

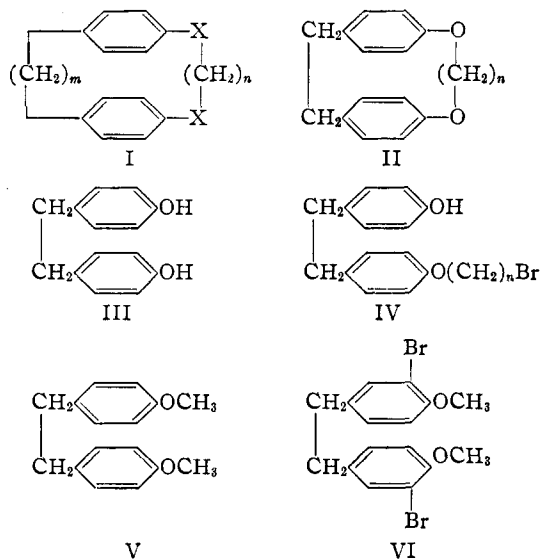
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Heterocycles Containing *p*-Phenylene Units. I. EthersBY REYNOLD C. FUSON AND HERBERT O. HOUSE¹

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A method has been developed for the synthesis of ethers of type II (in text) from 4,4'-dihydroxybiphenyl and polymethylene bromides. The members of this series in which *n* has values of 6 and 8 have been described.

Macrocycles containing two unsymmetrically substituted *p*-phenylene units, if of the appropriate size, may be expected to exhibit molecular asymmetry resulting from restricted rotation of the aromatic units.^{2,3} Heterocycles of type I, where X is the hetero atom and *m* has a value greater than one, should be especially suited to such a stereochemical study, the benzene rings being held approximately parallel and the hetero atoms permitting controlled introduction of the nuclear substituents requisite for asymmetry. Although carbocycles^{2,3,4} and heterocycles⁵⁻⁹ containing two *p*-phenylene units have been prepared, no synthetic method for the systematic preparation of heterocycles of type I has been described. The synthesis of such cycles where the hetero atom is oxygen (II) is reported in this paper, the method of ring closure being that of Lüttringhaus and co-workers.⁷⁻¹⁰



The required *p,p'*-dihydroxybiphenyl (III) was obtained from *p,p'*-dinitrobenzyl, which was produced by the action of air and alcoholic alkali on *p*-nitrotoluene. This novel coupling was first noted by Fischer and Hepp¹¹ and later studied more intensively by Green, Davies and Horsfall¹²

and by Plisov.¹³ The diphenol (III), on treatment with an excess of the polymethylene bromides and a limited amount of alkali,^{7-10,14} was converted to the *p*-(ω -bromo-*n*-alkoxy)-*p'*-hydroxybiphenyls (IV) where *n* had values of 4, 6, 8 and 10. The addition of these monoethers (IV), in high dilution, to a suspension of anhydrous potassium carbonate in refluxing isoamyl alcohol^{7-10,14} served to produce viscous oils from which the pure heterocycles (II) were obtained where *n* had values of 6 and 8. The viscous oils, resulting from the attempted preparation of the heterocycle II in which *n* = 4 and 10, could not be induced to crystallize.

The diphenol (III) was methylated to give *p,p'*-dimethoxybiphenyl (V) which served as a model compound for bromination studies. In glacial acetic acid, even at steam-bath temperature, only the dibromo derivative, believed to have the structure VI, could be obtained. The same compound was reported to result when the bromination was conducted in chloroform.¹⁵

The infrared spectra of the heterocycles (II), which would be expected to be relatively strain free, did not exhibit the abnormalities noted in the carbocycles (paracyclophanes) prepared by Cram and Steinberg.² Indeed the spectra differed from the spectrum of the open chain analog, *p,p'*-dimethoxybiphenyl (V), only in the details summarized in Table I.

TABLE I

Compound	Region of absorption characteristic of aromatic systems, cm. ⁻¹	Region of absorption characteristic of <i>p</i> -substitution, cm. ⁻¹
V	1610 (2) ^a 1582 (1) 1508 (4)	833 (4)
II (<i>n</i> = 6)	1612 (3) 1585 (1) 1514 (7)	822 (4) 805 (2)
II (<i>n</i> = 8)	1611 (3) 1582 (1) 1513 (7)	818 (5) 800 (2)

^a The numbers in parentheses indicate approximately the relative intensities of the bands in each of the spectra determined.

