it can be hoped that the properties will vary smoothly with structure.

A relationship between the boiling point and the molecular weight is shown in Fig. 4. The boiling points, after 10° is added for each first alkyl branch and 5° for each second branch, define a fairly smooth curve. This curve is essentially a graphical representation, and confirmation, of a correlation proposed by Francis.[14]

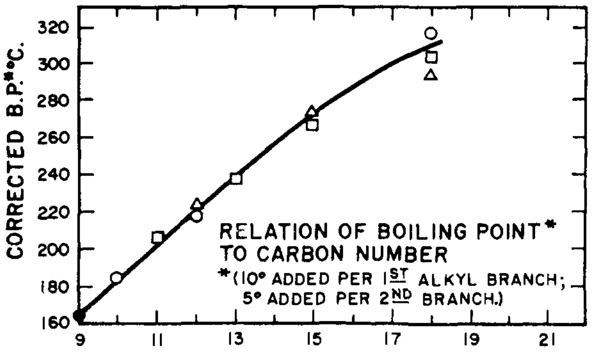

Fig. 4.—Relation of boiling point to carbon number of 1,3,5-trialkylbenzenes.

In Fig. 5, the specific refraction, calculated from the refractive index and density by the equation shown, is plotted against the number of carbon atoms in the molecule. 1,3,5-Trimethylbenzene is considered as the parent compound. The points along the upper curve belong to compounds formed by the replacement of one or more of the methyl groups of 1,3,5-trimethylbenzene by a primary or secondary alkyl group. The points along the lower curve represent compounds formed by the replacement of one or more methyl groups by a *t*-butyl group. The two curves show that normal and secondary groups give a higher specific refraction to the molecule than do tertiary groups.

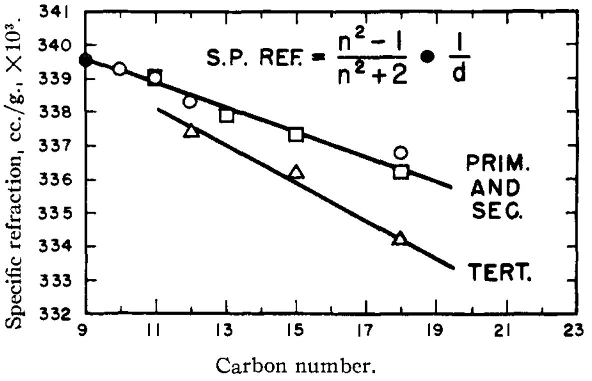

Fig. 5.—Relation of specific refraction to carbon number.

From a theoretical view, these curves are of interest because they show that normal and secondary alkyl groups increase the polarizability of a benzene ring more than do tertiary groups. From a practical view, they could be useful in assigning configuration to unknown trialkylbenzenes.

Acknowledgment.—The authors are indebted to Seymour Meyerson for obtaining and interpreting the mass spectrum; L. J. Schmauch for constructing the automatic slit mechanisms for the infrared spectrometers; Betty Ellen Ries for obtaining the ultraviolet spectra; M. C. Hoff and F. S. Jones for determining melting points; and R. J. Hengstebeck for making valuable suggestions.

WHITING, INDIANA

[14] A. W. Francis, *Chem. Revs.*, **42**, 107 (1948).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Synthesis and Fungistatic Activity of Some 3-Hydroxybiphenyl Derivatives

BY CHARLES K. BRADSHER, FRANCES C. BROWN AND HARDIN K. PORTER

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The reported toxicity of 2- and 3-phenanthrol toward *Aspergillus niger* has been confirmed and shown to be general for some fluorenols and hydroxybiphenyls. Introduction of an alkyl group into the 4-, 6- or 4′-position of 3-hydroxybiphenyl failed to enhance its fungistatic activity.

Of a group of more than eighty phenanthrene derivatives tested for fungistatic activity against *Aspergillus niger*, Steinberg[1] found 3-phenanthrol to be the most active. Using the same organism but another testing method[2] we have confirmed the high fungitoxic activity of 3-phenanthrol and its superiority in this respect to 2-phenanthrol. Tests on some related fluorenols and hydroxybiphenyls (Table I) revealed that 3-hydroxybiphenyl[3] was equal or superior to any in the group.

It is a well-known phenomenon that the introduction of an alkyl side-chain will often increase the *bactericidal* activity of simple phenols.[4] Thus it seemed worthwhile to determine whether a similar modification in the structure of 3-hydroxybiphenyl might increase its activity toward *A. niger*.

A survey of the literature revealed a description of two alkyl-3-hydroxybiphenyls,[5] formulated as the 4-propyl and 6-propyl derivatives. It has now been shown that the structure postulated for the first is correct while that for the second is erroneous.[6]

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[1] R. A. Steinberg, *J. Agr. Research*, **60**, 765 (1940).

[2] J. M. Leonard and V. L. Blackford, *J. Bact.*, **57**, 339 (1949).

[3] The activity of 3-hydroxybiphenyl and its congeners against certain wood-damaging fungi was discussed by I. Hatfield, *Proc. Am. Wood-Preservers' Assoc.*, **31**, 57 (1935).

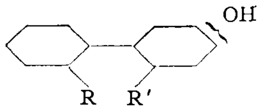
[4] For a review dealing in part with this subject see C. M. Suter, *Chem. Revs.*, **28**, 269 (1941).

