Aromatic Amination Studies with *N*-Benzoyloxypiperidine and Hydrazines[1]

PETER KOVACIC, ROBERT P. BENNETT, AND J. LINDSLEY FOOTE[2]

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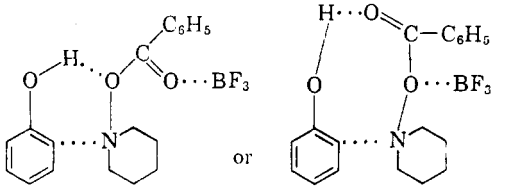
Direct aromatic amination is known to be effected under Friedel-Crafts conditions by hydroxylamine,[3] hydroxylammonium salts,[4-6] alkylhydroxylamines,[3] hydroxylamine-*O*-sulfonic acid[7,8] and hydrazoic acid.[9,10] In connection with our investigations in this area, we have had occasion to examine *N*-benzoyloxypiperidine, hydrazine, 1,1-dimethylhydrazine, and hydrazine sulfate as potential aminating agents. The results of these experiments are reported here.

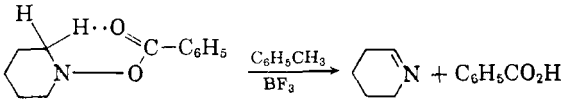
N-Benzoyloxypiperidine, prepared[11] from piperidine and benzoyl peroxide, reacted with phenol at elevated temperatures in the presence of boron trifluoride to produce *N*-(*o*-hydroxyphenyl)piperidine. A 10:1 molar ratio of phenol to aminating agent gave a 25% yield of aminated product and an 85% yield of benzoic acid, whereas a 20:1 molar ratio gave a 32% yield of *N*-(*o*-hydroxyphenyl)piperidine and a 98% yield of benzoic acid.

The basic product isolated was shown to be exclusively the *ortho* isomer by comparison (melting point, mixture melting point, infrared spectrum) with an authentic sample. The experimental results are reasonably interpreted on the basis of a cyclic structure in the transition state, which favors *ortho* substitution. Several sites are available



for coördination with the boron trifluoride. However, the effect of omitting boron trifluoride has not been determined. It is noteworthy that a similar type of cyclic transition state has been proposed in a number of cases for the exclusive or predominant *ortho*-alkylation reported for the systems: olefins-phenols-aluminum phenoxide[12]; olefins-aromatic amines-aluminum anilides[13]; styrene-aniline-anilinium chloride[14]; olefins-thiophenols-aluminum chloride.[15]

Amination of toluene was then attempted with *N*-benzoyloxypiperidine in the presence of boron trifluoride.[16] A 67% yield of benzoic acid was obtained, but the basic product was not piperidinotoluene. After distillation and several crystallizations, the basic material melted over a range from 61 to 70°. The elemental analysis, boiling range, and melting range are consistent with designation of the product as a mixture of lower molecular weight polymers derived from Δ^1-piperideine. In addition, the infrared spectrum gave no indication of aromatic structure. It is conceivable that the indicated scheme pertains. Schöpf and co-



$3C_5H_9N \longrightarrow$ tripiperideine

workers described[17] the preparation of Δ^1-piperideine trimers by the action of alkali on *N*-chloro- or *N*-hydroxypiperidine.

Hydrazine, 1,1-dimethylhydrazine, and hydrazine sulfate were investigated for their ability to aminate in the toluene-aluminum chloride system. Amination did not occur in any case.

EXPERIMENTAL[18]

N-Benzoyloxypiperidine-phenol.[19] The reaction apparatus, containing stirred phenol (30 g.), was purged with dry nitrogen and then boron trifluoride was introduced until heat was no longer evolved. *N*-Benzoyloxypiperidine (20.5 g., 0.1 mole), m.p. 61–63.5°, and phenol (64 g., to make 1 mole total) were added with cooling to the yellow liquid, and the system was protected by a drying tube. The mixture was heated at 140–145° for 30 min. The cooled, dark brown reaction mixture was poured into dilute hydrochloric acid and the resulting two layers were separated.

The nonaqueous fraction was extracted repeatedly with dilute hydrochloric acid. Treatment of the combined acid solutions with concentrated ammonium hydroxide in the cold resulted in the separation of a brown solid (0.15 g.).

The nonaqueous fraction was extracted repeatedly with dilute ammonium hydroxide and the combined extract was acidified with concentrated hydrochloric acid. The solid

(1) Part III of a series on "Direct Aromatic Amination"; from the Ph.D. theses of R. P. Bennett and J. L. Foote, Case Institute of Technology, 1960.

(2) National Science Foundation Fellow, 1958–60.

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(16) Whether or not boron trifluoride plays an active role in the transformation is not known.

(17) C. S. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Ann.*, **559**, 1 (1948).

(18) Melting points and boiling points are uncorrected.

(19) This investigation was initiated by the senior author at E. I. du Pont de Nemours & Co., Inc.

was filtered and dried, wt. 10.4 g. (85%), m.p. 115–122°. This product was crystallized from water and identified by melting point and mixture melting point as benzoic acid, m.p. 120.5–122°.

Subsequent repeated extractions of the nonaqueous fraction with dilute hydrochloric acid and basification of the combined extract produced a brown oil which solidified upon cooling. This solid was cambined with the basic product previously obtained, giving a total weight of 5 g., m.p. 71–75°. Crystallization from ligroin (b.p. 65–110°) yielded 4.5 g. (25%) of white crystals, m.p. 73–74.5°. A mixture melting point with authentic *N*-(*o*-hydroxyphenyl)piperidine was undepressed.

