Total Synthesis of Eupolauramine

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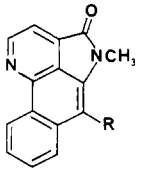
Received December 6, 1982

Eupolauramine (**1**) is a structurally unique azaphenanthrene

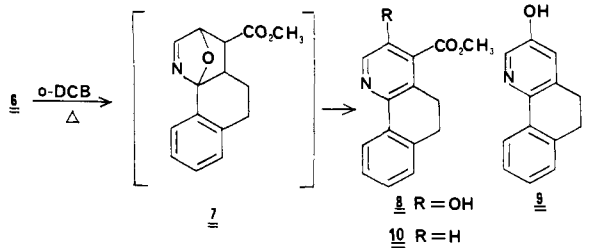


1 R=OCH$_3$
16 R=H
17 R=OH

alkaloid produced by *Eupomatia laurina*.[1] The biosynthesis of **1** is rather obscure, but it may arise in the plant from a precursor having an aporphine alkaloid skeleton.[2] We now report an 11-step total synthesis of eupolauramine that incorporates some novel features including (1) the first example of an intramolecular Diels–Alder cycloaddition of an oxazole and an olefinic dienophile to produce an annulated pyridine and (2) the use of arene oxide chemistry to construct the lactam ring of **1**.

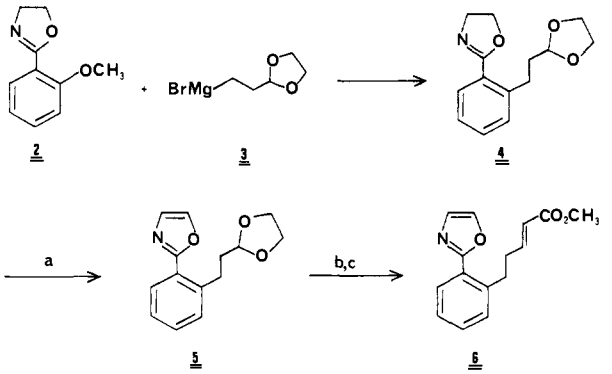
Our starting material for the synthesis was the methoxyoxazoline **2**, which was treated with Grignard reagent **3** as described by Meyers and Mihelich[3] to afford adduct **4** in 95% yield (Scheme I). Oxidation of **4** with nickel peroxide[4] gave the desired 2-aryloxazole derivative **5** (55%). Hydrolysis of the acetal group of **5** with aqueous acid produced the corresponding aldehyde (90%), which was condensed with methyl (dimethoxyphosphoryl)acetate to yield exclusively the trans-unsaturated ester **6** (90%).

When oxazole **6** was heated under argon in refluxing *o*-dichlorobenzene (4 h), a 1:1.7 mixture of pyridinols **8** and **9** (76% yield) was obtained. These compounds probably arise via Diels–Alder adduct **7**,[5,6] which undergoes *oxidative* fragmentation to produce **8** and **9**. Although there is some literature precedent for this type of oxidative pyridinol formation in a few intermolecular cases,[5,7] it is not at all clear at present how this transformation occurs. However, if thermolysis of **6** is done in the



7
8 R=OH
9
10 R=H

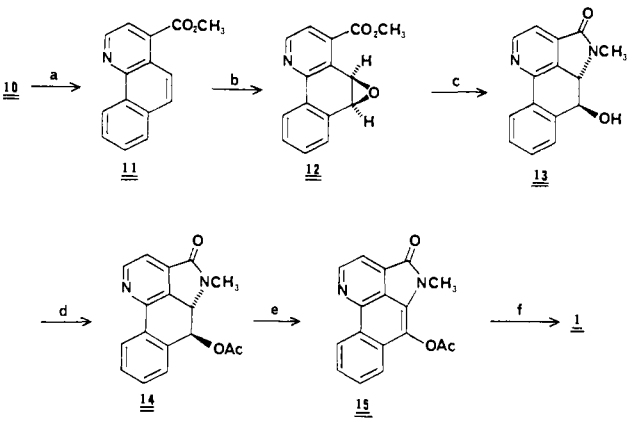
Scheme I[a]



2 **3** **4** **5** **6**

[a] Key: (a) NiO_2/PhH, Δ, 18 h, (b) 3 N HCl/THF, room temperature, 12 h, (c) CH_3OH/CH_3ONa, $(CH_3O)_2POCH_2CO_2CH_3$, room temperature, 5 h.