[5] S. E. Harris and W. G. Christiansen, *J. Am. Pharm. Assoc.*, **23**, 530 (1934).

[6] A molecular weight determination but no analysis was reported for the "3-hydroxy-6-propylbiphenyl" of Harris and Christiansen. Both the composition and structure of the product are unknown.

Table I

Fungistatic Action of Some Phenolic Compounds against *A. niger*



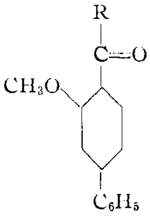
Name	R	R'	Inhibition, % at p.p.m. 50[a]	20	10
2-Phenanthrol[b]	—CH=CH—		40	34	30
3-Phenanthrol[b]	—CH=CH—		100	64	41
2-Fluorenol	—CH_2—		100	31	9
3-Fluorenol[c]	—CH_2—		46	16	0
3-OH-biphenyl	H	H	100	73	48
4-OH-biphenyl[d]	H	H	80	30	20

[a] All showed complete inhibition of growth at 100 p.p.m. [b] L. F. Fieser, This Journal, 51, 2460 (1929). [c] W. C. Lothrop, *ibid.*, 61, 2115 (1939). [d] Distillation Products Industries.

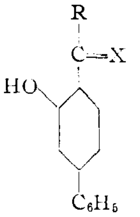
Our first plan was to study the acylation of 3-methoxybiphenyl by the Friedel–Crafts reaction. The necessary 3-methoxybiphenyl was prepared from 3-aminobiphenyl by the elegant but little-used procedure of Hodgson and Foster.[7] While the yield from the amine was only 57.5% this proved better than our over-all yield *via* the phenol. Indeed, our experience was that the best route to the phenol was *via* the ether.[8]

According to the previous reports the propionylation of 3-methoxybiphenyl occurs at the 6-position. Using carbon disulfide as a solvent and following as best we could the directions of Harris and Christiansen[5] we obtained a solid, m.p. 106–108°. This product could be obtained in much better yield (71%) when the propionylation was carried out in methylene chloride using the propionyl chloride–aluminum chloride Baddeley complex.[9] The product gave a red color with ferric chloride and proved identical with the hydroxy ketone obtained from 3-propionoxybiphenyl by the Fries reaction as described by Harris and Christiansen. These authors assigned to this Fries product the structure II since they believed that the possibility that acylation would occur at the other *ortho* (2) position was unlikely for steric reasons. We have demonstrated the correctness of their hypothesis by a synthesis starting with the known 3-nitro-4-bromobiphenyl. The nitrile IV obtained by the Rosenmund–von Braun reaction was found to undergo the Reinders and Ringer[10] displacement of the nitro group by methoxyl in excellent yield. The 3-methoxy-4-propiobiphenyl (I, R = C_2H_5) was converted to the 3-hydroxy analog (II, R = C_2H_5) by heating it in methylene chloride solution with aluminum chloride. This hydroxy ketone proved identical with the hydroxypropiobiphenyl of Harris and Christiansen.[5]

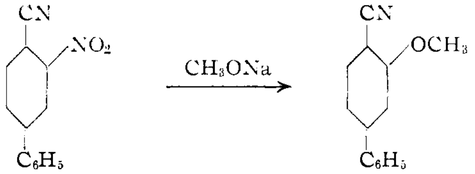
Through no modification of our Friedel–Crafts procedure were we able to obtain the "3-methoxy-6-propiobiphenyl" (m.p. 72°) of the earlier workers although we did find that by moderating the conditions, 3-methoxy-4-propiobiphenyl (I, m.p. 68.5–69°) was obtained. Our product gave no color with ferric chloride.[11]



I



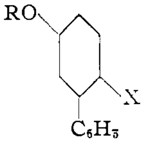
II, X = O
III, X = H_2



IV
V

By the reduction of the corresponding ketones II, 3-hydroxy-4-alkylbiphenyls (III, R = CH_3, C_2H_5 and C_3H_7) were obtained.

In order to prepare some 6-alkyl-3-hydroxybiphenyls (X)[12] we undertook the synthesis of 3-methoxy-6-cyanobiphenyl (VIII) which was unknown at that time. Our starting material was 3-hydroxy-6-aminobiphenyl[13] (VI) which afforded in 49% yield the 3-methoxy-6-iodobiphenyl (VII). The iodide VII was converted to the nitrile VIII by the Rosenmund–von Braun reaction. This synthesis was found less satisfactory than that recently published.[14] When the nitrile VIII was treated with ethylmagnesium bromide we obtained (on hydrolysis) a liquid ketone (IX, R = C_2H_5) entirely unlike that reported earlier as 3-methoxy-6-propiobiphenyl. The ketone was reduced by the Huang-Minlon[15] procedure and the ether cleaved to yield the liquid[16] 3-hydroxy-6-propylbiphenyl (X, R = C_3H_7). The next lower homolog, 3-hydroxy-6-ethylbiphenyl (X, R = CH_3) has also been prepared by the same general synthesis.



VI, R = H, X = NH_2
VII, R = CH_3, X = I
VIII, R = CH_3, X = CN
IX, R = CH_3, X = COR
X, R = H, X = CH_2R

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(7) H. H. Hodgson and C. K. Foster, *J. Chem. Soc.*, 581 (1942).