Experimental¹⁶

p,p'-Dinitrobenzyl.¹²—A mixture of 100 g. of *p*-nitrotoluene and 2 l. of 30% methanolic potassium hydroxide, cooled to 10°, was stirred vigorously while a rapid stream of air was introduced. The temperature of the reaction mixture was maintained at 5–10° for 2 hours by means of an ice-bath. After the cooling bath was removed, air was passed through the mixture, with vigorous stirring, for an

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(16) All melting points are corrected. The infrared spectra were determined and interpreted by Miss Helen Miklas. The microanalyses are by Mrs. Katherine Pih, Miss Emily Davis, Mrs. Jeanne Fortney, Mrs. Esther Fett and Mr. Joseph Nemeth.

- (1) Atomic Energy Commission Predoctoral Fellow, 1951–1952.
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additional 6 hours. The red-brown pasty mixture was filtered with suction and the residue, while still on the filter, was washed with 2 l. of boiling water followed by 300 ml. of ethanol. The residual solid was recrystallized from benzene; yield 75 g. (76%); recrystallization from benzene gave yellow needles melting at 179–180°.

***p,p'*-Diaminobibenzyl.**¹⁷ (A) **Reduction with Powdered Iron.**—A mixture of 200 g. of powdered iron, 126.2 g. of *p,p'*-dinitrobibenzyl, 500 ml. of water and 500 ml. of ethanol was heated to boiling, with stirring. A solution of 12 ml. of concentrated hydrochloric acid in 50 ml. of water and 50 ml. of ethanol was added dropwise to the refluxing mixture. The resulting mixture was boiled under reflux with stirring for 7 hours. After sufficient ethanol had been added to bring all the diamine into solution, the reaction mixture was made alkaline to litmus with 10% aqueous sodium hydroxide and filtered while hot. The cold solution deposited 92.5 g. (93.8%) of tan plates melting at 129–135°. A solution of the diamine in a boiling ethanol–water mixture, after being decolorized with Norit, was cooled to give white plates, m.p. 135–137°.

(B) **Catalytic Hydrogenation.**—A mixture of 100.0 g. of *p,p'*-dinitrobibenzyl, 32 g. of commercial Raney nickel and 1 l. of commercial absolute ethanol was placed in a 2-l. hydrogenation bomb and subjected to an initial hydrogen pressure of 1050 p.s.i. While the bomb was shaken, the temperature was slowly raised to 60°. The theoretical amount of hydrogen was taken up over a period of 4.5 hours. The mixture was heated to boiling, diluted with 1500 ml. of water, treated with Norit and filtered. The cold solution deposited tan plates melting at 132–136°, the yield of crude product being quantitative. The pure diamine melted at 135–136.5°.

***p,p'*-Dihydroxybibenzyl.**^{18,19}—To a solution of 21.7 g. of *p,p'*-diaminobibenzyl in 75 ml. of concentrated hydrochloric acid and 400 ml. of water, cooled to 5°, was added dropwise, with stirring, a solution of 14.1 g. of sodium nitrite in 100 ml. of water. After the addition was complete, the solution was stirred for 20 minutes and then the excess nitrous acid was destroyed with urea. The cold solution was added dropwise to the top of a tube through which a vigorous stream of steam was passed. The resulting mixture, collected at the bottom of the tube, was heated to boiling, cooled and filtered with suction. The residue was taken up in a solution of 40 g. of sodium hydroxide in 1 l. of water, decolorized with Norit and reacidified with concentrated hydrochloric acid. The resulting solid was recrystallized from an ethanol–water mixture to give tan plates melting over the range 181–195°. A solution of the diphenol in a boiling ethanol–water mixture, after being decolorized with Norit, was cooled to give 13.9 g. (64%) of white plates, m.p. 193–196°. An additional recrystallization from an ethanol–water mixture gave white plates melting at 195–196°.

Diacetate.—A solution of 1.0 g. of the diphenol in 20 ml. of acetic anhydride was boiled under reflux for 90 minutes. The hot reaction mixture was poured with stirring into 200 ml. of boiling water. The resulting mixture was cooled and filtered. Three recrystallizations of the residue from ethanol yielded the diacetate as white plates, m.p. 115–116°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.08. Found: C, 72.77; H, 6.28.