Scheme II[a]



10 **11** **12** **13** **14** **15**

[a] Key: (a) NBS, CCl_4, Δ, 12 h, (b) $NaOCl/H_2O/CH_2Cl_2$, *n*-Bu_4NHSO_4, room temperature, 4 h, (c) $(CH_3)_2AlNHCH_3/CH_2Cl_2$, room temperature, 4 h, (d) Ac_2O/py, room temperature, 2 h, (e) NBS, CCl_4, Δ, 2 h, (f) 20% KOH/acetone, $(CH_3O)_2SO_2$, room temperature, 2 h.

presence of 0.75 equiv of DBN (16 h), the cycloaddition reaction takes a different course, and the desired pyridine **10** is the *exclusive* product (76%). Undoubtedly DBN accelerates the loss of water from the initial adduct **7**, but its role may be more complex, since it also appears to significantly slow the rate of the Diels–Alder reaction. It should be noted that the ability of an oxazole to act as a heterodiene is critically dependent upon its substitution pattern.[5] In fact, it is reported that 2-aryloxazoles are not useful in intermolecular Diels–Alder reactions.[5a] Clearly, this is not the case in our intramolecular variation.

With compound **10** in hand, it was necessary to next develop a route for introduction of the remaining functionality of eupolauramine. Thus, oxidation of **10** (Scheme II) with *N*-bromosuccinimide afforded the azaphenanthrene ester **11** (90%). This compound could be cleanly converted via the method of Hamilton et al.[8] to the arene oxide **12** (69%). Treatment of **12** with dimethylaluminum *N*-methylamide[10,11] afforded the desired tetracyclic hydroxylactam **13** (49%). We have been unable to detect any products derived from regioisomeric opening of epoxide **12**, and the only other isolable compound was a small amount of the dehydration product **16**.

Much to our surprise, oxidation of the secondary hydroxyl group of **13** to produce demethyleupolauramine (**17**) could not be ef-

(1) (a) Bowden, B. F.; Picker, K.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1975**, *28*, 2681. (b) Bowden, B. F.; Freeman, H. C.; Jones, R. D. G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 658.

(2) For example, see the aristolochic acids and aristolactams: Mix, D. B.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 657. Shamma, M.; Moniot, J. L. "Isoquinoline Alkaloid Research 1972–1977"; Plenum Press: New York, 1978; pp 189–196.

(3) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.

(4) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.

(5) For reviews of Diels–Alder reactions of oxazoles see: (a) Karpeiskii, M. Y.; Florentev, V. L. *Russ. Chem. Rev. (Engl. Transl.)* **1969**, *38*, 540. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389. (c) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99.

(6) For some intramolecular Diels–Alder reactions of oxazoles with acetylenic dienophiles to produce furans see: Jacobi, P. A.; Craig, J. *J. Am. Chem. Soc.* **1978**, *100*, 7748. Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065.

(7) Yoshikawa, T.; Ishikawa, F.; Naito, T. *Chem. Pharm. Bull.* **1965**, *13*, 878.

(8) Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 8121.

(9) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

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(11) We are grateful to Dr. W. C. Taylor for a sample of authentic eupolauramine.

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fected, although many reagents were tried. In general, only **16** could be isolated from these attempted oxidations. However, it was possible to acetylate **13** to afford ester **14** (76%), which upon oxidation with NBS yield the aromatized acetate **15** (73%). This compound could be cleanly hydrolyzed and methylated in one step to give eupolauramine (**1**) in 82% yield identical with an authentic sample.[11]

Acknowledgment. We thank The National Science Foundation for support of this research on Grant CHE81-00132.

Registry No. 1, 58856-98-7; **2**, 74272-88-1; **3**, 18742-02-4; **4**, 84731-36-2; **5**, 84731-37-3; **5** aldehyde, 84731-38-4; **6**, 84731-39-5; **8**, 84731-40-8; **9**, 84731-41-9; **10**, 84731-42-0; **11**, 84731-43-1; **12**, 84731-44-2; **13**, 84731-45-3; **14**, 84731-46-4; **15**, 84731-47-5; **16**, 84731-48-6; **17**, 84731-49-7.

Supplementary Material Available: Listing of physical and spectral data for all new compounds (5 pages). Ordering information is given on any current masthead page.