(8) Within the limitations set forth by Hodgson and Foster (ref. 7) with regard to their method, the preparation of phenolic compounds from amines *via* the methyl ether may be recommended when the desired phenol is quite reactive and not sufficiently volatile with steam to allow its rapid removal from contact with the diazonium solution.

(9) The name Baddeley complex is suggested for the methylene chloride-soluble complex formed by addition of one mole of acyl halide to one mole of aluminum chloride; *cf.* Baddeley, *J. Chem. Soc.* suppl. S99 (1949).

(10) W. Reinders and W. E. Ringer, *Rec. trav. chim.*, **18**, 326 (1899).

(11) The earlier workers based their structural assignment on the absence of color when their product (m.p. 72°) was treated with ferric chloride.

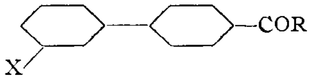
(12) While by accepted rules of nomenclature this and certain other compounds to be discussed would be classified as 5-hydroxy derivatives, it is felt that the present system makes clearer the structural relationship to other compounds mentioned in this paper.

(13) G. M. Kosolapoff (to Monsanto Chemical Company), U. S. Patent 2,355,593 (August 8, 1944).

(14) C. K. Bradsher and W. J. Jackson, Jr., This Journal, **74**, 4880 (1952).

(15) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

(16) Although it has been reported (ref. 5) that this material is a solid, melting at 140–141°, our sample has not solidified after standing for nearly two years.

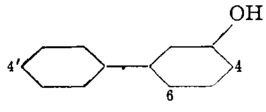


XI, X = NO_2
XII, X = NH_2
XIII, X = OCH_3
R = CH_3, C_2H_5, C_3H_7

For the synthesis of 3-hydroxy-4′-alkylbiphenyls, it was found convenient to begin with the acylation, by the Friedel–Crafts method, of 3-nitrobiphenyl. Berliner and Blommers[17] have shown that acetylation in this reaction occurred at the 4′-position, yielding XI (R = CH_3). In the same way we have carried out propionylation and butyrylation of 3-nitrobiphenyl to yield the expected ketones XI. The corresponding amines XII were obtained by reduction with stannous chloride and the amino group was then replaced by methoxyl using Hodgson and Foster's method.[7] The 3-methoxy-4′-acylbiphenyls (XIII) were reduced by the Huang-Minlon method with concurrent ether cleavage to yield the desired 3-hydroxy-4′-alkylbiphenyls.

TABLE II

FUNGISTATIC ACTIVITY OF SOME ALKYL DERIVATIVES OF 3-HYDROXYBIPHENYL (AGAINST *A. niger*)



Alkyl	Inhibition, % at p.p.m. 100[a]	50	20	10
None	100	100	73	48
4-C_2H_5	78	34	9	1
6-C_2H_5	100	73	58	48
6-C_3H_7	100	70	43	32
4′-C_2H_5	19	...	..	..

[a] All compounds listed in this table caused 100% inhibition at 250 p.p.m. Failing to cause complete inhibition at 250 p.p.m., and per cent. inhibition of growth: 4-C_3H_7, 72; 4-C_4H_9, 39; 4′-C_3H_7, 20; 4′-C_4H_9, 59.

Although several of the new alkyl-3-hydroxybiphenyls possess marked fungicidal activity it can be seen from Table II that present indications are that introduction of the alkyl group does not increase the toxicity of the parent compound toward *A. niger*. Since the greatest loss in toxicity was produced by introduction of an alkyl group into the most remote position in the molecule, it does not appear that this loss in activity can be attributed solely to a change in the *pK* of the phenolic hydroxyl group.

Experimental

3-Methoxybiphenyl.[7]—The diazotization of 3-aminobiphenyl (I)[18] was accomplished by treating the chilled (below 5°) and stirred solution of the amine (48 g.) in a solution containing concentrated hydrochloric acid (51.5 ml.) and water (290 ml.) with a solution of 20.5 g. of sodium nitrite in 57 ml. of water. To this solution was added 23.2 g. of zinc chloride, forming a white crystalline salt which was filtered off after 30 minutes stirring. The salt was dried overnight in a vacuum desiccator. The dried salt was added to 410 ml. of absolute methanol and after gentle application of heat nitrogen was evolved vigorously. When gas evolution subsided, the solution was refluxed for 30 minutes and then cooled. The methanol solution was concentrated to 150 ml. and the methanol gradually replaced by addition of benzene to the distilling liquid. The benzene solution was washed free of zinc salts and concentrated, and the residue remethylated with sodium hydroxide and dimethyl sulfate.[19] The methylation product was taken up in methylene chloride and the solution washed, dried and concentrated. The residue was fractionated under reduced pressure yielding 30 g. (57.5%) of a pale yellow liquid; b.p. 120–123° (1.5 mm.), n^{23}D 1.6118 (lit.[5] b.p. 140° (5 mm.)).

3-Hydroxybiphenyl was obtained in 63% yield from the ether II by the action of hydrobromic and acetic acids, m.p. 73–74.5° (lit.[20] 75° (uncor.)).

