[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Enzyme Models. III.[1] Synthesis of Some New Oxindole Derivatives

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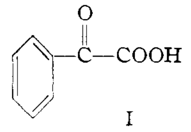
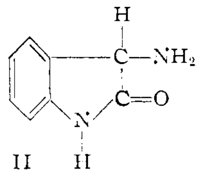
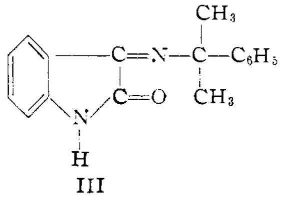
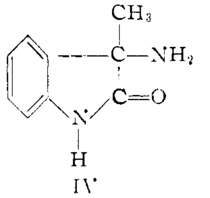
Several compounds related to 3-aminoöxindole have been synthesized *via* hydantoins derived from *ortho*-substituted acetophenones. These compounds are of interest as organic catalysts in the decarboxylation of benzoylformic acid. Previous work in this Laboratory[1] has indicated the probability of a cyclic transition state in the decarboxylation of benzoylformic acid (I) when catalyzed by 3-aminoöxindole II.


I


II

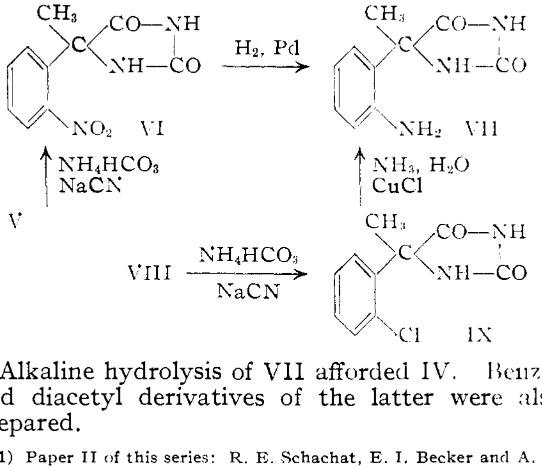
The purpose of this paper is to report the synthesis of a number of compounds designed to test this mechanism. Compounds which would prevent a cycle from occurring are 3-(α,α-dimethylbenzylimino)-oxindole (III), and 3-methyl-3-aminoöxindole (IV). The kinetic studies will be reported later.


III


IV

The Schiff base, III, was prepared by reaction of isatin with α,α-dimethylbenzylamine without particular difficulty.

Several routes were attempted in the synthesis of IV. Nitrosation of 3-methyloxindole, followed by hydrogenation, gave only resinous material. Similarly, treatment of 3-methyl-3-hydroxyoxindole with hydrochloric acid or thionyl chloride, followed by reaction with ammonia, gave no identifiable compounds. The successful synthesis of IV employed 5-methyl-5-(2-aminophenyl)-hydantoin (VII) as an intermediate, with either *o*-chloroacetophenone (VIII) or *o*-nitroacetophenone (V) as starting material.



Alkaline hydrolysis of VII afforded IV. Benzal and diacetyl derivatives of the latter were also prepared.

The synthesis of 3-benzylideneaminoöxindole (X) was reinvestigated. It was found that the tan-colored product obtained according to the previous preparation[3] could be purified further by crystallization from pyridine, the pure compound being colorless. Acid hydrolysis of X gave benzaldehyde and II as the only products, confirming the structure previously postulated. Alternatively, X was synthesized by direct reaction of II with benzaldehyde.

Characterization of II is rendered more difficult by its ease of oxidation and by the lack of any recorded derivatives with definite melting point. Investigation showed that usual methods of acetylation give a mixture of products which melts over a wide range. Careful acetylation at room temperature gave a pure monoacetyl derivative. Similarly, a previously unreported acetyl derivative of 1-methyl-3-aminoöxindole was prepared.

Experimental[4]

3-(α,α-Dimethylbenzylimino)-oxindole (III).—α,α-Dimethylbenzylamine was prepared according to Brander[5] by reaction of α,α-dimethylbenzyl chloride with liquid ammonia. Isatin (5.0 g., 34 mmoles) was mixed with 140 g. of *o*-xylene, 4.5 g. (33 mmoles) of α,α-dimethylbenzylamine, 10 g. of dimethylaniline and 30 g. of *n*-butyl alcohol. The mixture was refluxed for 2 hr. and then concentrated to 75 ml. On cooling, 5.8 g. of orange crystals was obtained. These were ground for 5 min. with cold 5% sodium hydroxide solution (to remove unchanged isatin) and then immediately filtered, washed with cold water, and vacuum dried at room temperature, yielding 3.5 g. (0.013 moles, 40%) of bright yellow crystals, m.p. 214–216°. After three recrystallizations from dioxane–benzene the product melted at 216–218°.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.60. Found: C, 76.89, 77.01; H, 5.95, 6.02; N, 10.5, 10.7.