Free-Radical Chain-Substitution Reactions of Alkylmercury Halides[1]

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Received October 4, 1982

We have previously reported that organomercury halides will participate in free-radical chain-reactions 1-3.[2,3] Although alkyl

$$(\text{alkyl})\text{HgX} + \text{R}_2\text{C}{=}\text{NO}_2^- \rightarrow (\text{alkyl})\text{C(R)}_2\text{NO}_2 + \text{Hg}^0 + \text{X}^- \quad (1)$$

$$\text{RCH}{=}\text{CHHgX} + \text{Q}^- \rightarrow \text{RCH}{=}\text{CHQ} + \text{Hg}^0 + \text{X}^- \quad (2)$$

$$(\text{Q}^- = (\text{RO})_2\text{PO}^-, \text{PhP(OR)O}^-, \text{RSO}_2^-, \text{RS}^-)$$

$$\text{RCH}{=}\text{CHHgX} + \text{QY} \rightarrow \text{RCH}{=}\text{CHQ} + \text{XHgY} \quad (3)$$

$$(\text{QY} = \text{RSSR, PhSeSePh, PhTeTePh, ArSO}_2\text{Cl})$$

$$(\text{alkyl})\text{HgX} + \text{QY} \rightarrow (\text{alkyl})\text{Y} + \text{XHgQ} \quad (4)$$

radicals are involved in reaction 1,[4] substitution in 1-alkenylmercurials (reactions 2 and 3) does not involve alkenyl radicals since the reaction with $Q^- = PhS^-$ or QY = PhSSPh proceeds readily in the presence of PhSH to yield the alkenylphenyl sulfide and not the alkene.[3,5] On the other hand the presently reported reaction 4, which also occurs by a free-radical chain mechanism, quite clearly does involve the alkyl free radical as an intermediate.[6]

Reaction of QY = PhSSPh, PhSeSePh, PhTeTePh, *p*-$MePhSO_2SePh$, or $PhSO_2Cl$ with alkylmercurials (RHgX, R = Δ^5-hexenyl, Δ^3-butenyl, *n*-hexyl, neopentyl, isopropyl, cyclohexyl, cyclopentylcarbinyl, 7-norbornyl), summarized in Table I, proceeds cleanly in the presence of free-radical chain initiation (*hν*, 25-45 °C; AIBN, 80 °C) to yield RY. Reaction is not observed in the dark in PhH solution while the photostimulated reaction is inhibited by 10 mol % of $(Me_3C)_2NO\cdot$. In the case of the Δ^5-hexenyl substituent, extensive cyclization occurs to yield the cyclopentylcarbinyl product. From the yields of uncyclized and cyclized products for Δ^5-hexenylmercury chloride, the rate constants for the S_H2 attack of the Δ^5-hexenyl radical upon PhYYPh is calculated to be 7.6×10^4 (Y = S), 1.2×10^7 (Y = Se), and 4.8×10^7 (Y = Te) L/(mol s).[7] The Δ^3-butenylmercury chloride gives no cyclized products.[8] Further evidence that the free alkyl radical is involved in reaction 4 is provided by the observation that $PhSO_2Cl$ yields RCl and no $PhSO_2R$, *p*-$MePhSO_2SePh$ yields only RSePh, and $BrCCl_3$ yields 1-bromohexane (56%) with *n*-hexylmercury chloride.[9] These products are consistent with the mechanism given in eq 4a-c).[10-12] The reaction does not occur

$$\text{Q}\cdot + \text{RHgX} \rightarrow \underset{\mathbf{1}}{\text{R}\dot{\text{H}}\text{g(Q)X}} \quad (4a)$$

$$\mathbf{1} \rightarrow \text{R}\cdot + \text{QHgX} \quad (4b)$$

$$\text{R}\cdot + \text{QY} \rightarrow \text{RY} + \text{Q}\cdot \quad (4c)$$

for PhHgX or (cyclopropyl)HgX, presumably because of the high bond-dissociation energies for **1** in reaction 4b. With Δ^5-hexenyl cyclization, the second-order rate constants for attack of the Δ^5-hexenyl radical on $PhSO_2Cl$ and *p*-$MePhSO_2SePh$ are found to be 3.7×10^4 and 3.0×10^6 L/(mol s).[7]

A modification of reaction 4 involves the participation of PhSH, either alone or in the presence of PhSSPh (reaction 5). Now

$$\text{RHgX} + \text{PhSH} \xrightarrow{h\nu} \text{RH} + \text{XHgSPh} \quad (5)$$

the alkyl radical can be trapped by PhSH to yield RH and PhS· (= Q·), which continues the chain. Again, Δ^5-hexenyl gives some cyclized product (methylcyclopentane) from which the value of $\sim 8 \times 10^7$ L/(mol s) can be calculated for the hydrogen abstraction reaction of Δ^5-hexenyl radical with PhSH.[13]