3-Methoxy-4-acetobiphenyl (I, R = CH_3).—To a solution of acetyl chloride (1.9 ml.) in 30 ml. of dry ethylene chloride 3.6 g. of aluminum chloride was added and the mixture was refluxed for 30 minutes to effect solution. To this a solution of 3-methoxybiphenyl (5.0 g.) in dry ethylene chloride was added over a period of 15 minutes the temperature being maintained at 35°. After an additional period of 30 minutes at this temperature, the reaction mixture was decomposed with ice and 10% hydrochloric acid. The product was taken up in methylene chloride and the solution washed and dried over anhydrous magnesium sulfate. The dry solution was concentrated and the residue distilled under reduced pressure yielding 2.9 g. (47.5%) of an oil, b.p. 176–180° (2 mm.), which solidified to a white solid, m.p. 75–76°. Recrystallized from ethanol, the product consisted of rectangular white plates, m.p. 77–78°.

Anal.[21] Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.40; H, 6.36.

An alcoholic solution of the compound gave no red color when treated with ferric chloride solution.

The **semicarbazone** of the ketone was prepared as white crystals from ethanol, m.p. 191–192°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: C, 67.82; H, 6.05. Found: C, 67.60; H, 6.09.

3-Hydroxy-4-acetobiphenyl (II, R = CH_3).—A Baddeley[9] complex from 10 ml. of acetyl chloride and 18.5 g. of aluminum chloride was prepared in dry methylene chloride (75 ml.) and to this solution was added 25 g. of 3-methoxybiphenyl in 75 ml. of methylene chloride. The mixture was refluxed for 11 hours and then allowed to stand at room temperature for 9 hours longer. When the product was worked up as in the case of I (R = CH_3) 19.5 g. of crude distillate, b.p. 164–180° (2.5 mm.), was obtained, m.p. 68–78°. After two recrystallizations from cyclohexane, clusters of white needles were obtained in an over-all yield of 50%, m.p. 89–91°. The analytical sample melted at 90.5–91.5°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70. Found: C, 79.25; H, 5.85.

The compound gave an intense red color when an ethanol solution was treated with ferric chloride. The compound was practically insoluble in aqueous 10% sodium hydroxide solution and only slightly soluble in Claisen alkali.

3-Methoxy-4-propiobiphenyl (I, R = C_2H_5). **(a) By the Friedel–Crafts Reaction.**—This compound was prepared in a manner analogous to that used in making the aceto analog (I, R = CH_3). From 5 g. of 3-methoxybiphenyl 2.40 g. (37%) of distillate, b.p. 173–185° (2 mm.), was obtained, solidifying to a white solid, m.p. 63–65°. Repeated recrystallization yielded colorless prisms, m.p. 68.5–69°.

(b) **By the Grignard Reaction.**—Ethylmagnesium bromide was prepared in the usual way from 9.4 g. of ethyl bromide and an ethereal solution containing 3.7 g. of 3-methoxy-4-cyanobiphenyl (V) added over a period of 20 minutes. The mixture was refluxed overnight and then hydrolyzed by boiling with 2 *N* hydrochloric acid, the ether being allowed to distil. The oil left at the end of the short hydrolysis period was taken up in ether, the ethereal solution washed, dried and concentrated. The residue 3.5 g. (82.5%) melted at 67–69° and on recrystallization from eth-

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(17) E. Berliner and E. A. Blommers, THIS JOURNAL, **73**, 2479 (1951).

(18) F. Fichter and A. Sulzberger, *Ber.*, **37**, 878 (1904).

(19) If this step was omitted the presence of a small amount of 3-hydroxybiphenyl rendered subsequent fractionation difficult. The methylation procedure was based upon that of J. Buck, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 619.

(20) P. Jacobson and A. Loeb, *Ber.*, **36**, 4082 (1903).

(21) Analyses by Micro-Tech Laboratories.

anol melted at 68–69°. There was no depression of melting point when samples prepared by procedure a and b were mixed.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.77; H, 6.86.

This compound gave no red color with ferric chloride.

The semicarbazone formed small colorless prisms from ethanol, m.p. 161–162°.

Anal. Calcd. for $C_{17}H_{19}O_2N_3$: C, 68.57; H, 6.44. Found: C, 68.58; H, 6.67.

3-Nitro-4-cyanobiphenyl (IV).—Cuprous cyanide (3.8 g.) and 3-nitro-4-bromobiphenyl[22] (11 g.) were heated for 40 hours at 150–160°. Vacuum distillation of the reaction product yielded a crude yellow solid which twice recrystallized from ethanol gave 3.7 g. (37%) of yellow crystals, m.p. 116.5–117.5°. The analytical sample melted at 119–119.5° (lit.[23] 117–119°).

Anal. Calcd. for $C_{13}H_8O_2N_2$: C, 69.63; H, 3.60. Found: C, 69.66; H, 3.61.

3-Methoxy-4-cyanobiphenyl (V).[10]—Sodium (1 g.) was dissolved in methanol (100 ml.) and to this solution 3-nitro-4-cyanobiphenyl (VII, 4.7 g.) was added and the mixture refluxed overnight. The chilled solution was filtered and poured into water. Yellow crystals, 3.85 g. (88%), were obtained, m.p. 81–86°. This material was used in the preparation of I (R = C_2H_5), but the analytical sample obtained by crystallization from ethanol melted at 86.5–87.5°.

Anal. Calcd. for $C_{14}H_{11}ON$: C, 80.36; H, 5.30; N, 6.71. Found: C, 80.28; H, 5.18; N, 6.57.

3-Hydroxy-4-propiobiphenyl (II, R = C_2H_5). (a) By the Method of Harris and Christiansen.[5]—From the Fries reaction using 3-propionoxybiphenyl the desired product (II, R = C_2H_5) was obtained in a yield of 73.5%, m.p. 109.5–110.5° (lit.[5] 109°).

