EXPERIMENTAL

β-Bromopropionyl isocyanate. The rearrangement of *N*-bromosuccinimide was carried out as indicated previously.[2] The *N*-bromosuccinimide should be crushed to break up lumps of material for maximum rate. We have carried out the rearrangement on scales which ranged from 0.2 to 50 g. *N*-bromosuccinimide without difficulty.

Reaction of compound I *with alcohols.* In preparative scale reactions a solution of chloroform containing 5 g. of rearranged *N*-bromosuccinimide was allowed to react with 0.7 mol. equivalent of the alcohol. The solution was cooled in an ice bath. If a precipitate appeared, the solution was filtered, and the precipitate was recrystallized from methanol. If the derivative did not precipitate, the solution was evaporated on a steam bath using an air jet. The residue was induced to crystallize with Dry Ice, and the material was recrystallized.

On a smaller scale, 0.5 g. *N*-bromosuccinimide was rearranged in 5 ml. chloroform (dried over calcium chloride), *ca.* 0.5 ml. allyl chloride, and a trace of benzoyl peroxide. The solution was refluxed 30 min. beyond the time required for the *N*-bromosuccinimide to dissolve, and cooled to room temperature. Then 0.2–0.4 ml. of the alcohol was added, and the solution was cooled or evaporated as required. A slight excess of the isocyanate appears desirable to give the most easily crystallized urethanes. With secondary alcohols less trouble was encountered with oils if the reaction mixture were worked up reasonably quickly (less than 2 hr.) rather than allowing the mixture to stand overnight.

DIVISION OF PHYSICAL SCIENCES
UNIVERSITY OF CALIFORNIA
RIVERSIDE, CALIF.

A New Base-Catalyzed Aromatization Reaction[1]

DIETER PAWELLEK AND C. K. BRADSHER

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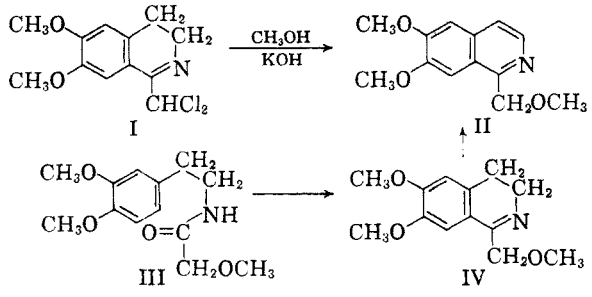
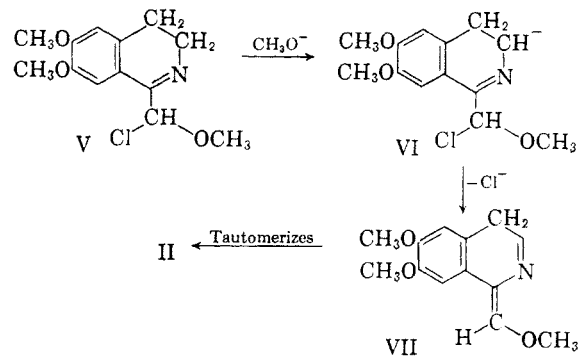
We have had occasion to study the effect of 5% methanolic potassium hydroxide solution on 1-dichloromethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline (I). The crystalline product, obtained in excellent yield, was shown to be halogen-free, and the infrared absorption spectrum was without significant absorption in the 5.83–5.90 region (aromatic aldehyde). The composition of the new compound did not correspond with that of a simple



acetal, but gave best agreement with the empirical formula $C_{13}H_{15}NO_3$.

Of the compounds which could have the observed composition the previously unknown 1-methoxymethyl-6,7-dimethoxyisoquinoline (II) appeared most likely, and an unequivocal synthesis was undertaken *via* the Bischler-Napieralski cyclization of *N*-homoveratrylmethoxyacetamide (III). Dehydrogenation of the cyclization product (IV) yielded 1 - methoxymethyl - 6,7 - dimethoxyisoquinoline identical in every respect with the product obtained by the action of methanolic potassium hydroxide on 1-dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I).

