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Synthesis of Substituted Diphenyl Ethers

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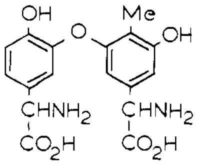
Several novel substituted diphenyl ethers (2–7) have been prepared by condensations of the appropriate potassium phenoxides and aryl bromides in the presence of Cu_2Cl_2 and Cu.

Ristocetin and related antibiotics contain a number of novel amino acids (*1*). Most of these amino acids are phenylglycines or phenylserines with hydroxyl groups and other substituents situated on the aromatic nuclei. A unique feature of the antibiotics is that the aromatic rings of the amino acids are coupled in dimeric or trimeric structures by either biphenyl (Ar–Ar′) or diphenyl ether (Ar–O–Ar′) linkages. The complexity of the coupled amino acids has complicated structure proofs; unequivocal elucidation of structures requires degradations, model studies, and independent syntheses. Six previously unreported diphenyl ethers were prepared in connection with our studies of dimeric amino acid **1** (*2*). The model compounds (**2–7**) are diphenyl ethers bearing two methoxy groups and two or three methyl groups in various arrangements. These compounds were synthesized by Ullmann condensations of potassium salts of substituted phenols with the appropriate aryl bromides in the presence of copper and cuprous ion as shown below.



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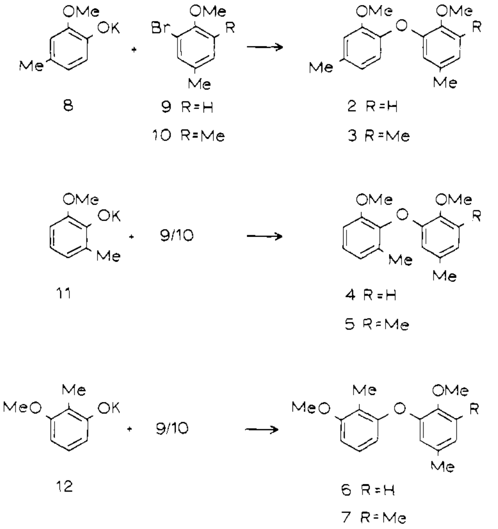
Although it is now apparent that these diphenyl ethers do not in actuality bear any significant relationship to the structure of **1**, it is possible that future studies of antibiotics in this series will result in isolation of dimeric amino acids with one or more of these substitution patterns.



Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727 spectrometer. NMR spectra were recorded on a JEOL MH-100 spectrometer using tetramethylsilane as an internal standard.

General Procedure for the Preparation of 2–7. Potassium methoxide (0.04 mol) was prepared by addition of excess dry MeOH under N_2 to 1.56 g (0.04 mol) of potassium metal in a 25-mL, three-necked flask equipped with a mechanical stirrer and a condenser. The phenol (0.032 mol), aryl bromide (0.04 mol), Cu_2Cl_2 (0.5 g), and Cu powder (0.5 g) were added. The mixture was heated to 100 °C under a stream of N_2 to remove MeOH and then at 200 °C for 7 h under a blanket of N_2. The mixture was cooled to room temperature, CH_2Cl_2 was added, and the mixture was decolorized with activated charcoal. The solution was washed with 5% NaOH and with H_2O and dried over $MgSO_4$. The solvent was evaporated and the product was isolated by distillation with a short-path apparatus.

The reaction of **8** (*3*) with **9** (*4*) gave diphenyl ether **2** (2-methoxy-1-(2-methoxy-4-methylphenoxy)-5-methylbenzene), bp 120–130 °C (0.25 mm), in 19% yield: NMR (CCl_4) δ 2.16 (Me), 2.26 (Me), 3.70 (2 × MeO), 6.58 (aryl multiplet); IR (neat) 2840, 1230, 1210, 1030 cm^{-1}; mass spectrum *m/e* 258 (M^+).

Analytical data were satisfactory.

The reaction of **8** with **10** (*5*) gave diphenyl ether **3** (3,5-dimethyl-2-methoxy-1-(2-methoxy-4-methylphenoxy)benzene), bp 130–140 °C (0.25 mm), in 22% yield: NMR (CCl_4) δ 2.18 (Me), 2.24 (Me), 2.34 (Me), 3.74 (MeO), 3.86 (MeO), 6.56 (aryl multiplet); IR (neat) 2830, 1220, 1040 cm^{-1}; mass spectrum *m/e* 272 (M^+).