(b) **By the Friedel–Crafts Reaction.**—By a procedure analogous to that used in the preparation of the lower homolog (II, R = CH_3) 5.0 g. of 3-methoxybiphenyl yielded 4.65 g. (71%) of white cubical crystals from ethanol, m.p. 107–108°. Recrystallized, this compound melted at 110.5–111°.

(c) By Ether Cleavage of 3-Methoxy-4′-propiobiphenyl (I, R = C_2H_5).—A mixture consisting of 3-methoxy-4-propiobiphenyl (0.50 g.), aluminum chloride (0.50 g.) and methylene chloride (10 ml.) was refluxed overnight. The product (0.25 g., 53%) melted at 107.5–109°, but on recrystallization melted at 109.5–110.5°.

Mixed melting point determinations indicated that all three preparations were identical.

3-Hydroxy-4-butyrobiphenyl (II, R = C_3H_7) was prepared by the Friedel–Crafts synthesis in the same manner as the lower homologs. After one recrystallization a 59.5% yield of elongated yellow plates was obtained, m.p. 78–80°. A sample recrystallized from ethanol melted at 80.5–81°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.66; H, 6.57.

3-Hydroxy-4-ethylbiphenyl (III, R = CH_3).—Amalgamated zinc (8 g.), 20% hydrochloric acid (30 ml.) and 3-hydroxy-4-acetobiphenyl (2 g.) were refluxed together overnight. The mixture was extracted with methylene chloride, the washed and dried extract concentrated and the residue distilled under reduced pressure. Recrystallization from petroleum ether (b.p. 30–60°) gave 0.3 g. (16%) of small white crystals, m.p. 64–65°. The analytical sample melted at 65–65.5°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.58; H, 7.19.

3-Hydroxy-4-propylbiphenyl (III, R = C_2H_5) was prepared from II (R = C_2H_5) as in the case of the homolog. From petroleum ether a 53% yield of irregular white plates was obtained, m.p. 56–57° which on recrystallization melted at 57–58° (lit.[5] 56–56.5°).

3-Hydroxy-4-butylbiphenyl (III, R = C_3H_7) was prepared by the Huang-Minlon[15] modification of the Wolff–Kishner reaction after preliminary attempts at Clemmensen reduction had failed. A mixture consisting of 3-hydroxy-4-butyrobiphenyl (II, R = C_3H_7; 4.05 g.) potassium hydroxide (3.6 g.), 85% hydrazine hydrate (2.3 ml.) and diethylene glycol (23 ml.) was refluxed for 90 minutes, the condenser removed and the mixture distilled until the temperature of the liquid reached 195°. After an additional 2.5 hours of refluxing, the mixture was poured into water and extracted with ether. The ethereal extract was concentrated and the residue, twice recrystallized from petroleum ether, obtained as white microcrystals, m.p. 74–75°; yield 2 g. (52.5%). The pure product melted at 74.5–75°. Like its homologs (R = C_2H_5 and C_3H_7) it was insoluble in 10% sodium hydroxide solution.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.18; H, 8.04.

3-Hydroxy-6-aminobiphenyl (VI), m.p. 116–117°, was prepared from 2-nitrobiphenyl in 36% yield by the method of Kosolapoff.[13] By acetylation with acetic anhydride in dilute acetic acid followed by methylation at room temperature with methyl sulfate, 3-methoxy-6-acetaminobiphenyl was obtained, m.p. 112.5–113°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.62; H, 6.48; N, 5.95.

3-Methoxy-6-iodobiphenyl (VII).[24]—A mixture of 3-hydroxy-6-aminobiphenyl (VI, 38.9 g.), ice (115 g.), water (115 ml.) and sulfuric acid (15 ml.) was stirred at 0° and a solution of sodium nitrite (15.1 g. in 31 ml. of water) was added gradually during one hour. A positive starch–iodide test was observed. After stirring for 20 minutes longer additional sulfuric acid (43 ml.) was added followed by the gradual addition of a cold solution of 42 g. of potassium iodide in 43 ml. of water. A viscous brown precipitate formed and the evolution of nitrogen was apparent. Copper bronze was added, the mixture heated slowly to 80° and maintained at this temperature for 2.5 hours. The resulting red oil was extracted from the solution with methylene chloride and the extract washed with water and sodium thiosulfate. The solvent was removed and the residue dissolved in sodium hydroxide and methylated in the usual way with methyl sulfate. The crude 3-methoxy-6-iodobiphenyl (VII) was fractionated at 6 mm. pressure yielding 26.5 g. (49.5%) of a light amber oil, b.p. 173–181°. The analytical sample, b.p. 166–169° (3 mm.), probably contained a small amount of 3-methoxybiphenyl.

Anal. Calcd. for $C_{13}H_{11}OI$: C, 50.34; H, 3.58. Found: C, 50.86; H, 3.76.

2-Cyano-5-methoxybiphenyl (VIII).—A mixture of 2-iodo-5-methoxybiphenyl (11.6 g.) and cuprous cyanide (4 g.) was heated with stirring at 260° for 6 hours. The reaction mixture was vacuum distilled yielding 4.4 g. of a yellow solid, m.p. 60–72°. Several recrystallizations from methanol yielded colorless needles, m.p. 85–86.5°, which did not depress the melting point of a sample (m.p. 85–86.5°) prepared by the method of Bradsher and Jackson.[14]

3-Methoxy-6-propiobiphenyl (IX, R = C_2H_5) was prepared from VIII by the method used earlier[14] for the preparation of a homolog (IX, R = CH_3). The product was obtained as a liquid; b.p. 171.5–173° (2.5 mm.) (lit.[5] m.p. 72°), n^{30}_D 1.5971.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.24; H, 6.81.