5-Methyl-5-(2-nitrophenyl)-hydantoin (VI).—*o*-Nitroacetophenone (V) was prepared by reaction of *o*-nitrobenzoyl chloride with magnesio-diethyl malonate.[6] The procedure was modified in that benzene was employed instead of ether in the reaction mixture, the resulting increase in reflux temperature enabling the magnesium to be dissolved in a much shorter time.

Reaction of V with ammonium carbonate and sodium cyanide according to the procedure reported for other ketones[7,8] did not yield any measurable quantity of hydantoin as product, most of the starting material being recovered unchanged. Lowering the *p*H of the reaction mixture, together with the use of a closed reaction vessel to avoid loss of volatiles, enabled the reaction to proceed in good yield.

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(1) Paper II of this series: R. E. Schachat, E. I. Becker and A. D. McLaren, *J. Phys. Chem.*, **56**, 722 (1952).

(2) To whom inquiries should be sent.

(3) R. E. Schachat, E. I. Becker and A. D. McLaren, *J. Org. Chem.*, **16**, 1349 (1951).

(4) Melting and boiling points are corrected. Analyses are by Drs. Weiler and Strauss, Oxford, England; by Dr. K. Ritter, Basel, Switzerland; and by N. J. Alicino, Metuchen, N. J.

(5) M. M. Brander, *Rec. trav. chim.*, **37**, 67 (1918).

(6) G. A. Reynolds and C. R. Hauser, *Org. Syntheses*, **30**, 70 (1950).

(7) H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, [2] **140**, 291 (1934); H. T. Bucherer and V. A. Lieb, *ibid.*, [2] **141**, 5 (1934).

(8) H. R. Henze and R. J. Speer, THIS JOURNAL, **64**, 522 (1942).

V (37 g., 0.224 mole) was mixed in a pressure bottle with 100 ml. of methanol, 75 ml. of water, 25 g. (0.46 mole) of ammonium chloride, 40 g. (0.51 mole) of ammonium bicarbonate and 25 g. (0.51 mole) of sodium cyanide. The bottle was tightly stoppered and shaken for 14 hr. at 60–70°. The reaction mixture was evaporated to 150 ml. and then cautiously acidified with concentrated hydrochloric acid (hood) to *p*H 4. After diluting to 250 ml. with water and re-evaporating to 150 ml., the solution was cooled and filtered. Extraction with benzene yielded approximately 5 g. of unreacted V from the crystals and the filtrate. After recrystallization from methanol–toluene the faintly yellow product weighed 35.7 g. (0.153 mole, 68%) and melted at 192–194°. After several recrystallizations the melting point was 193.7–194.7°.

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.07; H, 3.86; N, 17.87. Found: C, 51.02, 51.09; H, 3.71, 3.81; N, 17.70.

5-Methyl-5-(2-aminophenyl)-hydantoin (VII).—VI (16 g., 0.068 mole) was hydrogenated in 100 ml. of methanol over 1.0 g. of 5% palladium-on-carbon at 50 p.s.i. and 20–30°. Reaction was complete in 2 hr. After filtering the catalyst, crystallization was induced by seeding. After 24 hr. at 20° the slurry was filtered, affording 13.3 g. (0.065 mole, 95%) of white crystals, m.p. 295–297°. After recrystallization from water, the m.p. was 298–300°, undepressed by admixture with the product from the ammonolysis of IX. A qualitative test showed that the compound could be diazotized and coupled with β-naphthol to give an orange-red dye.

