., Ser. C*, **267**, 507 (1968); *Chem. Abstr.*, **70**, 37860 (1969); (b) B. Sarry and W. Hanke, *Z. Anorg. Allg. Chem.*, **296**, 229 (1958).

(4) See M. F. Semmelhack, *Org. React.*, **19**, in press, for a detailed modification of the original synthesis of bis(1,5-cyclooctadiene)nickel by G. Wilke and coworkers.[5]

(5) B. Bogdanovic, M. Kroner, and G. Wilke, *Justus Liebigs Ann. Chem.*, **699**, 1 (1966).

(6) G. J. Sloan and W. R. Vaughan, *J. Org. Chem.*, **22**, 750 (1957).

(7) G. Wilke, *Angew. Chem., Int. Ed. Engl.*, **2**, 105 (1963).

(8) G. Wilke, B. Bogdanovic, P. Hardt, P. Heimbach, W. Keim, M. Kröner, W. Oberkirch, K. Tanaka, E. Steinrücke, D. Walter, and H. Zimmerman, *ibid.*, **5**, 160 (1966).

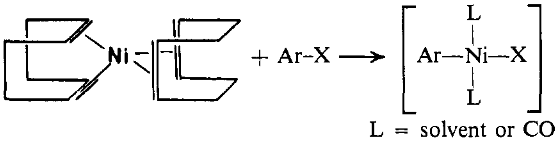
(9) N. Bauld, *Tetrahedron Lett.*, 1841 (1963).

the expense of the coupling reaction. The reaction of 6-bromopiperonyl alcohol under the usual conditions affords piperonyl alcohol in 31% yield accompanied by 51% of unreacted aryl halide and none of the corresponding biaryl. This side pathway is a limitation of the aryl coupling reaction, but is under investigation as a mild and selective method of reducing aromatic carbon–halogen bonds. Removal of the proton source by forming the sodium salt (*e.g.*, entries 21 and 22 in Table I) appears to strongly deactivate the aryl halide toward coupling.

The only solvent which has been found to be satisfactory for the coupling reaction is dimethylformamide. No reaction of aryl halides and bis(1,5-cyclooctadiene)nickel occurs at moderate temperature in less polar solvents such as tetrahydrofuran or toluene; dimethyl sulfoxide and hexamethylphosphoric triamide are not useful due to rapid decomposition of the nickel reagent in these solvents.

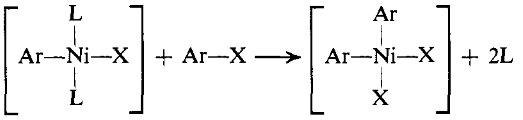
The reactivity of the aryl halides is approximately in the order I > Br > Cl; phenol *p*-toluenesulfonate esters are completely unreactive. Generally, both electron-attracting and electron-donating substituents allow efficient coupling with no significant difference in rate, but nitro groups strongly inhibit coupling. Both 2-nitro- and 4-nitrobromobenzene are recovered unreacted under the usual conditions.

A preliminary study of the mechanism of the reaction implicates a transient aryl–nickel intermediate. Under the usual conditions, iodobenzene and bis(1,5-cyclooctadiene)nickel were allowed to react in dimethylformamide while aliquots were removed at intervals, partitioned between water and pentane, and the pentane solution was analyzed by glpc. The analyses showed clearly the rapid disappearance of iodobenzene and slower formation of biphenyl. The above results are accommodated by the tentative reaction sequence of eq 2–4, in accord with recent suggestions for other metal-promoted coupling of aryl halides,[1] and the general theory of oxidative addition to low-valent transition metals.[10] Alternative pathways *via* direct bimolecular reaction of an arylnickel halide with an aryl halide or *via* free-radical intermediates cannot be excluded at this time.

