hexane:ethyl acetate. The eluant was concentrated at reduced pressure, and the residue was distilled to afford a colorless liquid (0.9 g, 79%), which solidified upon standing: bp 120 °C (0.02 mm), $[\alpha]^{25}_D$ −0.48° (c, 10.4, $CHCl_3$); IR (neat) 3300 (s), 3100 (m), 2900 (s), 1690 (s), 1550 (m), 1450 (m), 1175 (s), 735 (s), 695 (s) $cm^{-1}$; NMR ($CDCl_3$) δ 1.61 (m, 4 H, $CH_2CH_2$), 2.60 (m, 1 H, CHD), 3.32 (m, 2 H, $CH_2$), 7.2 (s, 5 H, Ar).

Anal. Calcd for $C_{12}H_{14}F_3NO$: C, 58.77; H, 5.75; N, 5.71. Found: C, 58.49; H, 5.88; N, 5.63.

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**Registry No.** 2, 10606-75-4; 3, 89398-25-4; 4, 89398-26-5; 5, 53729-87-6; 6, 89398-27-6; 7, 87867-32-1; 8, 89398-28-7; 9, 89398-29-8; 10, 89398-30-1; 11, 89398-31-2; (S)-(+)-mandelic acid, 17199-29-0; diethyl malonate, 105-53-3; ethyl[4-$^2H_1$]4-phenyl-2-(ethoxycarbonyl)butanoate, 89398-33-4; [4-$^2H_1$]4-phenyl-2-carboxybutanoic acid, 89398-32-3.

## Hydrogen-Bonded Complexes. 5. Phenol–Amine Complexes

John E. Barry, Manuel Finkelstein, and Sidney D. Ross*

*Research and Development Center, Sprague Electric Company, North Adams, Massachusetts 01247*

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Our previous studies[1-3] have shown that phenols (picric acid in particular) form crystalline, hydrogen-bonded complexes with amides having phenol–amide ratios of 1:1, 1:2, and 1:3;[1] that phenols (the dihydroxybenzenes in particular) form complexes with lactams having phenol–lactam ratios of 1:1, 1:2, 1:3, and even 3:4;[2] and that phenols (both picric acid and the dihydroxybenzenes) form complexes with ureas having phenol–urea ratios of 1:1, 1:2, 2:1, and 3:1.[3]

Most investigations of hydrogen-bonded complexes are carried out by using spectroscopic measurements in solution, but this experimental approach provides no insight into the variety of stable, crystallizable complexes that can be prepared. We have focused on those complexes that can be isolated and recrystallized as solids. The gamut of available stoichiometries in these complexes is broad, and the stoichiometry in any new case is as yet unpredictable. Such an inability to predict is an indication that our knowledge is limited and that further studies are appropriate.

In a recent study of the reactions of phenols with quaternary ammonium hydroxides in water Hanson, McCulloch, and McInnes[4] demonstrated that the anion of the quaternary ammonium phenolate that formed was associated with one to four additional phenol molecules in an intricate hydrogen-bonded network. These represent a series of hydrogen-bonded complexes having phenol to phenolate anion ratios of 1:1, 2:1, 3:1, and 4:1. It was also noted in this work that pyrocatechol reacts with di-*n*-butylamine and with tri-*n*-butylamine to form complexes having phenol–amine ratios of 3:1 and 2:1, respectively. We have extended this latter pair of observations with a comprehensive study that involved the preparation of more than 30 crystalline complexes from the dihydroxybenzenes or 2,3-dihydroxynaphthalene and amines. The phenol–amine ratios observed included values of 1:1, 2:1, 3:1, and 3:2. The present report will describe the preparations and properties of these complexes and will discuss their structures.