It is interesting to speculate if the observed α attack of radicals Q· upon 1-alkenylmercurials[3] invovles **1′** as an interemdiate (eq 3a-d). Such an explanation is quite consistent with the observation that an unsymmetrical reagent QY such as $PhSO_2Cl$ yields only the sulfone (RQ) in reaction 3 but only the alkyl chloride (RY) in reaction 4.

$$\text{RCH}{=}\text{CHHgCl} + \text{Q}\cdot \rightarrow \underset{\mathbf{1'}}{\text{RCH}{=}\text{CHHgQCl}} \quad (3a)$$

$$\mathbf{1'} \rightarrow \text{R}\dot{\text{C}}\text{HCHQHgCl} \quad (3b)$$

$$\text{R}\dot{\text{C}}\text{HCHQHgCl} \rightarrow \text{RCH}{=}\text{CHQ} + \text{HgCl} \quad (3c)$$

$$\text{HgCl} + \text{QY} \rightarrow \text{Q}\cdot + \text{YHgCl} \quad (3d)$$

The reactions of benzylmercurials took a somewhat different course than the reactions of primary alkylmercurials in that significant yields of bibenzyl were often observed. Furthermore, the bibenzyl must be formed by a chain process since 5-10 mol % of $(Me_3C)_2NO\cdot$ inhibited these reactions for extended periods of time. Photostimulated reaction of $PhCH_2HgCl$ with 1 equiv

(1) Supported by Grant CHE-8119343 from the National Science Foundation and a scholarship to H. T. from Yarmouk University, Irbid, Jordan.

(2) Russell, G. A.; Hershberger, J.; Owens, K. *J. Am. Chem. Soc.* **1979**, *101*, 1312.

(3) Russell, G. A.; Hershberger, J. *J. Am. Chem. Soc.* **1980**, *102*, 7603.

(4) Russell, G. A.; Hershberger, J.; Owens, K. *J. Organomet. Chem.* **1982**, *225*, 43.

(5) The phenyl radical abstracts hydrogen from PhSH at an essentially diffusion-controlled rate (Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589) while a primary alkyl radical abstracts hydrogen from PhSH ~20 times as readily as S_H2 attack on PhSSPh and has essentially no reactivity toward PhS^- (unpublished results with J. Tanko).

(6) The thermal reaction of PhSeSePh and PhTeTePh with dialkylmercurials has been reported without mechanistic interpretation: Okamoto, Y.; Yano, T. *J. Organomet. Chem.* **1971**, *29*, 99.

(7) Based on a unimolecular cyclization rate constant of 1×10^5 s^{-1} for the Δ^5-hexenyl radical (Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317).

(8) Free-radical reactions leading to cyclopropylcarbinyl products have been reported for homoallylcobalt compounds: Ashcroft, M. R.; Bury, A.; Cooksey, C. J.; Davies, A. G.; Gupta, B. D.; Johnson, M. D.; Morris, H. *J. Organomet. Chem.* **1980**, *195*, 89.

(9) *n*-Alkylmercury chlorides or $(n\text{-Bu})_2Hg$ react with $CCl_3\cdot$ to give alkyl radicals with little involvement of the elimination reaction observed for certain dialkylmercurials by Nugent and Kochi: Nugent, W. A.; Kochi, J. K. *J. Organomet. Chem.* **1977**, *124*, 327.

(10) The S_H2 reaction, R· + PhSHgR′ → PhSR + HgR′, has been observed for R = *i*-Pr, R′ = Ph and for R = R′ = *n*-Bu. However, PhSSPh is much more reactive than PhSHgBu and undoubtedly more reactive than PhSHgCl in this process.

(11) The reaction of RHgX with polyhaloalkanes in the presence of $NaBH_4$ to yield RCl or RBr apparently involves the reaction sequence 4a-c among other processes: Giese, B. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 173, 174.

(12) Racemization of chiral organomercurials by a free-radical chain quite likely proceeds by reactions 4a,b; for pertinent references see: Jensen, F. R.; Rickborn, B. "Electrophilic Substitution of Organomercurials"; McGraw-Hill: New York, 1968.

(13) Electrophilic cleavage of the Δ^5-hexenyl moiety by PhSH is discounted because of the total inhibition of the reaction by $(Me_3C)_2NO\cdot$ (Table I).

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