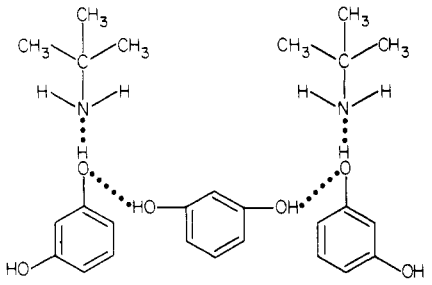
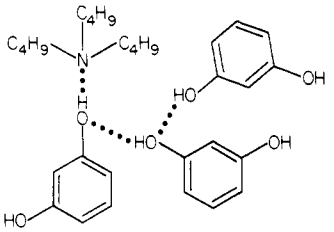


I



II

for predicting the phenol–amine ratio. It is clear from the results in Table I that neither the size of the amine nor its base strength is controlling. The actual organization in the solid state is determined by crystalline dimensions and geometric considerations not presently available to us.

Experimental Section

Materials. The phenols and amines were reagent-grade chemicals from either the Aldrich Chemical Co. or the Eastman Kodak Co., and they were used without further purification.

The following preparations of hydrogen-bonded phenol–amine complexes are typical.

Pyrocatechol–Morpholine 2:1 Complex. Morpholine (2.89 g, 0.033 mol) was added to pyrocatechol (6.6 g, 0.06 mol) dissolved in methylene chloride (75 mL). Hexane (75 mL) was added, and the solution was refrigerated. The yield of product was 8.5 g (92%); mp 66–69 °C. Recrystallization from methylene chloride (100 mL)–hexane (25 mL) did not alter the melting point.

Pyrocatechol–Morpholine 3:2 Complex. Morpholine (2.89 g, 0.033 mol) was added to pyrocatechol (6.6 g, 0.06 mol) dissolved in ether (50 mL). Hexane (20 mL) was then added, and on refrigeration the product slowly crystallized; yield 7.6 g (91%); mp 77–80 °C. Recrystallization from ether (100 mL)–hexane (25 mL) did not alter the melting point. The same product was also obtained with ethyl acetate as the reaction solvent.

Resorcinol–Tri-*n*-propylamine 3:1 Complex. Tri-*n*-propylamine (3.78 g, 0.0264 mol) was added to resorcinol (6.6 g, 0.06 mol) dissolved in ethyl acetate (50 mL). Hexane (50 mL) was added, and on cooling the product crystallized; yield, 7.4 g (78%); mp 124–128 °C. Recrystallization from ethyl acetate (50 mL)–hexane (50 mL) yielded 5.1 g (54%); mp 126–130 °C.

2,3-Dihydroxynaphthalene–Piperidine 1:1 Complex. 2,3-Dihydroxynaphthalene (4.8 g, 0.03 mol) dissolved in ethyl acetate (75 mL) was treated dropwise with a solution of piperidine (2.58 g, 0.03 mol) in ethyl acetate (25 mL). The white crystalline product began to precipitate after half the amine was added; yield 6.6 g (89%); mp 120–127 °C. Recrystallization from ethyl acetate changed the melting point slightly to 121–127 °C.

GC Determination of Phenol–Amine Ratios. The procedure has been described in detail.[2] The only adjustment required for the present work was in the column temperatures, and these were varied to maximize the separation of the phenol and amine components.

IR Measurements. A Perkin-Elmer Model 281B IR spectrophotometer was used. The samples were run as Fluorolube mulls between NaCl plates.

Registry No. Pyrocatechol–butylamine complex (2:1), 89577-85-5; pyrocatechol–*tert*-butylamine complex (2:1), 89577-86-6; pyrocatechol–piperidine complex (2:1), 89577-87-7; pyrocatechol–morpholine complex (2:1), 89577-88-8; pyrocatechol–morpholine complex (3:2), 89577-89-9; pyrocatechol–dipropylamine complex (2:1), 89577-90-2; pyrocatechol–dibutylamine complex (3:1), 82215-65-4; pyrocatechol–tripropylamine complex (2:1), 89577-91-3; pyrocatechol–tributylamine complex (2:1), 82215-64-3; resorcinol–butylamine complex (2:1), 89596-54-3; resorcinol–*tert*-butylamine complex (3:2), 89577-92-4; resorcinol–morpholine complex (1:1), 89577-93-5; resorcinol–diethylamine complex (2:1), 89577-94-6; resorcinol–dipropylamine complex (2:1), 89577-95-7; resorcinol–dibutylamine complex (2:1), 89596-55-4; resorcinol–tripropylamine complex (3:1), 89577-96-8; resorcinol–tributylamine complex (3:1), 89577-97-9; hydroquinone–butylamine complex (1:1), 89577-98-0; hydroquinone–*tert*-butylamine complex (2:1), 89577-99-1; hydroquinone–morpholine complex (1:1), 89578-00-7; hydroquinone–dipropylamine complex (2:1), 89578-01-8; hydroquinone–dibutylamine complex (3:1), 89578-02-9; hydroquinone–tripropylamine complex (3:1), 89578-03-0; 2,3-dihydroxynaphthalene–butylamine complex (2:1), 89578-04-1; 2,3-dihydroxynaphthalene–*tert*-butylamine complex (1:1), 89578-05-2; 2,3-dihydroxynaphthalene–morpholine complex (1:1), 89578-06-3; 2,3-dihydroxynaphthalene–piperidine complex (1:1), 89578-07-4; 2,3-dihydroxynaphthalene–dipropylamine complex (2:1), 89578-08-5; 2,3-dihydroxynaphthalene–dibutylamine complex (2:1), 89578-09-6; 2,3-dihydroxynaphthalene–tripropylamine complex (2:1), 89596-53-2; 2,3-dihydroxynaphthalene–tributylamine complex (2:1), 89578-10-9.