### Results and Discussion

We encountered no difficulty in repeating the reported[4] preparations, in water as the solvent, of the di-*n*-butylamine and tri-*n*-butylamine complexes of pyrocatechol. However, it was more efficient to form the complexes in organic solvents, since this greatly facilitated the isolation and drying of the products. Suitable solvents were ether, ethyl acetate, and methylene chloride. A typical preparation involved mixing the amine and phenol in the solvent of choice, warming until a clear solution resulted, and then adding just enough hexane to bring about slow crystallization. The isolated complexes were then recrystallized from the same solvents.

The complexes that were prepared are listed in Table I, where the phenol–amine ratios are given in the third column. Since all of the observed ratios were 1 or greater and since the nitrogen contents of the complexes decrease rapidly as the values of the ratios increase from 1 to 2 to 3, a nitrogen analysis determines both the empirical formula of the complex and the phenol–amine ratio. As noted previously[2] gas chromatography (GC) provides a simple and precise method for determining these ratios. The two previously reported complexes, the pyrocatechol–di-*n*-butylamine complex and the pyrocatechol–tri-*n*-butylamine complex, were used to confirm the validity of the GC procedure. The ratio for the di-*n*-butylamine product was determined to be exactly 3.00 to 1 and for the tri-*n*-butylamine complex the value found was 2.00 ± 0.006 to 1. The asterisks in column 3 indicate products whose phenol–amine ratios were either confirmed or determined by GC.

The hydroquinone–di-*n*-butylamine complex was chosen as a substrate for exploring the impact on the composition of the complex of first changing the initial concentrations of the reagents and then changing the reaction solvent. Our initial preparation resulted in a good yield of a complex having a phenol–amine ratio of 3:1. Because of the separation of the two hydroxyl groups in hydroquinone it was our hope that we would succeed in isolating the complex having a phenol–amine ratio of 1:1 and even the complex with a ratio of 1:2. This was a reasonable expectation, since in our previous study[2] of hydrogen-bonded complexes of hydroquinone with lactams we obtained a product with a phenol–lactam ratio of 1:1 with *N*-methylpyrrolidinone and products with a ratio of 1:2 with three other lactams.

These hopes were not realized. Starting with initial hydroquinone–di-*n*-butylamine ratios of 0.504:1, 1.01:1, and 2.53:1, the only product obtained was the complex with the phenol–amine ratio at 3:1 and in yields of 58%, 83%, and 93%, respectively. The solvent in these experiments was ethyl acetate. The reaction was also run in ether, a less polar solvent, and in acetonitrile, a more polar solvent. In both solvents the only product obtained was the 3:1 complex. In a similar set of experiments with the 2:1 pyrocatechol–tri-*n*-butylamine complex the product composition again proved to be insensitive to both the initial concentrations and the choice of reaction solvent.

But it would be unwise to draw general conclusions from the above results! We have encountered one case where

(1) Barry, J. E.; Finkelstein, M.; Ross, S. D. *Tetrahedron* **1976**, *32*, 223.
(2) Barry, J. E.; Cipollini, N. E.; Finkelstein, M.; Ross, S. D. *Tetrahedron*, **1981**, *37*, 1669.
(3) Barry, J. E.; Finkelstein, M.; Hutchins, G. A.; Ross, S. D. *Tetrahedron* **1983**, *39*, 2151.
(4) Hanson, A. W.; McCulloch, A. W.; McInnes, A. G. *Tetrahedron Lett.* **1982**, *23*, 607.