The ligroin-insoluble brown residue (0.5 g.) from crystallization was shown by infrared analysis not to be hydroxyphenylpiperidine and was not investigated further.

When the reaction was rerun with a 20:1 molar ratio of phenol to *N*-benzoyloxypiperidine, a 98% yield of benzoic acid and a 32% yield of *N*-(*o*-hydroxyphenyl)piperidine were obtained.

N-(o-Hydroxyphenyl)piperidine. The preparation was adapted from a procedure by Reed.[20] After steam distillation, the product (67% yield) was further purified by crystallization from ligroin (b.p. 65–110°), m.p. 74.2–75°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.53: H, 8.53; N, 7.90. Found: C, 74.78, H, 8.29; N, 8.10.

N-Benzoyloxypiperidine-toluene.[19] A solution of *N*-benzoyloxypiperidine (38.9 g., 0.19 mole) in toluene (174.8 g., 1.9 moles) was stirred and cooled to 15° in an ice bath. Boron trifluoride was passed into the solution until the gas was no longer absorbed. The reaction mixture, subsequently kept under nitrogen, was heated at 102–107° for 1 hr.

The cooled reaction mixture was extracted repeatedly with dilute ammonium hydroxide. The combined basic extract was extracted with ether which was then added to the organic phase. Acidification of the basic fraction with concentrated hydrochloric acid gave 15.6 g. (67%) of benzoic acid, m.p. 121–123°.

The organic solution was then extracted repeatedly with dilute hydrochloric acid. The combined acid extract was extracted with ether. The acid fraction was made basic with concentrated potassium hydroxide solution producing an oil which was taken up in ether. Removal of the ether from the dried solution left a yellow oil which solidified on standing, wt. 14.2 g. Distillation through an Ace Minilab head gave 7.1 g. of a colorless, viscous oil, b.p. 47–85° (12 mm.) (mostly at 62–63°). The residue in the distillation flask was a dark brown, extremely viscous substance which would not solidify, wt. 5.6 g.

Upon cooling and scratching, the distillate turned to a white crystalline solid, m.p. 62° (damp at 40°), which was crystallized twice from acetone, m.p. 61–70°; lit.[17] α-tripiperideine, m.p. 61–62°; β-tripiperideine, m.p. 72–74°.

Anal.[21] Calcd. for $C_{15}H_{27}N_3$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.98; H, 10.66; N, 16.74.

Hydrazines and aromatics. General procedure. The mixture of hydrazine compound, aluminum chloride, and toluene (1:2:10 molar ratio) was heated with efficient stirring for 1–2 hr. at 100–110°. The cooled two-phase mixture was poured onto ice and sufficient sodium hydroxide was added to dissolve aluminum hydroxide, followed by standard work-up procedures. No aromatic amine product was obtained in any of the experiments.

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DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
CASE INSTITUTE OF TECHNOLOGY
CLEVELAND 6, OHIO

(20) M. C. Reed, U. S. Patent 2,001,584 (1935); *Chem. Abstr.*, 29, 4376 (1935).

(21) By Geller Laboratories, Bardonia, N. Y.

Isolation of 5-Hydroxy-3,6,7,3′,4′-pentamethoxyflavone from *Kuhnia eupatorioides* L. var. *pyramidalis*[1]

WERNER HERZ

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In the course of our studies on sesquiterpene lactones from *Compositae* of this region, we had occasion to investigate *Kuhnia eupatorioides* L. var. *pyramidalis*.[2]

Extraction of the above-ground parts with chloroform followed by the usual work-up[3] gave a gum which was chromatographed over alumina. The only crystalline material which could be isolated was a yellow substance, m.p. 158–159°, which on the basis of its infrared (chelated hydroxyl at 3100–3200, phenyl ketone at 1660 and strong phenyl absorption at 1600 cm.$^{-1}$) and ultraviolet spectrum (λ_{max} 256, 273, and 348 mμ, log ε 4.38, 4.33, and 4.48) appeared to be a hydroxyflavone. The presence of one phenolic hydroxyl and five methoxyl functions suggested by the formula $C_{20}H_{20}O_8$ could be confirmed by conversion to a methyl ether, m.p. 141°, with dimethyl sulfate, and by preparation of an acetate, m.p. 161°. That the free hydroxyl group was in the 5-position of the flavone nucleus was indicated by the infrared spectrum, the color reactions[4] and the resistance to methylation with diazomethane.

The physical and chemical properties of our compound were in good agreement with the properties reported for 5-hydroxy-3,6,7,3′,4′-pentamethoxyflavone (artemetin, artemisetin), a substance synthesized[5] in 1929 and subsequently isolated from *Artemisia arborescens*[6] and *Artemisia absinthium*.[7] A mixed melting point of our material with an authentic sample gave no depression. (m.p. and mixed m.p. reported as 161°.)[8]

The occurrence of quercetagetin derivatives in *Compositae* is thus not limited to members of the tribe *Anthemideae*.

(1) Supported in part by a grant (RG-5814) from the United States Public Health Service.

(2) We are indebted to Professor R. K. Godfrey for collecting and identifying this plant.

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(8) I wish to thank Dr. V. Herout for carrying out the mixed melting point determination.