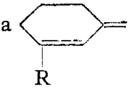
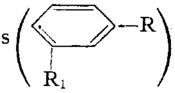
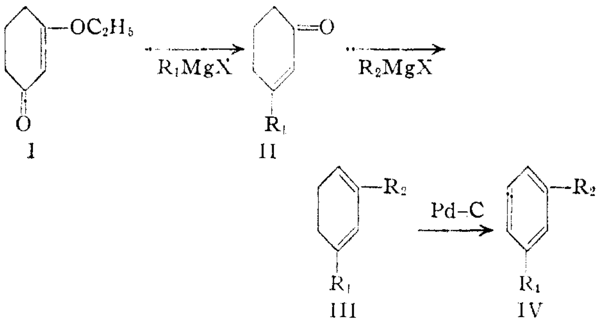
[Contribution from the Chemical Laboratories of the University of Maryland]

m-Diarylbenzenes

By G. Forrest Woods, Fred T. Reed, Thomas E. Arthur and Herbert Ezekiel

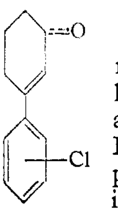
The use of the ethyl enol ether of dihydroresorcinol has been extended to the preparation of cyclohexenones of the formula  where R is α-naphthyl, β-naphthyl, the 3-chlorophenyls and 3′-chlorobiphenyl. From these ketones, by Grignard reactions followed by dehydration and dehydrogenation, a series of 1,3-disubstituted benzenes  were obtained wherein the substituents are: α- and β-naphthyl, 3-chlorophenyl and 3′-chlorobiphenyl.

The monoethyl ether of dihydroresorcinol (I) has been used for the synthesis of 3-aryl-Δ^2-cyclohexenones (II) and polyphenyls (IV) as[1]



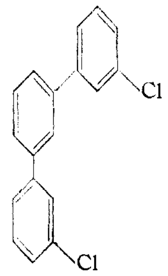
Substances of the formula (II) have been prepared earlier where R_1 was phenyl, the tolyl and the xenyl groups; and compounds of structures (IV) have been obtained, among others, in which R_1 and R_2 were phenyl and the xenyl groups in the various possible modes of combination. This paper is a report on the preparation of more complex ketones (II) and diarylbenzenes (IV).

The chlorophenylcyclohexenones (V) were synthesized by the reaction of the enol ether with the appropriate Grignard reagent made from iodochloro- or bromochlorobenzene. Aromatization of these chlorophenylcyclohexenones with palladium–charcoal inevitably led to the evolution of hydrogen chloride and the production of 3-hydroxybiphenyl. From (V) the corresponding dichloroterphenyl (VI) was prepared. It is interesting to note that the aromatization of the diene precursor of (VI) with palladium–charcoal did not generate hydrogen chloride. In like manner the chloro-ketone (VII) and the dichloroquinquephenyl (VIII) were synthesized.

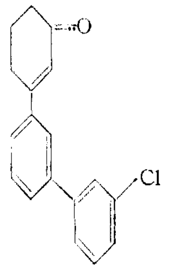


V

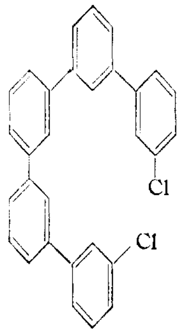
The Grignard reagent for these substances was prepared from 3-chloro-3′-iodobiphenyl which was obtained by the following series of reactions: An Ullmann reaction between 1,3-chloroiodobenzene and 1,3-iodonitrobenzene yielded 3-chloro-3′-nitrophenyl. Reduction of the latter with stannous chloride afforded 3-chloro-3′-aminobiphenyl the amino group of which was replaced with the iodo group upon treatment with potassium iodide after diazotization. We made one attempt, which was a failure, to cyclize (VIII) by a Fittig reaction. This was not repeated since the problem of obtaining (VIII) both from the point of sufficient yields and the general difficulty of manipulation was too great.