Since this type of aromatization reaction does not appear to have been reported before, speculation concerning a possible mechanism is in order. A logical sequence of events would involve a simple



nucleophilic displacement of chlorine by methoxide ion to yield V. This would be followed by the abstraction of a proton to yield some of the anion (VI). The loss of a chloride ion from anion VI would, through the sequential shift of electrons lead to structure VII, which would be expected to tautomerize to 1-methoxymethyl-6,7-dimethoxyisoquinoline (II).

The new aromatization reaction occurs in 80–94% yield and is thus of preparative as well as theoretical interest.

EXPERIMENTAL[2]

1-Dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I). A mixture containing 12 g. of *N*-homoveratryl-1,1-dichloroacetamide,[3] 100 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed for about 2 hr. when the majority of the solvent was removed under vacuum and the residue carefully decomposed with water and dilute hydrochloride acid. After the acidic solution had been extracted with ether to remove any neutral material, the aqueous solution was made basic and the dihydroquinoline derivative extracted with ether or benzene. The product afforded 7.0 g. (64%) of colorless plates from ligroin, m.p. 90–90.5°. A dilute hydrochloric acid solution of the product was not fluorescent.

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: N, 5.13; Cl, 25.65. Found: N, 5.22; Cl, 25.80.

(1) This research was supported by a research grant (H-2170) from The National Heart Institute of The National Institutes of Health.

(2) Except as noted all melting points were determined on the Fisher-Johns block and are uncorrected. The analyses were carried out by Drs. Weiler and Strauss, Oxford, England.

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **74**, 6125 (1952).

1-Methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV). A mixture containing 15 g. of *N*-homoveratrylmethoxyacetamide[4] (III), 150 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed and worked up as in the preparation of I. The product, 6 g. (43%), was isolated by distillation, b.p. 150–160° (0.7 mm.). The analytical sample boiled at 149° (0.7 mm.).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.30; H, 7.24; N, 5.96. Found: C, 65.96; H, 7.29; N, 5.97.

1-Methoxymethyl-6,7-dimethoxyisoquinoline (II). (a) *By action of methanolic potassium hydroxide on* I. A 1-g. sample of the dichloromethylisoquinoline (I) was refluxed with 10 ml. of 5% methanolic potassium hydroxide solution for 1 hr. (steam bath). The dichloro compound (I) dissolved, and precipitation of potassium chloride was soon observed. At the end of the hour the weight of the inorganic salt corresponded closely with that expected if 2 mol. equivalents of potassium chloride had formed. The filtrate was diluted with water and extracted repeatedly with benzene. The solution was treated with Norit, dried, concentrated and diluted with petroleum ether. The product which separated in 80–94% yield melted at 110–120°, and showed a negative test for halide. Recrystallized from ligroin it melted at 122.5–123.5°. A solution of the product in dilute hydrochloric acid gave a bright yellow fluorescence.

(b) *By dehydrogenation of 1-methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline* (IV). Dehydrogenation of the dihydroisoquinoline IV with 10% palladium charcoal catalyst was effected by heating at 160–175°. The product, b.p. 160–165° (1 mm.), obtained in 60% yield, solidified and on crystallization from ligroin, had m.p. 122–123°. This material did not depress the melting point of the product obtained by Procedure (a).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.02. Found: C, 67.30; H, 6.52; N, 6.39.

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DUKE UNIVERSITY
DURHAM, N. C.

(4) This material, m.p. 40–43°, was prepared by the reaction of methoxyacetyl chloride [R. Leimu, *Ber.*, **70**, 1040 (1937)] with homoveratrylamine.