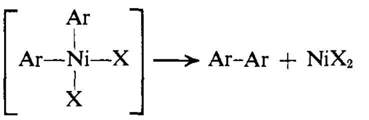


(2)

L = solvent or COD



$$\left[\begin{array}{c} L \\ | \\ Ar{-}Ni{-}X \\ | \\ L \end{array}\right] + Ar{-}X \longrightarrow \left[\begin{array}{c} Ar \\ | \\ Ar{-}Ni{-}X \\ | \\ X \end{array}\right] + 2L \qquad (3)$$



$$\left[\begin{array}{c} Ar \\ | \\ Ar{-}Ni{-}X \\ | \\ X \end{array}\right] \longrightarrow Ar{-}Ar + NiX_2 \qquad (4)$$

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[10] J. P. Collman, *Accounts Chem. Res.*, **1**, 136 (1968).

[11] National Science Foundation Graduate Fellow, 1969–1972.

[12] National Science Foundation Undergraduate Research Participant, 1970.

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## The Mechanism of Azoalkane Fragmentation

*Sir:*

Azoalkanes have been used for many years as a convenient source of alkyl radicals, and for almost as many years chemists have pondered details of the initial reaction.[1] Two schemes have been dominant, and a choice has been made more often than proven. A review presenting a strong case for the formation of three fragments in the rate-determining step (eq 1) has recently appeared.[2]

$$R{-}N{=}N{-}R' \longrightarrow R\cdot + N_2 + \cdot R' \qquad (1)$$

Almost simultaneously the alternative two-fragment process (eq 2) has been supported in the literature by an

$$R{-}N{=}N{-}R' \longrightarrow R\cdot + \cdot N{=}N{-}R' \xrightarrow{\text{fast}} N_2 + \cdot R' \qquad (2)$$

analysis of the existing kinetic and thermodynamic data.[3] Even more recently there has appeared a communication[4] wherein the authors have trapped the hitherto elusive intermediate $\cdot N{=}N{-}R'$.

We have studied the azo compounds **1–4** to prove a choice between the two equations. The synthesis of **1–4** was achieved by the mercuric oxide oxidation of the corresponding hydrazine, $RNHNHCH_2CH{=}CH_2$, which was in turn obtained by the hydrolytic decarboxylation of *N*-alkyl-*N*′-allylbicarbamate.[5]

Thermolysis of **1** at 57 Torr and 131.6° produced methane (36%), 1-butene (33%), 1,5-hexadiene (19%), azomethane (4.6%), propene (0.7%), ethane (0.7%), and pentane (0.4%) based on the nitrogen formed at 30% completion. Nitric oxide[6] was found to suppress the radical chains, eliminate hydrocarbon formation, and decrease the thermolysis rate. The rate showed a slight increase upon further increasing the nitric oxide pressure. Experiments with $^{15}NO$ indicated that some of the nitrogen[7] was derived from the nitric oxide and that the rate constant was unchanged upon

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[1] H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961, Chapter 12.

[2] C. Rüchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970).

[3] S. W. Benson and H. E. O'Neal, *Nat. Stand. Ref. Data Ser., Nat. Bur. Stand.*, **No. 21**, 31 (1970).

[4] N. A. Porter, M. E. Landis, and L. J. Marnott, *J. Amer. Chem. Soc.*, **93**, 795 (1971).

[5] All new compounds gave satisfactory spectral and elemental analyses.

[6] The nitric oxide studies carried out here were modelled from the detailed study on azomethane of W. Forst and O. K. Rice, *Can. J. Chem.*, **41**, 562 (1963).

[7] Mass spectrometric analysis of the nitrogen produced from the runs of **1** with $^{15}NO$ at 126.35° for 90 min indicates that the ratio of $^{15}N^{15}N$ to $^{14}N^{14}N$ is less than 0.05 when the $^{15}NO$ to **1** ratio is less than 0.20. The formation of nitrogen from nitric oxide has been postulated by several workers as due to a reaction with nitrosoalkanes. See ref 6 and J. F Brown, Jr., *J. Amer. Chem. Soc.*, **79**, 2480 (1957); M. I. Christie, *Proc. Roy. Soc., Ser. A*, **249**, 248 (1958); B. G. Gowenlock and M. J. Healey, *J. Chem. Soc. B*, 1014 (1968).