5-Methyl-5-(2-chlorophenyl)-hydantoin (IX).—*o*-Chloroacetophenone (VIII) was prepared analogously to V. In a 500-ml. flask, equipped with mechanical agitation, was placed 28 g. (0.181 mole) of VIII, 40 g. (0.8 mole) of sodium cyanide, 90 g. (0.94 mole) of ammonium carbonate, 50 g. (0.93 mole) of ammonium chloride, 50 g. (0.48 mole) of sodium bisulfite, 100 ml. of water and 150 ml. of methanol. The mixture was stirred at 20–30° for 48 hr., and the compound was then isolated according to the procedure given above for VI. The white crystalline product melted at 195–198° and weighed 25 g. (0.112 mole, 61%). After recrystallization either from water or from methanol–toluene the m.p. was 200.2–201.0°.

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; Cl, 15.78; N, 12.47. Found: C, 53.60; H, 4.04; Cl, 15.86; N, 12.33.

Ammonolysis of IX.—Investigation of the ammonolysis of IX indicated that the reaction proceeded better in aqueous solution than in methanol, and that cuprous chloride was necessary as a catalyst. Cupric chloride was ineffective, while cuprous oxide induced deep-seated decomposition, and metallic copper caused dehalogenation of the starting material. The following procedure gave the best yield: IX (10.0 g., 0.044 mole) was placed in an autoclave with 110 g. (1.8 moles) of 28% aqueous ammonia, and a fresh cuprous chloride slurry (prepared from 6.0 g. (0.035 mole) of cupric chloride dihydrate and 5 g. of saturated ammonium bisulfite solution) was added. The mixture was stirred at 80–95° for 48 hr. After cooling, the blue solution was filtered and the white crystals were washed with cold water. No isolable material was found in the filtrate. After recrystallizing from water, the product, VII, weighed 2.9 g. (0.0141 mole, 32%), m.p. 297–298°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.29, 58.02; H, 5.59, 5.77; N, 20.45.

Dehalogenation of IX by Copper–Ammonia.—Fifteen grams (0.067 mole) of IX was placed in an autoclave with 120 g. (2 moles) of 28% aqueous ammonia, 0.1 g. (0.6 mmole) of cupric chloride dihydrate and 6.0 g. (0.094 mole) of copper powder. After stirring at 110° for 24 hr., the mixture was cooled and filtered. The filtrate was evaporated almost to dryness and then taken up in 100 ml. of 5 *N* hydrochloric acid. The product was filtered, washed with cold water and recrystallized from water, giving 8.0 g. (0.042 mole, 62%) of 5-methyl-5-phenylhydantoin, m.p. 193.5–195.5°. Authentic material, prepared from acetophenone by the method of Bucherer,[7] melted at 195–196°, and a mixture of the two substances melted at 194–195°.

Hydrolysis of VII.—Only alkaline hydrolysis was practicable, since extensive decomposition occurred when VII was refluxed with 5 *N* hydrochloric acid. A solution of 17.0 g. (0.083 mole) of VII and 30.0 g. (0.75 mole) of sodium hydroxide in 400 ml. of water was refluxed in a stainless steel flask under nitrogen for 48 hr. The solution was neutralized to *p*H 5 with concentrated hydrochloric acid, and concentrated to 50 ml. The slurry was repeatedly extracted with boiling methanol, and the residual inorganic salts discarded. The hydrochloride of IV could be obtained by concentration of the methanol solution, but was found to lose hydrochloric acid slowly on recrystallization. The product was therefore isolated as the free base. A slight excess of aqueous ammonia was added to the methanol solution of the hydrochloride, and the solution was evaporated to dryness. Repeated extraction with boiling toluene yielded 9.0 g. of crude IV (0.055 mole, 66%), m.p. 180–190°. Two recrystallizations from toluene and two from butanol gave 3.2 g. (0.020 mole, 24%) of pure material, m.p. 182.2–183.2°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.28. Found: C, 66.71, 66.55; H, 6.38, 6.24; N, 17.12, 17.05.

Diacetyl-3-methyl-3-aminoöxindole.—Crude IV-hydrochloride (1.8 g., 9.1 mmoles) was added to a mixture of sodium acetate anhydrous (1.6 g., 0.02 mole), 5 ml. of acetic acid and 20 g. (0.20 mole) of acetic anhydride and evaporated to dryness on the steam-bath. The product was extracted with boiling toluene, yielding 1.5 g. (6.1 mmoles, 67%) of white crystals, m.p. 191–192°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.54; H, 5.89; N, 11.22.