***p,p'*-Dimethoxybibenzyl.**¹⁹—To a solution of 3.20 g. of *p,p'*-dihydroxybibenzyl and 20 g. of sodium hydroxide in 60 ml. of water was added 2.0 ml. of methyl sulfate. The mixture, after being boiled under reflux for 14 hours, was cooled, diluted with an equal volume of water and filtered. The dimethyl ether, after decolorization with Norit, was recrystallized from ethanol; yield 1.35 g. (37.4%), m.p. 115–123°. A recrystallization from petroleum ether (b.p. 90–120°) followed by two additional recrystallizations from ethanol gave 0.91 g. (25%) of long white needles, m.p. 125.5–126.5°. The infrared spectrum of the ether exhibits, in addition to those listed in the table, an absorption band at 1244 cm^{-1} , attributable to a phenyl–oxygen group, and a second at 1052 cm^{-1} , attributable to a carbon–oxygen grouping.

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(19) E. M. Richardson and E. E. Reid, *This Journal*, **62**, 413 (1940).

Bromination of *p,p'*-Dimethoxybibenzyl.¹⁸—A solution of 0.86 g. of bromine in 30 ml. of glacial acetic acid was added dropwise to a stirred solution of 0.20 g. of *p,p'*-dimethoxybibenzyl in 30 ml. of glacial acetic acid. The resulting mixture, after being stirred for 35 minutes, was poured into 300 ml. of water. The solid was recrystallized from ethanol; yield 0.20 g. (61%), m.p. 143–146°. Two additional recrystallizations of the dibromide from ethanol gave white needles, m.p. 146.5–147.5°.

Anal. Calcd. for $C_{18}H_{18}Br_2O_2$: C, 48.00; H, 4.03; Br, 39.94. Found: C, 47.93; H, 4.00; Br, 39.80.

***p*-Hydroxy-*p'*-(ω -bromo-*n*-butoxy)-bibenzyl.**—To a refluxing solution of 10.00 g. (0.0468 mole) of *p,p'*-dihydroxybibenzyl and 58.4 g. (0.270 mole) of tetramethylene bromide in 200 ml. of commercial absolute ethanol was added over an 85-minute period, with stirring, 16.0 ml. (0.0288 mole) of 1.49 *N* ethanolic potassium hydroxide. The mixture was boiled under reflux, with stirring, for an additional 80 minutes and then poured into 800 ml. of boiling water. After removal of the dihalide layer, the hot, aqueous phase was extracted with two 200-ml. portions of petroleum ether (b.p. 90–120°). The remaining water solution was heated to boiling and, after being decolorized with Norit, was chilled; 3.51 g. of the unchanged diphenol was recovered. After removal of the solvent from the combined dihalide and petroleum ether layers by distillation, the residue was distilled *in vacuo*; 40.4 g. of the unchanged dihalide was isolated. The material remaining in the pot was dissolved in boiling ethanol and the solution was decolorized with Norit. The residue, obtained by removing the ethanol under an air blast, was extracted with two 100-ml. portions of boiling petroleum ether (b.p. 90–120°). The cool extract deposited white crystalline material which was sublimed at a pressure of 0.1 mm. while the temperature of the heating jacket was slowly raised to 215°. After a solution of the sublimate in boiling methanol was decolorized with Norit, the solvent was removed under an air blast. The residue was recrystallized twice from ethanol–water mixtures and, finally, twice from petroleum ether (b.p. 90–120°) to give 1.62 g. (16.2%) of white plates melting at 101–102°. The infrared spectrum of the material exhibits an absorption band at 3345 cm^{-1} , attributable to a hydroxyl group.

Anal. Calcd. for $C_{18}H_{21}BrO_2$: C, 61.90; H, 6.06; Br, 22.88. Found: C, 62.22; H, 6.20; Br, 22.88.

***p*-Hydroxy-*p'*-(ω -bromo-*n*-hexoxy)-bibenzyl.**—By the procedure just described 10 g. of the dihydroxybibenzyl was treated with 50 g. of hexamethylene bromide, the period of addition being 65 minutes and the time of subsequent refluxing 150 minutes. The diphenol recovered amounted to 4.07 g.; 47.4 g. of the dihalide was also recovered. A boiling methanolic solution of the material remaining after distillation of the dihalide was decolorized with Norit and chilled to give a white solid melting at 75–80°. The solid was sublimed at a pressure of 0.1 mm. while the temperature of the heating jacket was slowly raised to 215°. The sublimate was recrystallized once from an ethanol–water mixture and then twice from petroleum ether (b.p. 90–120°) to yield 1.71 g. (15.7%) of white plates melting at 84–85.5°. An additional recrystallization from petroleum ether (b.p. 90–120°) gave white plates, m.p. 85–86°. The infrared spectrum of the material exhibits an absorption band at 3384 cm^{-1} , attributable to a hydroxyl group.