The semicarbazone of the compound was prepared as white granular crystals, m.p. 194–195°.

Anal. Calcd. for $C_{17}H_{19}O_2N_3$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.33; H, 6.35; N, 13.91.

3-Hydroxy-6-propylbiphenyl (X, R = C_2H_5).—The ketone (IX, R = C_2H_5) was reduced by the Huang-Minlon[15] technique essentially as described for the preparation of 3-hydroxy-4-butylbiphenyl (V, R = C_3H_7). The crude oil obtained appeared to be insoluble in 10% sodium hydroxide solution or Claisen alkali, but gave the phosphomolybdic acid phenol test[25] as well as a color test with diazotized sulfanilic acid, indicating the presence of some of the phenolic derivative. The crude product was refluxed for 36 hours with 240 ml. of acetic acid and 140 ml. of 48% hydrobromic acid. The resulting solution was diluted with water and extracted with ether. The ethereal extract was washed with water and then with Claisen alkali. The alkaline solution was saturated with carbon dioxide and extracted with ether. The ethereal extract was washed, dried and concentrated.

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[22] Distillation Products Industries.

[23] J. E. Jones, *J. Org. Chem.*, **10**, 537 (1945).

[24] *Cf.*, F. B. Dains and F. Eberley, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 355.

[25] V. M. Platkonskaya and S. G. Vatkina, *J. Applied Chem.* (*U.S.S.R.*), **10**, 202 (1937); *C. A.*, **31**, 4232 (1937).

The residue was fractionated at 2 mm. pressure yielding 3-hydroxy-6-propylbiphenyl as an oil, b.p. 143–150°; 45% yield. The analytical sample boiled at 143–146° (2 mm.); $n^{28}D$ 1.5888. This material has stood longer than two years without crystallizing (lit.[5] m.p. 140–141°).

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.56; H, 7.25.

3-Methoxy-6-ethylbiphenyl[26] was produced by reduction of 14.6 g. of the appropriate ketone (IX, R = CH_3)[14] using the Huang-Minlon method. At the end of the reaction, the strongly alkaline diethylene glycol solution was diluted with an equal volume of water and extracted with ether. The ethereal layer was washed, dried and concentrated. The residue was distilled yielding 6.2 g. (45%) of an oil, b.p. 131–139° (2 mm.). The analytical sample boiled at 133.5° (2 mm.); $n^{25}D$ 1.5781.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.04; H, 7.48.

3-Hydroxy-6-ethylbiphenyl (X, R = CH_3).—The alkaline diethylene glycol solution (above) was acidified and the acidic fraction removed by ether extraction. The residue obtained by evaporation of the ether was combined with the 3-methoxy-6-ethylbiphenyl obtained above and the whole refluxed for 17 hours with 70 ml. of acetic acid and 50 ml. of hydrobromic acid. The solution was diluted with water and extracted with ether. The washed and dried ethereal extract was concentrated and the resulting residue purified by vacuum distillation. The product was an oil, b.p. 152–158° (3 mm.), yield 7.2 g. (56% from IX, R = CH_3). The analytical sample boiled at 148° (3 mm.); $n^{25}D$ 1.5994.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.46; H, 7.11.

3-Nitro-4′-acetobiphenyl (XIV, R = CH_3) was prepared by a procedure essentially that of Berliner and Blommers,[17] m.p. 110.5–111° (lit.[17] 109–110°).

The oxime was obtained as light yellow needles from ethanol, m.p. 146–146.5°.

Anal. Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.61; H, 4.72. Found: C, 65.84; H, 4.60.

3-Nitro-4′-propiobiphenyl (XI, R = C_2H_5) was prepared from 3-nitrobiphenyl in 80% yield in a manner analogous to that used in making the homolog (XI, R = CH_3). The product, m.p. 108–110°, on recrystallization from ethanol was obtained as flat ivory needles m.p. 109–110°.

Anal. Calcd. for $C_{15}H_{13}O_3N$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.82; H, 5.24; N, 5.31.

The oxime was obtained from ethanol as irregular ivory plates, m.p. 136.5–137.5°.

Anal. Calcd. for $C_{15}H_{14}O_3N_2$: C, 66.65; H, 5.22. Found: C, 66.42; H, 5.11.

3-Nitro-4′-butyrobiphenyl (XI, R = C_3H_7) was obtained in 55% yield (m.p. 70–71°) by the method employed in making the homologs. The analytical sample was obtained from ethanol as ivory microcrystals, m.p. 71–71.5°.

Anal. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.62; N, 5.20. Found: C, 71.71; H, 5.28; N, 4.96.

3-Amino-4′-acetobiphenyl (XII, R = CH_3).—To a solution of stannous chloride dihydrate (14 g.) in 60 ml. of concentrated hydrochloric acid 5 g. of 3-nitro-4′-acetobiphenyl (XI, R = CH_3) was added with stirring. The mixture was heated on the steam-bath for 1.5 hours and then poured into 140 ml. of 40% sodium hydroxide solution maintained at 20°. After the mixture had been allowed to stand overnight, the product was collected and washed with water. Recrystallization of the product from alcohol yielded 3.3 g. (75%) of golden needles, m.p. 160–161°. A pure sample melted at 160–161° (lit.[17] 157.5–160.5°).