3-Benzylideneamino-3-methyloxindole.—To a solution of IV (0.5 g., 3.1 mmoles) in 10 ml. of methanol was added 1.0 g. (9.5 mmoles) of benzaldehyde. The mixture was evaporated to 2 ml., taken up in benzene, and re-evaporated. The sirup was then taken up in cyclohexane and crystallized with difficulty at room temperature. After recrystallization from benzene–cyclohexane followed by methanol–water, the product weighed 0.15 g. (0.6 mmoles, 19%) and melted at 145.2–146.0°.

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20. Found: C, 76.57; H, 5.77; N, 11.2.

Monoacetyl-3-aminoöxindole.—The hydrochloride of 3-aminoöxindole (II-HCl) was prepared by hydrogenation of β-isatoxime in aqueous alcoholic hydrochloric acid, similar to the method of DiCarlo and Lindwall.[9] To a solution of II-HCl (0.92 g., 5.0 mmoles) in a mixture of 2.0 g. of water and 5.0 g. of acetic acid there was added 15 g. of acetic anhydride and 0.60 g. (7.3 mmoles) of anhydrous sodium acetate. The mixture was stirred at room temperature until all particles were dissolved (10 min.), and then was evaporated to dryness in a vacuum desiccator over sodium hydroxide. The cake was taken up in 30 ml. of cold water, ground thoroughly, and filtered. After three recrystallizations from isopropyl alcohol–benzene, there was obtained 0.10 g. of white crystalline material (0.52 mmole, 10%), m.p. 248–249.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.17; H, 5.32; N, 14.5.

1-Methyl-3-acetylaminoöxindole.—Hydrogenation of the oxime of 1-methylisatin and hydrochloric acid solution produced the hydrochloride of 1-methyl-3-aminoöxindole. The acetylation procedure described above for 3-aminoöxindole gave a white crystalline product, m.p. 213–214°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.70; H, 5.91; N, 13.72. Found: C, 64.60; H, 6.04; N, 13.45.

X from Isatin and Benzylamine.—Five grams of X, prepared as previously reported,[3] was mixed with 200 g. of dry pyridine, held at the boil for 30 min., and filtered. The undissolved portion was treated with additional pyridine in the same way. The cooled solution was diluted with an equal volume of cyclohexane and filtered after a 24-hr. crystallization period. The pure white product, approximately 20% of the crude X, melted with decomposition at 250–252° (darkening at 245°).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 75.84, 76.24; H, 4.82, 4.89; N, 12.1, 11.8.

X from 3-Aminoöxindole and Benzaldehyde.—In a flask flushed with nitrogen was placed 6.4 g. (0.020 mole) of II-*p*-toluenesulfonate, 2.5 g. (0.03 mole) of anhydrous sodium

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[9] F. J. DiCarlo and H. G. Lindwall, THIS JOURNAL, **67**, 199 (1945).

acetate, 2.0 g. (0.019 mole) of benzaldehyde and 100 ml. of methanol. The mixture was heated in a water-bath for 1 hr. and then cooled and filtered. After washing with cold water and with methanol, and vacuum-drying, the white powdery product, X, weighed 0.9 g. (0.0038 mole, 19%), m.p. 243–244° dec., undepressed by admixture with X obtained from the isatin–benzylamine reaction.

Acid Hydrolysis of X.—Recrystallized X (0.80 g., 3.4 mmoles) from the isatin–benzylamine reaction, was mixed in a Claisen flask with 50 ml. of 2 *N* hydrochloric acid and 0.5 g. of silicone antifoaming agent. The mixture was distilled slowly, fresh water being added to keep the flask level constant. The distillate was caught in a filtered solution of 1.2 g. of 2,4-dinitrophenylhydrazine in 300 ml. of 2 *N* hydrochloric acid. Approximately 1 hr. was needed for the X to dissolve completely, and in 3 hr. the steam distillation was complete. Benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 238–240.5° (0.83 g., 2.9 mmoles, 85%), was obtained by filtration of the distillate. A mixture melting point with authentic benzaldehyde 2,4-dinitrophenylhydrazone was not depressed.

The acid solution in the flask was evaporated under nitrogen to 10 ml., and taken up with a mixture of 50 ml. of isopropyl alcohol and similar volumes of *n*-butyl alcohol and ether. After refrigeration 0.35 g. (1.9 mmoles, 56%) of impure II-HCl separated. When acetylated at room temperature as described above for the preparation of monoacetyl-3-aminoöxindole, the unrecrystallized acetyl derivative melted at 245–249°. The mixture with pure monoacetyl-3-aminoöxindole melted at 247–250°.