Anal. Calcd. for $C_{20}H_{25}BrO_2$: C, 63.66; H, 6.63; Br, 21.18. Found: C, 63.89; H, 6.69; Br, 21.16.

It was found in this case that the use of a greater excess of the dihalide both increases the yield of the desired product and allows the product to be isolated in a satisfactory state of purity without recourse to sublimation. Thus the treatment of 12.00 g. (0.0562 mole) of *p,p'*-dihydroxybibenzyl and 150 g. (0.615 mole) of hexamethylene dibromide with 20.0 ml. (0.0294 mole) of 1.49 *N* ethanolic potassium hydroxide yielded 3.40 g. (30.6%) of white plates melting at 83–85°. The unchanged diphenol recovered amounted to 4.9 g.; the unchanged dihalide weighed 107.0 g.

***p*-Hydroxy-*p'*-(ω -bromo-*n*-octyloxy)-bibenzyl.**—The alkylation procedure was applied to a mixture of 10 g. of *p,p'*-dihydroxybibenzyl and 61.2 g. of octamethylene bromide. The mixing time was 80 minutes and the duration of the subsequent refluxing was 110 minutes. The unchanged diphenol amounted to 4.07 g., the dihalide to 40.2 g. A boiling ethanolic solution of the material remaining in the pot

after distillation of the dihalide was decolorized with Norit. The residue, left by evaporation of the solvent under an air blast, was extracted with petroleum ether (b.p. 90–120°) and the solvent removed from the extract under an air blast. The product was sublimed at a pressure of 0.1 mm. while the temperature of the heating jacket was slowly raised to 240°. The sublimate was recrystallized once from an ethanol-water mixture and then twice from petroleum ether (b.p. 90–120°) to give 3.10 g. (26.5%) of white plates, m.p. 89–90°. The infrared spectrum of the material exhibits an absorption band at 3381 cm.⁻¹, attributable to a hydroxyl group.

Anal. Calcd. for C₂₂H₂₉BrO₂: C, 65.17; H, 7.21; Br, 19.71. Found: C, 65.43; H, 7.20; Br, 19.69.

***p*-Hydroxy-*p'*-(ω -bromo-*n*-decyloxy)-bibenzyl.**—Ten grams of *p,p'*-dihydroxybibenzyl and 60.0 g. of decamethylene bromide were employed, the mixing time being 3 hours after which the mixture was heated under reflux for 40 minutes. The unchanged diphenol amounted to 1.6 g., the dihalide to 49.8 g. The residue after distillation of the dihalide was extracted with 200 ml. of boiling petroleum ether (b.p. 90–120°). The cool extract deposited white crystals melting at 79–87°. The product was sublimed at a pressure of 0.05–0.09 mm. while the temperature of the heating jacket was slowly raised to 230°. The yield was 2.36 g. (19.0%) of white sublimate melting at 90–94°. Recrystallization from an ethanol-water mixture, from methanol and, finally, from petroleum ether (b.p. 90–120°) gave white plates, m.p. 93–94.5°. The infrared spectrum of the compound exhibits an absorption band at 3387 cm.⁻¹, attributable to a hydroxyl group.

Anal. Calcd. for C₂₄H₃₃BrO₂: C, 66.50; H, 7.67; Br, 18.44. Found: C, 66.48; H, 7.89; Br, 18.70.

Cyclization of *p*-Hydroxy-*p'*-(ω -bromo-*n*-octyloxy)-bibenzyl.—A 1-l., three-necked, creased flask was fitted with a stainless steel stirrer driven by a 10,000 r.p.m. motor, controlled by a variac, and the high-dilution apparatus described by Leonard and Sentz.²⁰ A solution of 1.34 g. (0.0033 mole) of *p*-hydroxy-*p'*-(ω -bromo-*n*-octyloxy)-bibenzyl in 55 ml. of isoamyl alcohol was added in high dilution, over a period of 2 hours and with stirring, to a suspension of 3.00 g. (0.0218 mole) of anhydrous potassium carbonate in 250 ml. of refluxing isoamyl alcohol. After the addition was complete, the mixture was boiled under reflux, with stirring, for an additional hour, cooled and filtered. After the solvent was removed from the filtrate by distillation *in vacuo*, the residue was taken up in boiling ethanol and decolorized with Norit. The cold solution deposited an amorphous white solid which, since it melted over a wide range