Analytical data were satisfactory.

The reaction of **11** (*3*, *6*) with **9** gave diphenyl ether **4** (2-methoxy-1-(2-methoxy-6-methylphenoxy)-5-methylbenzene), bp 120–130 °C (0.25 mm), in 10% yield: NMR (CCl_4) δ 2.04 (Me), 2.10 (Me), 3.56 (MeO), 3.74 (MeO), 6.50 (aryl multiplet); IR (neat) 2840, 1230, 1030 cm^{-1}; mass spectrum *m/e* 258 (M^+).

Analytical data were satisfactory.

The reaction of **11** with **10** gave diphenyl ether **5** (3,5-dimethyl-2-methoxy-1-(2-methoxy-6-methylphenoxy)benzene), bp 130–140 °C (0.25 mm) in 12% yield: NMR (CCl_4) δ 2.06 (Me), 2.16 (Me), 2.20 (Me), 3.66 (MeO), 3.86 (MeO), 6.40 (aryl multiplet); IR (neat) 2840, 1230, 1040 cm^{-1}; mass spectrum *m/e* 272 (M^+).

Analytical data were satisfactory.

The reaction of **12** (Aldrich Chemical Co.) with **9** gave diphenyl ether **6** (2-methoxy-1-(3-methoxy-2-methylphenoxy)-5-methylbenzene), bp 120–130 °C (0.25 mm), in 42% yield: NMR (CCl_4) δ 2.18 (2 × Me), 3.62 (MeO), 3.70 (MeO), 6.54 (aryl multiplet); IR (CCl_4) 2850, 1230, 1040 cm^{-1}; mass spectrum *m/e* 258 (M^+).

Analytical data were satisfactory.

The reaction of **12** with **10** gave diphenyl ether **7** (3,5-dimethyl-2-methoxy-1-(3-methoxy-2-methylphenoxy)benzene), bp 130–140 °C (0.25 mm), in 23% yield: NMR (CCl_4) δ 2.16 (2 × Me), 2.20 (Me), 3.76 (2 × MeO), 6.62 (aryl multiplet); IR (CH_2Cl_2) 2850, 1240, 1020 cm^{-1}; mass spectrum *m/e* 272 (M^+).

Analytical data were satisfactory.

Literature Cited

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Corrections

In the calibration data for the paper, "Enthalpies of Formation and Calculated Detonation Properties of Some Thermally Stable Explosives," by Prince E. Rouse, Jr. (*J. Chem. Eng. Data*, **21**, 16 (1976)), systematic deviations, which were ignored in the calculation of the constants, *A* and *B*, suggest the possibility that the oxygen used in the combustions contained varying amounts of reactive impurities. This hypothesis is strengthened by the fact that the variances of groups of values of the quantity $\Delta t/(\Delta E_{BA} \cdot wt_{BA} + \Delta E_a + \Delta E_w - \Delta E_c)$ measured for a given sample size were significantly different at widely spaced times in the course of the measurements and, for groups of measurements made in close succession, varied with the size of the samples, being smallest for the largest samples.

Since the reaction of an explosive with an unknown reactive gas could produce a heat effect significantly different from that produced by reaction with oxygen, the accuracies of the reported enthalpies of formation were vitiated to unknown extents.

For the paper, "A Simple Formula for the Heat Capacity of Polyatomic Gases, with Constants for 143 Substances", by Philip A. Thompson (*J. Chem. Eng. Data*, **22**, (1977)), eq 10 and 20 should be corrected as follows:

$$\frac{\delta \hat{c}_v}{\hat{c}_v} = \frac{c_\omega - c_\alpha}{c_\omega x^2 + c_\alpha} \frac{2x^2}{1 + x^2} \left[\frac{\delta B}{B} - \frac{B\tau}{x} \frac{\delta \tau}{\tau} \right] \tag{10}$$

$$\frac{S^*}{R} = \frac{(c_\alpha + 1) + (c_\omega + 1)(B\tau)^2}{1 + (B\tau)^2} \ln (x + B\tau) + \frac{c_\omega - c_\alpha}{1 + (B\tau)^2} \left[\frac{1}{2} \ln (x^2 + 1) - B\tau \tan^{-1} x \right] \tag{20}$$