VI



VII



VIII

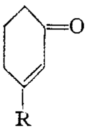
Both the naphthylcyclohexenones (II) were synthesized. The β-naphthyl ketone was a solid but 3-(α-naphthyl)-Δ^2-cyclohexenone was a glass. Purification of the former was simple while it was most difficult for the latter. Continuing from these ketones the 1,3-di-(1-naphthyl)- and 1,3-di-(2-naphthyl)-benzenes (IV) were prepared; but the mixed dinaphthylbenzene (IV) 1-(1-naphthyl)-3-(2-naphthyl)-benzene could not be obtained in a sufficient state of purity for identification, starting from either ketone precursor. The difficulty in this step, as well as mentioned above for the ketones, was attributable to the relatively large amounts of the coupling products formed in the preparation of the naphthyl Grignard reagents.

The ultraviolet absorption spectra of the dinaphthylbenzenes, Fig. 1, determined with a Beckman quartz spectrophotometer with isoöctane as the solvent are almost identical with those of α-phenylnaphthylene and β-phenylnaphthylene, respectively.[2]

Acknowledgments.—The authors wish to acknowledge that this work was supported in part by a contract with the Office of Naval Research. The analyses reported herein were performed by Mrs. Mary Aldridge and Mr. Byron Baer of this University.

Experimental

Preparation of 3-Substituted-Δ^2-cyclohexenones: These substances were prepared by typical reactions of the appropriate Grignard reagent with 3-ethoxy-Δ^2-cyclohexenone. The products were isolated by the following procedure: (1) the Grignard addition complex was decomposed with dilute sulfuric acid, (2) the total resulting mixture was steam distilled, (3) the residue in the steam pot was extracted with ether and the ether solution was washed with dilute so-



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(1) (a) Woods and Tucker, This Journal, **70**, 3340 (1948); (b) Woods and Reed, *ibid.*, **71**, 1348 (1949); (c) Woods, Van Artsdale and Reed, *ibid.*, **72**, 3221 (1950).

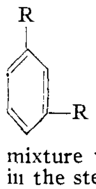
(2) Friedel, Orchin and Reggel, *ibid.*, **70**, 199 (1948).

dium hydroxide and with water and dried over magnesium sulfate, (4) the residue was distilled after removal of the solvent under reduced pressure and recrystallized from petroleum ether except for 3-(α-naphthyl)- and 3-(3′-chlorobiphenyl)-Δ^2-cyclohexenone. The former was distilled in a Hickman still, and the latter was isolated directly as a solid after the steam distillation process and the residue was recrystallized from petroleum ether.

3-Aryl-Δ^2-cyclohexenones							2,4-Dinitrophenylhydrazone (Red)				
			Analyses, %					Analyses, %			
			Calcd.		Found			Calcd.		Found	
R	B.p. and m.p., °C.	Yield, %	C	H	C	H	M.p., °C.	C	H	C	H
α-Naphthyl	B. 165–175 (0.5 mm.)	54	86.46	6.35	86.78	6.61	223–224	65.67	4.50	65.70	4.66
β-Naphthyl	98–99	70	86.46	6.35	86.43	6.56	259–261	65.67	4.50	65.67	4.54
2-Chlorophenyl	27.6–28.0	34	69.74	5.37	69.69	5.45	198–199.5	55.89	3.91	56.23	4.15
3-Chlorophenyl	45.5–46.0	70	69.74	5.37	69.79	5.61	241–242	55.89	3.91	55.87	3.94
4-Chlorophenyl	54.4–55.0	65	69.74	5.37	69.63	5.61	222.5–223	55.89	3.91	56.09	4.18
3′-Chlorobiphenyl	80–81	20	76.44	5.35	76.41	5.62	219–220	62.27	4.14	62.48	4.15

Preparation of 3-Phenylphenol from (Chlorophenyl)-Δ^2-cyclohexenones.—Chlorophenylcyclohexenone (10 g.) was added to 1.5 g. of 10% palladium–charcoal catalyst in 35 ml. of *p*-cymene. The mixture was heated under reflux for eight to 12 hours. (3-(2-Chlorophenyl)-Δ^2-cyclohexenone failed to react below 190° and was refluxed 24 hours.) Vigorous evolution of hydrogen chloride took place. The catalyst was removed by filtration and *p*-cymene distilled under reduced pressure. Distillation of the residue gave impure phenylphenol in 45–67% yield. It was purified by ether extraction of its sodium hydroxide solution and subsequent precipitation by hydrochloric acid followed by several recrystallizations from petroleum ether, m.p. 72–76° (no depression with an authentic sample[1a]).