even after repeated reprecipitation, was assumed to be polymeric. Evaporation of the mother liquor under an air blast left only a yellow oil which was taken up in acetone. The acetone was removed on a steam-bath and the residue distilled *in vacuo* in a short-path still. The yield was 0.32 g. (30%) of yellow oil, collected at a bath temperature of 230–240° under a pressure of 0.3 mm. The material gives a negative Beilstein halogen test and its infrared spectrum exhibits no absorption band ascribable to a hydroxyl group. After standing several weeks, the oil crystallized in yellow needles which were dissolved in a minimum quantity of petroleum ether (b.p. 30–60°). The solution when cooled in a solid carbon dioxide-acetone-bath deposited white needles which were quickly collected on a filter. Following this procedure the material was recrystallized once more from petroleum ether (b.p. 30–60°) and, finally, once from *n*-hexane to give white needles, m.p. 56.5–58°. The infrared spectrum of the cyclic diether exhibits, in addition to those listed in the table, absorption bands at 1236 and 1248 cm.⁻¹, attributable to a phenyl-oxygen group, and at 1018 cm.⁻¹, attributable to a carbon-oxygen grouping.

Anal. Calcd. for C₂₂H₂₈O₂: C, 81.44; H, 8.70; mol. wt., 324.4. Found: C, 81.25; H, 8.74; mol. wt. (Rast), 312.

Cyclization of *p*-Hydroxy-*p'*-(ω -bromo-*n*-hexoxy)-bibenzyl.—A solution of 1.03 g. (0.00276 mole) of *p*-hydroxy-*p'*-(ω -bromo-*n*-hexoxy)-bibenzyl in 60 ml. of isoamyl alcohol was added, in high dilution, over a period of 2.25 hours, to a stirred suspension of 3.00 g. (0.0218 mole) of anhydrous potassium carbonate in 300 ml. of refluxing isoamyl alcohol. After the addition was complete, the mixture was boiled under reflux, with stirring, for an additional 30 minutes and worked up as described previously. The yield was 0.21 g. (26%) of yellow oil, collected at a bath temperature of 195–280° under a pressure of 0.3 mm. Since a Beilstein halogen test indicated that the oil was not halogen free, the material was redistilled at a bath temperature of 205–220° under a pressure of 0.3 mm. to give a light-yellow, halogen-free oil. The infrared spectrum of the material exhibits no absorption band ascribable to a hydroxyl group. The oil was dissolved in *n*-hexane and the solution cooled in a solid carbon dioxide-acetone-bath. A white solid separated which was dissolved in *n*-hexane and reprecipitated by cooling as before. The resulting white solid melted at 43–44.5°. The infrared spectrum of the diether exhibits, in addition to those listed in the table, an absorption band at 1248 cm.⁻¹, attributable to a phenyl-oxygen group, and a second weak, broad band at 1005–1040 cm.⁻¹, attributable to a carbon-oxygen grouping.

Anal. Calcd. for C₂₀H₂₄O₂: C, 81.04; H, 8.16; mol. wt., 296.4. Found: C, 80.90; H, 8.41; mol. wt. (Rast), 266.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Heterocycles Containing *p*-Phenylene Units. II. Amines

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A method of synthesis of heterocycles of type II (in text) has been developed. The macrocyclic diamines in which *n* has values of 4, 6, 8 and 10 are described.

Heterocycles of type I, where X is the hetero atom and *m* has a value greater than one, are expected to be of especial interest in a study of the stereochemistry of cycles containing two *p*-phenylene units.² In particular heterocycles of type I where the hetero atom is nitrogen(II) are of interest. Following the introduction of either one or two appropriate nuclear substituents, the basic hetero atoms could serve as functional groups for the resolution of the compound if the rotation of

the aromatic units proves to be restricted. This paper reports a synthetic route to heterocycles of type II, the method of ring closure being a modification of that previously described by several investigators.^{3–8} The use of dimethylformamide

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(6) K. Ziegler and P. Orth, *Ber.*, **66**, 1887 (1933).

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(1) Atomic Energy Commission Predoctoral Fellow, 1951–1952.

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