Study of the Double Fries Rearrangement. II. Rearrangement of Diesters of 4,4′-Biphenol

RESAN PAKKAL,[1] FORREST D. THOMAS, II, AND W. CONARD FERNELIUS

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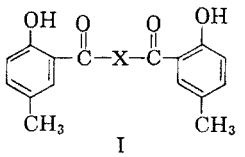
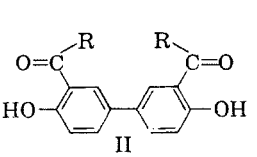
The preparation of a series of bis(*o*-hydroxyketones) of type I where X represents $(CH_2)n$ or *m*- or *p*-phenylene has been reported.[2]



I



II

(1) Appointment supported by the International Cooperation Administration under the Visiting Research Scientists Program administered by the National Academy of Sciences of the United States of America.

(2) F. D. Thomas II, M. Shamma, and W. Conard Fernelius, *J. Am. Chem. Soc.*, **80**, 5864 (1958).

A similar series of type II where the bis-functional starting material was a biphenol rather than a dicarboxylic acid was also desired. Although there has been a moderate amount of work on the Fries rearrangement of esters of polyhydroxybenzenes,[3] only two studies report the rearrangement of diesters of 4,4′-biphenol[4] to give 3,3′-diacetyl-4,4′-biphenol[4a,b] and 3,3′-dipropanoyl-4,4′-biphenol,[4a] whereas attempts to prepare 3,3′-dilauroyl-4,4′-biphenol were unsuccessful.[4b]

In the present study a number of esters of 4,4′-biphenol was prepared by treating the phenol with a series of acid halides in chlorobenzene solution. Each of these esters, when subjected to the Fries rearrangement under conditions previously described,[2] gave the corresponding 3,3′-diacyl-4,4′-biphenols in yields ranging from 19 to 92%.

Infrared spectra. The infrared spectra of the bis(*o*-hydroxyketones) show no absorption in the region of 2.77–2.79 μ (3610–3584 cm.$^{-1}$) characteristic of the free phenolic hydroxyl group, but they do exhibit one rather sharp absorption band in the region of 3.32–3.46 μ (3012–2890 cm.$^{-1}$). This corresponds to the broad absorption bands extending from 2.8–3.6 μ (3571–2778 cm.$^{-1}$) reported by Martin[5] for salicylaldehyde and *o*-hydroxyacetophenone which were attributed to the absorption of the hydroxyl group hydrogen bonded to the carbonyl group and, in part, to the carbon-hydrogen stretching frequency. Gordy[6] noted that the characteristic carbonyl group absorption of acetophenone at 5.96 μ (1678 cm.$^{-1}$) was shifted, in the case of *o*-hydroxyacetophenone, to 6.17 μ (1621 cm.$^{-1}$), due probably, to hydrogen bonding with the *o*-hydroxyl group. In a similar manner, each of the bis(*o*-hydroxyketones) exhibited one sharp absorption peak in the 6.10–6.14 μ (1639–1629 cm.$^{-1}$) region which could also be attributed to the absorption of the carbonyl group hydrogen-bonded to the *o*-hydroxyl group.

EXPERIMENTAL[7]

A. *4,4′-Biphenol esters.* All of the esters of 4,4′-biphenol were prepared from the same molar proportions and in the same general way as described for 4,4′-biphenol diacetate. Pertinent information is assembled in Table I.

4,4′-Biphenol diacetate. A solution of acetyl chloride (8.6 g., 0.11 mol.) in 25 ml. of dry chlorobenzene was added dropwise to a solution of 4,4′-biphenol (9.3 g., 0.05 mol.) and 25

(3) A. H. Blatt, *Organic Reactions*, Vol. I, Chap. 11, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 342–369. See Table E., pp. 364–366.

(4) (a) R. W. Stoughton, R. Baltzly, and A. Bass, *J. Am. Chem. Soc.*, **56**, 2007 (1934). (b) N. Boon-Long, *J. Pharm. Assoc. Siam*, **1**, No. 4, 5 (1948). [*Chem. Abstr.*, **43**, 5017h (1949)].

(5) A. E. Martin, *Nature*, **166**, 474 (1950).

(6) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

(7) All melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The 4,4′-biphenol was a gift of the Dow Chemical Company.