The phenylurethan, m.p. 132.5–134° (no depression with an authentic sample), was prepared in the usual manner and recrystallized from petroleum ether.



Preparation of 1,3-Disubstituted Benzenes: The procedure is essentially the same as that given for the preparation of the ketones. The α,β-unsaturated ketone dissolved in ether was added to an excess (20–50%) of the appropriate Grignard reagent. The Grignard addition complex was decomposed with dilute sulfuric acid. The whole mixture was subjected to steam distillation. The residue in the steam pot was extracted with ether and the solution dried over magnesium sulfate. After removal of the solvent, the residue was distilled in a Hickman still apparatus. The exception to this was di-(β-naphthyl)-cyclohexadiene which was obtained as a solid when the ether in the above solution was displaced with petroleum ether. This solid was used directly in the following aromatization process.

The dienes were added to a refluxing mixture of palladium–charcoal in *p*-cymene. Heating was continued for three to four hours, the solution was filtered to remove the catalyst, and the filtrate was steam distilled. The residue in the steam pot was extracted with ether. Upon displacement of the ether with petroleum ether the two dinaphthylbenzene compounds crystallized upon standing. Petroleum ether was used for recrystallization. The other two chloride bearing compounds were glasses. These were distilled in a Hickman still; hence, no boiling point is reported. The yields of (1) and (2) were 40 and 33%, respectively (from the ketone), and 15–25% of (3) and (4). Severe loss of material took place upon distillation of (3) and (4) by the technique used.

1,3-DIARYLBENZENES

			Analyses, %			
			Calcd.		Found	
	R	M.p., °C.	C	H	C	H
(1)	α-Naphthyl	131–132	94.52	5.48	94.46	5.88
(2)	β-Naphthyl	143–144	94.52	5.48	94.31	5.33
(3)	3-Chlorophenyl		72.25	4.04	71.91	4.52
(4)	3′-Chlorobiphenyl		79.82	4.47	79.87	5.23

3-Chloro-3-iodobiphenyl.—The Ullmann reaction was carried out in a 1-liter 3-neck round-bottom flask to which were attached a thermometer, a short air condenser, and a very efficient mechanical stirrer. In the flask were placed 330 g. (1.34 moles) of *m*-nitroiodobenzene and 320 g. (1.34 moles) of *m*-chloroiodobenzene. Heat was applied until the temperature reached 200°, when the addition of 250 g. of copper-bronze was begun. The temperature rose to 235° rapidly. Heating was discontinued and the addition of copper halted until the temperature returned to 200°. This temperature was maintained during the addition of the rest of the copper and for an additional 1.5 hours. The reaction mixture was cooled, 500 ml. of benzene were added, the solution filtered, and the inorganic material on the filter washed with 500 ml. of hot benzene. The washings were combined with the filtrate and the volume reduced approximately one-half by the evaporation of the benzene. This solution on cooling yielded a precipitate of 3,3′-dinitrobiphenyl which was removed by filtration. The filtrate was distilled at reduced pressure. That fraction which crystallized in the condenser when water cooled, but liquefied when steam was passed through the condenser jacket, was collected. This solid distillate was recrystallized from ethanol; yield 71 g. (28%) of 3-chloro-3-nitrobiphenyl, m.p. 89°. *Anal.* Calcd. for $C_{12}H_8O_2NCl$: C, 61.69; H, 3.43; N, 6.00. Found: C, 61.26; H, 3.56; N, 5.92.