Routes to Mitomycins. An Improved Synthesis of 7-Methoxymitosene Using Palladium Catalysis

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The synthesis of 7-methoxymitosene (**6**), an analogue of the mitomycin antitumor antibiotics possessing antibacterial activity, has received considerable attention in recent years.[1] Previously we described a convenient one-flask synthesis of *N*-aryl vinylogous carbamate **3** through homoproline addition to dibromoquinone **1** followed by irradiation.[1a] A protection–photocyclization–deprotection sequence then converted **3** to **5** (61%), the requisite precursor of 7-methoxymitosene. We now report an efficient synthesis of **6** that gives a significantly increased yield and utilizes a mild palladium-catalyzed ring closure to form the 2,3,5,8-tetrahydro-5,8-dioxopyrrolo-1*H*-indole **5**.

Since enamines, aryl halides, and vinyl halides undergo palladation,[2] we undertook to test hydroquinone **3** and quinone **4** as potential ring-closure educts. That treatment of **3** with palladium acetate gave partial conversion to **5** was encouraging, but the major reaction path was reduction of palladium acetate to palladium black with concomitant oxidation of **3** to **4**. To avoid this consumption of palladium acetate, we first dehydrogenated **3** with 10% palladium on carbon and then treated quinone-vinylogous carbamate **4** with palladium acetate in acetonitrile. Slow and only partial conversion to **5** took place over the course of 1 day; further reaction with heating caused side-product formation. The same reaction, however, in the presence of triethylamine gave clean conversion to **5** in 97% yield

(1) (a) Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404. (c) Coates, R. M.; MacManus, P. A. *Ibid.* **1982**, *47*, 4822. (d) Kametani, T.; Takahashi, K.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 389. (e) Allen, G. R.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877; *J. Org. Chem.* **1965**, *30*, 2897. Also see references cited in the above.

(2) (a) Tsuji, J. "Reactivity and Structure Concepts in Organic Chemistry, Vol. 10; Organic Synthesis with Palladium Compounds"; Springer-Verlag: New York, 1980. (b) Heck, R. F. "Organic Reactions"; Wiley: New York, 1982; Vol. 27, Chapter 2. (c) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571.

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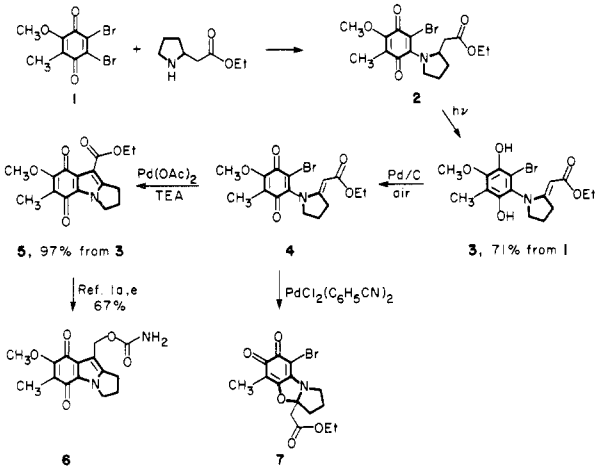
from **3**. We briefly studied the reaction of another soluble palladium(II) species, $PdCl_2(PhCN)_2$.[3] Treatment of **4** with this catalyst formed *o*-quinone **7**, as did treatment with acid.[1a]

The extension of this ring-closure methodology to the chirospecific synthesis of 1,2-substituted mitomycin analogues is under way.



(3) Kharasch, M. S.; Seyler, R. C.; Mayo, F. R. *J. Am. Chem. Soc.* **1938**, *60*, 882.