The picrate melted at 208° with decomposition.

The hydrochloride was prepared in chloroform solution. The analytical sample was prepared by crystallization from alcohol as white cubes which did not melt at 350°.

Anal. Calcd. for $C_{14}H_{14}ONCl$: C, 67.87; H, 5.70; N, 5.66; Cl, 14.31. Found: C, 68.25; H, 5.66; N, 5.59; Cl, 14.06.

3-Amino-4′-propiobiphenyl (XII, R = C_2H_5) was prepared as in the case of the lower homolog (XII, R = CH_3). The product was obtained as irregular pale-yellow crystals, m.p. 132–133°. The analytical sample was crystallized from ethanol, m.p. 133–134°.

Anal. Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.31; H, 6.67; N, 5.96.

The picrate of the amine melted at 183–184°.

3-Amino-4′-butyrobiphenyl (XII, R = C_3H_7) was prepared in 68% yield by the method used in the preparation of the aceto analog (XII, R = CH_3), m.p. 102–104°. The analytical sample was obtained from ethanol as small irregular ivory plates, m.p. 103–104°.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.27; H, 7.20; N, 5.48.

The picrate melted at 166–167° with decomposition.

3-Methoxy-4′-acetobiphenyl (XIII, R = CH_3).—The diazotization of 6.5 g. of 3-amino-4′-acetobiphenyl (XII, R = CH_3), dissolved in a mixture containing 10.4 ml. of concentrated hydrochloric acid in 33 ml. of water, was carried out at 0–5° by addition of 2.6 g. of sodium nitrite dissolved in a small quantity of water. When diazotization was complete 7.6 g. of zinc chloride was added to the stirred solution causing the formation of the zinc chloride–diazonium chloride complex. The complex was collected, washed with ether and dried. The dried complex was added to 130 ml. of absolute methanol. As the mixture was gently heated nitrogen was evolved copiously and the complex dissolved. At the end of one hour addition of a few drops of the reaction mixture to an alkaline solution of β-naphthol gave no color, indicating that the reaction was complete. The reaction mixture was worked up as in the case of 3-methoxybiphenyl (II). Vacuum distillation of the concentrate yielded 4.7 g. (68%) of white crystalline material, m.p. 43–48°. The analytical sample was obtained from isooctane as a white microcrystalline powder, m.p. 51–52°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.57; H, 5.95.

3-Methoxy-4′-propiobiphenyl (XIII, R = C_2H_5) was prepared as in the case of the lower homolog (XIII, R = CH_3) from 3-amino-4′-propiobiphenyl as a crude product, m.p. 71–80° (92% yield). The analytical sample was obtained from alcohol as pale yellow irregular plates, m.p. 87–88°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.82; H, 6.57.

3-Methoxy-4′-butyrobiphenyl (XIII, R = C_3H_7) was prepared as a crude product, m.p. 54–56° (64% yield). Recrystallization from ethanol yielded irregular white plates, m.p. 62–63°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 79.86; H, 7.10.

3-Hydroxy-4′-ethylbiphenyl.—A mixture of 3-methoxy-4′-acetobiphenyl (5.05 g.), potassium hydroxide (3.8 g.), 85% hydrazine hydrate (3.1 ml.) and 31 ml. of diethylene glycol was refluxed for 1.5 hours. The condenser was removed and the mixture distilled until the temperature reached 195° and then refluxing was resumed for an additional 3.5 hours. The solution was diluted with water, extracted with ether, and the ethereal extract was dried over anhydrous magnesium sulfate. The yield of crude white crystalline material was 3.2 g. (72.5%), m.p. 75–77°. Recrystallization of a sample from petroleum ether (b.p. 30–60°) yielded white needle-shaped crystals, m.p. 77.5–78.5°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.58; H, 7.12.

This material was soluble in 10% aqueous sodium hydroxide solution. An alkaline solution of the compound gave a red precipitate with diazotized sulfanilic acid. An ethanolic solution of the compound, treated with a drop of phosphomolybdic acid and then with ammonium hydroxide, gave a blue color.[25]

3-Hydroxy-4′-propylbiphenyl was prepared from 3-methoxy-4′-propiobiphenyl in a manner analogous to that employed in the preparation of the homolog above; m.p. 85–86.5° (43% yield). The analytical sample was obtained from petroleum ether as white needles, m.p. 85.5–86.5°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.74; H, 7.73.

This compound gave the same tests for phenolic hydroxyl as were shown by the lower homolog (R = CH_3).

3-Hydroxy-4′-butylbiphenyl was prepared in a manner analogous to that used in the preparation of the homologs above; m.p. 73.5–75° (85% yield). An analytical sample

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(26) We are indebted to Mr. Preston H. Leake for carrying out this and the following preparation.

was obtained from petroleum ether as white needles, m.p. 76–76.5°.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.66; H, 8.01.

The compound gave chemical tests similar to those obtained with the lower homologs.