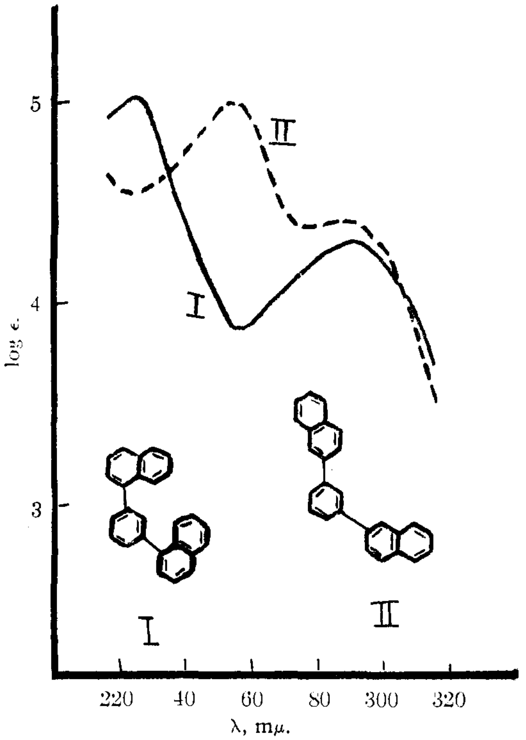


Fig. 1.

Reduction of this compound was accomplished by dissolution of 110 g. (0.47 mole) in 300 ml. of glacial acetic acid, heating to 105°, and adding a solution of 320 g. (1.41 moles) of stannous chloride dihydrate in 350 ml. of concentrated hydrochloric acid. While maintaining the temperature at 110° for one hour, a heavy white precipitate of the stannic chloride–amine hydrochloride complex appeared. After chilling, the mixture was filtered on a sintered glass funnel. The precipitate obtained in this manner was decomposed with potassium hydroxide solution and the resulting mixture was extracted with ether. After evaporation of the ether, a viscous residue of 3-chloro-3-aminobiphenyl remained which was not purified further. The yield of this material was almost quantitative. A small sample was treated with aqueous hydrochloric acid and a precipitate of the amine hydrochloride immediately formed which, after a single recrystallization in water, melted with decomposition at 227°. *Anal.* Calcd. for $C_{12}H_{11}NCl$: C, 60.02; H, 4.62. Found: C, 59.89, 60.03; H, 4.83, 4.94.

The total crude 3-chloro-3-aminobiphenyl was added to a solution of 500 ml. of sulfuric acid in 1000 ml. of water. After the mixture was cooled to 5°, a solution of sodium nitrite in water was added (temperature maintained at 5–10°) until a positive test with potassium iodide–starch paper was obtained. The diazotization reaction proceeded very slowly, probably due to the insolubility of the amine sulfate. A solution of 125 g. (0.75 mole) of potassium iodide in a minimum of water was added and the mixture was allowed to warm to room temperature and stand for eight hours. The organic layer which had settled to the bottom was extracted with ether, washed with sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Distillation of this solution under reduced pressure yielded crude 3-chloro-3-iodobiphenyl boiling at 160–170° (1.0 mm.). This material was further purified by dissolution in 30–60° petroleum ether, passing through a column of activated alumina and redistilling; yield 74 g. (50% from 3-chloro-3-nitrobiphenyl). *Anal.* Calcd. for $C_{12}H_8ICl$: C, 45.82; H, 2.56. Found: C, 46.11; H, 2.70.

COLLEGE PARK, MARYLAND RECEIVED DECEMBER 6, 1950

[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Chemistry of the Benzylpyridines. II. Nuclear Substituted 2-Benzylpyridines[1]

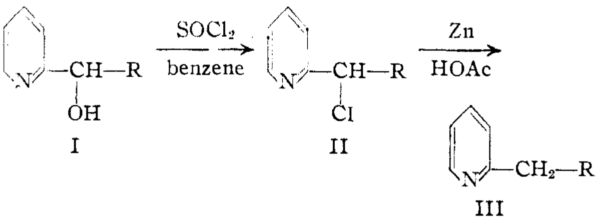
BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK AND MARGARET SHERLOCK

A series of nuclear substituted 2-benzylpyridines has been prepared by the conversion of the appropriately substituted phenyl-2-pyridylcarbinols to the corresponding chlorides, followed by reductive dehalogenation with zinc and acetic acid. A substantial improvement in the synthesis of the phenyl-2-pyridylcarbinols also is described.