Experimental Section

Materials. Acetonitrile was distilled from calcium hydride, and triethylamine was refluxed with, and distilled from, tosyl chloride. Palladium acetate was obtained from Aldrich Chemical Company. The use of a sample of palladium acetate obtained from Engelhard Industries caused considerable side-product formation during ring closure. Although the elemental analysis of this catalyst was acceptable (Calcd. C, 21.4; H, 2.7. Found. C, 21.2; H, 2.8), the Engelhard material proved to be insoluble in hot acetone, chloroform, acetonitrile, and benzene. Subsequent reactions were carried out only with Aldrich palladium acetate, which displayed the reported solubility properties.[2a]

Palladium Oxidation of Hydroquinone 3 to Quinone 4 and Palladium-Catalyzed Ring Closure of 4 to 5. To a stirred suspension of **3** (25.0 mg, 65 μmol) in ethyl acetate (1.0 mL) at room temperature in an air atmosphere was added 10% Pd/C (12 mg). After 75 min the catalyst was filtered off, and the solution was evaporated to give a residue, **4** (24.9 mg, 100%), identical with material prepared previously.[1a] This residue was dissolved in acetonitrile (1.0 mL), and the solution was added to $Pd(OAc)_2$ (1.0 mg, 4.4 μmol) in acetonitrile (100 μL) with stirring. Triethylamine (6.6 mg, 65 μmol) was then added, and the mixture was stirred for an additional 2 h at which time it was partitioned between water (3 mL) and dichloromethane (7 mL). The organic layer was washed with water (2 mL), dried ($MgSO_4$), filtered, and evaporated to a yellow solid (21 mg). Filtration of a solution of this solid in dichloromethane through a plug of SiO_2 (100 mg) and evaporation of the filtrate provided pure **5** (19.2 mg, 97%), identical with material prepared by the previous route.[1a]

Communications

A Regiocontrolled Annulation Approach to Highly Substituted Aromatic Compounds[1]

Summary: The thermal combination of cyclobutenone derivatives with heterosubstituted acetylenes provides a regiocontrolled route to highly substituted aromatic compounds.

Sir: Hexasubstituted aromatic rings are common features incorporated in the structures of a variety of biologically active natural products.[3] The conventional synthetic approach to highly substituted arenes of this type involves the elaboration of simple aromatic precursors via electrophilic substitution and metalation–alkylation reactions. Unfortunately, these strategies lack convergence and frequently are not applicable to the synthesis of the more highly substituted aromatic compounds. As the number of substituents about an aromatic ring increases, so also does the difficulty in controlling the regiochemical course of the introduction of additional substituents. For the synthesis of such systems we consequently favor *annulation strategies* in which the aromatic ring is assembled in a single step, with all (or most) substituents already in place.[4]

In connection with our interest in the synthesis of certain antitumor antibiotics,[3] we have developed an efficient regiocontrolled annulation approach to highly substituted aromatic systems. As formulated in Scheme I, this annulation involves the *one-step* thermal combination of a heterosubstituted alkyne with a cyclobutenone derivative and proceeds via a cascade of four pericyclic reactions.[5] Heating a cyclobutenone derivative above 80 °C results in a reversible four-electron electrocyclic cleavage to generate a vinylketene,[6a] which combines with a ketenophilic acetylene derivative (X = OR, SR, NR_2) in a regiospecific [2 + 2] cycloaddition.[7] Reversible electrocyclic cleavage[6a] of the resulting 2-vinylcyclobutenone then furnishes a

(1) This work was presented (in part) at the 183rd National Meeting of the American Chemical Society, March 30, 1982.

(2) Alfred P. Sloan Research Fellow, 1981–1985.

(3) Mycophenolic acid: Birkinshaw, J. H.; Raistrick, H.; Ross, D. J. *Biochem. J.* **1952**, *50*, 630. Mitomycins: Franck, R. W. *Progr. Chem. Org. Nat. Prod.* **1979**, *38*, 1. Ascochlorin: Ellestad, G. A.; Evans, R. H.; Kunstmann, M. P. *Tetrahedron* **1969**, *25*, 1323. Ascofuranone: Sasaki, H.; Hosokawa, T.; Sawada, M.; Ando, K. *J. Antibiotics* **1973**, *26*, 676.

(4) For examples of previous (generally multistep) annulation approaches to benzene derivatives, see footnote 6 in Boger and Mullican (Boger, D. L.; Mullican, M. D. *J. Org. Chem.* **1980**, *45*, 5002) and also: Barton, D. H. R.; Dressaire, G.; Willis, B. J.; Barrett, A. G. M.; Pfeffer, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 665. Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1983**, *24*, 4939. Chan, T. H.; Brownbridge, P. *Tetrahedron* **1981**, *37* (Suppl. 1), 387. Jaxa-Chamiec, A. A.; Sammes, P. G.; Kennewell, P. D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 170. Schultz, A. G.; Shen, M. *Tetrahedron Lett.* **1981**, *22*, 1775. Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200. Tius, M. A.; Thurkauf, A. *Ibid.* **1983**, *48*, 3839. Dötz, K. H.; Pruskil, I.; Muhlemeier, J. *Chem. Ber.* **1982**, *115*, 1278 and references cited therein.

(5) For the application of a related "pericyclic cascade" in an annulation approach to eight-membered rings, see: Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

(6) For reviews, see: (a) Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980; pp 124–190. (b) Reference 6a, pp 260–375.

(7) For previous examples of vinylketene [2 + 2] cycloadditions, see: Reference 5. Jackson, D. A.; Rey, M.; Dreiding, A. S. *Tetrahedron Lett.* **1983**, *24*, 4817. Trahanovsky, W. S.; Surber, B. W.; Wilkes, M. C.; Preckel, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 6779 and references cited therein.

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