2-Methoxyfluorene.—A diazonium chloride solution was prepared from 7.7 g. of 2-aminofluorene[27] and was treated with 8 g. of zinc chloride. The resulting precipitates, dried *in vacuo*, weighed 9.5 g. This complex salt was refluxed for 36 hours in 100 ml. of methanol. The resulting mixture was filtered while still warm and the filtrate chilled yielding 5.5 g. (66%) of a white solid, m.p. 98–102°. Upon recrystallization this product melted at 106–108° (lit.[27] 106–108°).

2-Hydroxyfluorene.—A solution containing 1 g. of 2-methoxyfluorene in a mixture of glacial acetic acid (20 ml.) and 48% hydrobromic acid (12 ml.) was refluxed for 36 hours. The phenolic material was separated from the reaction mixture in the usual way giving 0.5 g. (54%) of a cream-colored solid, m.p. 160–164°. Recrystallization of this product from dilute acetic acid gave material melting at 167–169° (lit.[27] sintering at 166°, m.p. 168° uncor.).

Biological Testing.—The testing procedure was essentially that of Leonard and Blackford.[2] Measurement was made of the inhibition of the rate of radial growth of test cultures of *Aspergillus niger*[28] caused by dispersion of known concentrations of the test compound in the agar medium.

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(27) O. Diels, *Ber.*, **34**, 1758 (1901).

(28) T. C. 215-4247 Steinberg. We are indebted to Mrs. Rita S. Kardon and Mrs. Barbara S. Bayless for carrying out these tests.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

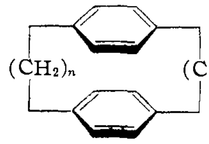
Macro Rings. IV. The Preparation of Three New Paracyclophanes[1]

BY NORMAN L. ALLINGER AND DONALD J. CRAM[2]

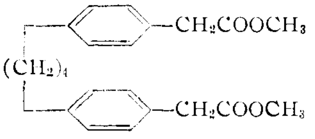
RECEIVED DECEMBER 15, 1953

The three paracyclophanes (I) with the 3- and 4-, 4- and 5-, and 5- and 5-membered methylene bridges have been prepared. These syntheses further illustrate the generality of the method involving hydrogenation of the benzene rings prior to an acyloin ring closure followed by dehydrogenation at a later stage. The stereochemistry of the fully hydrogenated paracyclophanes is discussed.

The preceding paper in this series[3] reported the synthesis and properties of the paracyclophane (I) with $n = m = 4$. The acyloin ring closure fails on esters of the phenylacetic type,[4] such as II, but if the benzene rings of II are hydrogenated, the resulting dicyclohexyl compounds can be closed to give an acyloin ultimately convertible to I with $n = m = 4$. The method is obviously applicable to the synthesis of compounds having methylene bridges of this size or larger, but smaller only to the limit where steric factors prohibit ring closure.

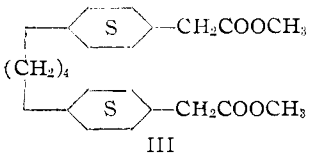


I



II

In the previously reported synthesis of I with $n = m = 4$, the saturated ester III underwent acyloin ring closure only if the groups on the cyclohexane rings were oriented *cis–cis*, polymer resulting from starting materials of other configurations.



III

In the present investigation three new paracyclophanes were prepared by the general sequence formulated. The appropriate hydrocarbon IV was acetylated to give the corresponding diketone V, and in one case a mixture of the mono- and diketone ($n = 5$). This monoketone VI was propionylated to give VII, and along with the other two homologous diketones was submitted to the modified Willgerodt reaction.[5] The resulting thiomorpholides were hydrolyzed to the corresponding acids which were subsequently esterified. The over-all yields of ester from diketone were satisfactory (40–60%) except in the case of the unsymmetrical diketone, VII, which gave only a 15% yield of ester The aromatic rings were then hydrogenated to give the corresponding cyclohexyl compounds IX as *cis–cis*, *cis–trans* and *trans–trans* mixtures. The mixtures obtained were used directly in the acyloin ring closure,[3] no separation of isomers being attempted. Only one acyloin XB was obtained in a crystalline state, the others being isolated as oils which appeared to decompose appreciably when distilled. Therefore the crude acyloins were subjected directly to a modified[6] Clemmensen reduction followed by a catalytic reduction which converted olefinic by-product to the desired saturated material.[3]

The saturated hydrocarbon XIB ($n = 5, m = 4$) was obtained as a single pure compound in a yield of 19% (based on diester IXB), which is comparable to that obtained in the previous preparation[3] of the analogous substance with $n = m = 4$ (22%). The configuration of XIB was demonstrated to be *cis–cis* by its preparation from the parent paracyclophane (XIIB) by hydrogenation, a single isomer being obtained. Scale molecular models of XIB and XIIB indicate that neither can one ring of XIIB turn to right angles to the other ring nor is there room in between the two rings for catalyst with its absorbed hydrogen. The same considerations apply to the partially reduced intermediates in XIIB → XIB. Therefore XIB must possess the *cis–cis*

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(1) This work was sponsored by the Office of Naval Research.

(2) Requests for reprints should be addressed to this author.

(3) D. J. Cram and N. L. Allinger, THIS JOURNAL, **76**, 726 (1954).

(4) D. J. Cram and H. Steinberg, *ibid.*, **73**, 5691 (1951).

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(6) K. Wiesner, D. M. MacDonald, R. B. Ingram and R. B. Kelly, *Canadian J. Res.*, **B28**, 561 (1950).