As part of an extensive research program on the preparation of histamine antagonists, nuclear substituted 2-benzylpyridines were required as intermediates. Although three methods have been described for the preparation of 2- and 4-benzylpyridine, the nuclear substituted compounds, except in isolated cases,[2] are not known. Chichibabin[3] obtained a mixture of 2- and 4-benzylpyridines by the reaction of pyridine, benzyl chloride and a copper catalyst. The 2- and 4-isomers were separated by fractional crystallization of the picrates, which when decomposed yielded the pure, free bases. Separation of the isomers has been effected by fractional distillation of the crude mixture of isomers, thus eliminating the tedious picrate purification step.[4] 4-Benzylpyridine also has been obtained as a by-product of the reaction of pyridine and benzylmagnesium chloride.[5]

Recently an elegant synthesis of 2- and 4-benzylpyridines has been described.[6] Phenylacetonitrile is alkylated with 2- or 4-chloropyridine and the intermediate phenyl-2- or phenyl-4-pyridylacetonitrile is hydrolyzed and decarboxylated with sulfuric acid. This method is well suited for the preparation of substituted 2- and 4-benzylpyridines, provided the requisite substituted phenylacetonitriles are accessible.[7]

However, it appeared to us that a more direct synthesis of substituted 2-benzylpyridines could be effected by the conversion of the previously described aryl-2-pyridylcarbinols[8] in accordance with the equation



R = phenyl or substituted phenyl

This approach to the substituted 2-benzylpyridines seemed attractive in view of a substantial improvement in the synthesis of the intermediate carbinols and the availability of substituted benzaldehydes. In place of 2-pyridylmagnesium bromide,[9] it was found that the reaction of 2-pyridyllithium with aromatic aldehydes gave 70–90% yields of the carbinols I. These yields are in sharp contrast with those obtained by other methods.[8] The conversion of the carbinols to the corresponding 2-benzylpyridines proceeded in good yields by treatment of I with thionyl chloride in benzene,[10] followed by reductive dehalogenation of the chloride II, with zinc and acetic acid.[11,12] The *o*- and *p*-hydroxy-2-

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(1) This is part of a paper presented before the Division of Medicinal Chemistry of the American Chemical Society, Chicago, April, 1948.

(2) F. Bryans and F. L. Pyman, *J. Chem. Soc.*, 549 (1929).

(3) A. E. Chichibabin, *Chem. Centr.*, [2] **72**, 127 (1901); [2] **87**, 146 (1916). Recent modifications of this procedure have been reported by: (a) F. B. La Forge, THIS JOURNAL, **50**, 2484 (1928); (b) K. E. Crook and S. M. McElvain, *ibid.*, **52**, 4006 (1930); (c) P. C. Teague, *ibid.*, **69**, 714 (1947).

(4) K. E. Crook, *ibid.*, **70**, 416 (1948).

(5) W. L. C. Veer and S. Goldschmidt, *Rec. trav. chim.*, **65**, 793 (1946).

(6) L. Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944).

(7) Further applications of this synthesis will be described in a forthcoming paper from our laboratories.

(8) (a) N. Sperber, D. Papa, E. Schwenk and M. Sherlock, THIS JOURNAL, **71**, 887 (1949); (b) C. H. Tilford, R. S. Shelton and M. G. Van Campen, Jr., *ibid.*, **70**, 4001 (1948).

(9) J. Overhoff and W. Proost, *Rec. trav. chim.*, **57**, 179 (1938).

(10) K. E. Hamlin, A. W. Weston, F. E. Fischer and R. J. Michaels, Jr., THIS JOURNAL, **71**, 2731 (1949), have prepared phenyl-2-pyridylmethyl chloride by the reaction of the carbinol with hydrogen chloride in an inert solvent.

(11) After this work was completed, R. Grewe, A. Mondon and E. Nolte, *Ann.*, **564**, 161 (1949), described the preparation of 1-(5,6,7,8-tetrahydroisoquinolyl)-phenylcarbinol which was subsequently reduced to the methane derivative with red phosphorus and hydriodic acid in a yield of 90%. The corresponding *p*-methoxy derivative was also obtained by conversion of the carbinol to the bromide with hydrogen bromide–acetic acid, followed by treatment with zinc.

(12) A. W. Ruddy and J. S. Buckley, Jr., THIS JOURNAL, **72**, 718 (1950), have prepared a series of 3-amino-1-phenylpropanes by converting the 1-propanols to the chlorides with thionyl chloride followed by dehalogenation with a palladium-on-charcoal catalyst.