0022-3263/84/1949-1669$01.50/0 

Table I.[a] Phenol-Amine Complexes

| phenol (A) | amine (B) | A:B ratio | crystallizing solvents | mp, °C | yield, % |
|---|---|---|---|---|---|
| pyrocatechol | *n*-butylamine | 2:1* | ether-hexane | 76-81 | 97 |
| pyrocatechol | *tert*-butylamine | 2:1 | ethyl acetate-hexane | 96-98 | 77 |
| pyrocatechol | piperidine | 2:1 | methylene chloride-hexane | 84-86 | 88 |
| pyrocatechol | morpholine | 2:1* | methylene chloride-hexane | 66-69 | 92 |
| pyrocatechol | morpholine | 3:2* | ether-hexane | 77-80 | 91 |
| pyrocatechol | di-*n*-propylamine | 2:1 | ether-hexane | 64-68 | 96 |
| pyrocatechol | di-*n*-butylamine | 3:1* | methylene chloride-hexane | 84-87 | 95‡ |
| pyrocatechol | tri-*n*-propylamine | 2:1 | ether-hexane | 75-78 | 83 |
| pyrocatechol | tri-*n*-butylamine | 2:1* | ether-hexane | 88-90 | 83‡ |
| resorcinol | *n*-butylamine | 2:1 | ether-hexane | 91-94 | 85 |
| resorcinol | *tert*-butylamine | 3:2* | ethyl acetate-hexane | 109-114 | 95 |
| resorcinol | morpholine | 1:1 | ether-hexane | 51-55 | 94 |
| resorcinol | diethylamine[5] | 2:1 | ethyl acetate | 113 | 87 |
| resorcinol | di-*n*-propylamine | 2:1 | ether-hexane | 122-127 | 97 |
| resorcinol | di-*n*-butylamine | 2:1* | ethyl acetate | 140-146 | 92 |
| resorcinol | tri-*n*-propylamine | 3:1 | ethyl acetate-hexane | 126-130 | 78 |
| resorcinol | tri-*n*-butylamine | 3:1 | ether-hexane | 77-79 | 54 |
| hydroquinone | *n*-butylamine | 1:1* | ethyl acetate-hexane | 56-58 | 94‡ |
| hydroquinone | *tert*-butylamine | 2:1 | ethyl acetate-hexane | 140-145 | 98 |
| hydroquinone | morpholine | 1:1 | ethyl acetate-hexane | 68-73 | 92 |
| hydroquinone | di-*n*-propylamine | 2:1 | ethyl acetate-hexane | 114-117 | 74 |
| hydroquinone | di-*n*-butylamine | 3:1* | ethyl acetate-hexane | 110-113 | 82 |
| hydroquinone | tri-*n*-propylamine | 3:1 | ethyl acetate-hexane | 125-128 | 65 |
| 2,3-dihydroxynaphthalene | *n*-butylamine | 2:1 | methylene chloride | 119-120 | 94 |
| 2,3-dihydroxynaphthalene | *tert*-butylamine | 1:1 | ethyl acetate | 155-157 | 63 |
| 2,3-dihydroxynaphthalene | morpholine | 1:1 | ethyl acetate-hexane | 116-118 | 92 |
| 2,3-dihydroxynaphthalene | piperidine | 1:1 | ethyl acetate | 121-127 | 89 |
| 2,3-dihydroxynaphthalene | di-*n*-propylamine | 2:1 | ether-ethyl acetate | 114-116 | 69 |
| 2,3-dihydroxynaphthalene | di-*n*-butylamine | 2:1 | ethyl acetate | 137-139 | 89 |
| 2,3-dihydroxynaphthalene | tri-*n*-propylamine | 2:1 | ether-hexane | 77-79 | 75 |
| 2,3-dihydroxynaphthalene | tri-*n*-butylamine | 2:1 | ether-hexane | 116-119 | 83 |

[a] All of the compounds in Table I except those indicated by daggers (‡) were analyzed for nitrogen and gave satisfactory results. For the 28 analyses the average deviation from the calculated value was 2.0% and the maximum deviation was 5.4%.

a change in reaction solvent results in a change in the product composition. In methylene chloride, with the initial pyrocatechol–morpholine ratio at 1.8:1, the 2:1 complex, mp 66–69 °C, was obtained in 92% yield, and this 2:1 phenol–amine ratio was established by a nitrogen determination and confirmed by GC analysis. Using the same initial molar ratio of the reagents but changing the solvent from methylene chloride to ether, we obtained an 82% yield of a different complex, mp 77–80 °C, which by both a nitrogen determination and GC analysis was shown to have a phenol–amine ratio of 3:2. The use of ethyl acetate as the reaction solvent also resulted in formation of the 3:2 complex.

The complexes listed in Table I could all be recrystallized in good yield and with a nearly constant melting point. Only four of the products were unstable at room temperature, and these decomposed only after some weeks. The products that decomposed were the 2:1 pyrocatechol–*n*-butylamine complex, the 3:2 pyrocatechol–morpholine complex, the 2:1 pyrocatechol–di-*n*-propylamine complex, and the 1:1 hydroquinone–morpholine complex.

We have determined the infrared spectra of the three complexes of resorcinol with *n*-butylamine, di-*n*-butylamine, and tri-*n*-butylamine, all as mulls in Fluorolube. All three complexes show multiple absorptions, characteristics of hydrogen-bonded structures, in the region 2500–3500 $cm^{-1}$, and both the di-*n*-butylamine and tri-*n*-butylamine complexes appear to lack absorption at a frequency characteristic of the $NH^+$ stretching frequency.[6] This evidence coupled with the ready solubility of these complexes in nonpolar solvents such as ether, methylene chloride, and ethyl acetate leads us to favor hydrogen-bonded structures rather than structures involving an actual proton transfer from the phenolic hydroxyl to the amine for these products. We recognize that this does not constitute proof, since the infrared evidence is not compelling, and it is possible that the complexes dissolve by first dissociating into the amine and phenol components.

If two simple postulates are accepted it becomes possible to write reasonable structures for these hydrogen-bonded structures. The postulates are that (1) the amine serves only as an acceptor in hydrogen bonding and it can accept only a single hydrogen and (2) the phenolic hydroxyl group can function as both an acceptor and a donor in hydrogen bonding, and the oxygen of a hydroxyl group whose hydrogen atom participates in a hydrogen bond is a better acceptor than the oxygen of a free hydroxyl group.

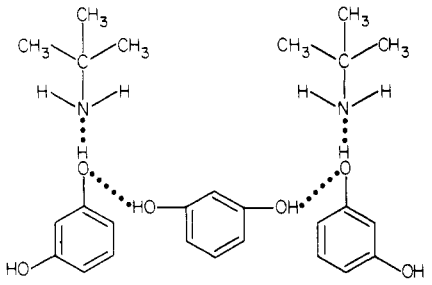
These postulates do not change significantly if the proton is fully transferred to the amine. Only a single cation is formed, and the phenolate ion is the preferred locus for formation of a hydrogen bond. The second hydrogen bond will be formed to the oxygen whose hydrogen was donated to form the first hydrogen bond.

The structures of both the 1:1 and the 2:1 complexes are obvious. A suggested structure for the 3:2 complexes is that shown in I for the resorcinol–*tert*-butylamine complex, and the 3:1 complexes can be depicted as in II for the resorcinol–tri-*n*-butylamine complex.

Although the postulates permit facile rationalization of whatever structures form, they provide no a priori basis

(5) For previous preparations of the resorcinol–diethylamine complex, see: Arshid, F. M.; Giles, C. H.; McClure, E. C.; Ogilvie, A.; Rose, T. J. *J. Chem. Soc.* **1955**, 67. Aarna, A.; Melder, L. *Chem. Abstr.* **1964**, *60*, 5196e.

(6) For a discussion of the infrared spectra of substituted ammonium ions, see: Bellamy, L. J. "The Infra-red Spectra of Complex Molecules", 3rd ed., Chapman and Hall: London, 1975; p 289.



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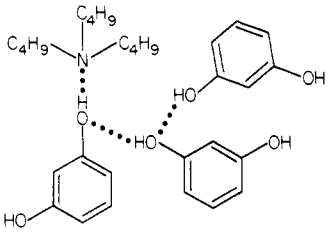

II

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.

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

Jay R. Luly and Henry Rapoport*

*Department of Chemistry, University of California, Berkeley, California 94720*

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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.

0022-3263/84/1949-1671$01.50/0 