3-Methyloxindole.—The Brunner cyclization[10] of β-propionylphenylhydrazine was employed. It was found that calcium hydride gave a better yield than lime in this reaction, but it also should be mentioned that sodium amide was much inferior in this case. The product was purified by vacuum distillation in a short path system, b.p. 132° (1.5 mm.), with over-all yields varying from 38–50%, m.p. 121.5–123.5°. After recrystallization from toluene and butanol, with 25% recovery, the product was pure white, m.p. 123.8–124.6°. When crystallized from water the melting point was unchanged, failing to corroborate the reports of earlier workers.[10,11]

Anal. Calcd. for C_9H_9NO: C, 73.46; H, 6.16; N, 9.52. Found: C, 73.36; H, 6.22; N, 9.80.

Treatment of 3-methyloxindole with nitrous acid in water solution, or with butyl nitrite in methanol, gave sirupy polymeric products which could neither be sublimed nor crystallized. No evidence of nitrosation was found.

3-Methyl-3-hydroxyoxindole.—To a solution of 20.0 g. (0.113 mole) of *o*-acetylaminoacetophenone in 150 ml. of methanol was added 32 g. (0.28 mole) of ammonium carbonate, 13.0 g. (0.20 mole) of potassium cyanide and 150 ml. of water. After stirring in an open beaker for 1 hr. at 50°, the mixture was slowly boiled down (hood) to a volume of 200 ml. Hydrochloric acid was cautiously added to *p*H 4, and the mixture was then evaporated to dryness and extracted with hot methanol. Evaporation of the methanol gave 11 g. of crude product. Recrystallization from water gave 9.5 g. (0.058 mole, 51%) of white crystals, m.p. 159.5–160.5° (reported[12] 160°).

Anal. Calcd. for $C_9H_9O_2N$: C, 66.24; H, 5.56; N, 8.59. Found: C, 66.35, 66.35; H, 5.48, 5.54; N, 8.21, 8.43.

Reaction of 3-methyl-3-hydroxyoxindole with either concentrated hydrochloric acid or with thionyl chloride gave non-crystalline polymeric material which could not be purified.

Acknowledgment.—The authors hereby thank the National Aniline Division, Allied Chemical and Dye Corporation, for a generous gift of isatin.

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[10] K. Brunner, *Monatsh.*, **18**, 533 (1897).

[11] P. Trinius, *Ann.*, **227**, 274 (1885).

[12] M. Kohn and A. Ostersetzer, *Monatsh.*, **32**, 911 (1911).

BROOKLYN, NEW YORK

NOTES

Preparation of Acenaphthylene from Acenaphthene[1]

BY ARTHUR G. ANDERSON, JR., AND ROBERT G. ANDERSON

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In connection with efforts to introduce further unsaturation into the pyracene molecule the conversion of acenaphthene to acenaphthylene was investigated. Two practical routes were found.[2]

Bromination of acenaphthene with two moles of N-bromosuccinimide gave 1,2-dibromoacenaphthene. Debromination of this intermediate with zinc and alcohol or tetrahydrofuran gave acenaphthylene in 80% yield. The over-all yield was *ca.* 45% when the dibromo compound was isolated and purified (56%) but was raised to 67% when the crude dibromo derivative was used.

The second method involved vapor phase pyrolysis of 1-acenaphthenyl acetate. Conditions were found which gave a 71% yield for this step and a 53% over-all yield from acenaphthene was realized. Subsequently it was discovered that a similar method had been reported in a patent.[3]

Experimental[4]

1,2-Dibromoacenaphthene.—A mixture of 19.7 g. (0.128 mole) of acenaphthene, 45.6 g. (0.256 mole) of N-bromosuccinimide, 250 ml. of dry carbon tetrachloride and a few crystals of benzoyl peroxide was heated under reflux for 30 minutes. The solid succinimide was separated and the solvent removed from the filtrate. The yellow solid remaining could be used in the dehalogenation reaction. Recrystallization from absolute ethanol–benzene and then from absolute ethanol gave 19.9 g. (56%) of product as colorless needles, m.p. 120.5–123°.[5]

Acenaphthylene. A. From 1,2-Dibromoacenaphthene.—A solution of 12.3 g. (0.039 mole) of purified 1,2-dibromoacenaphthene in 250 ml. of absolute ethanol[6] was added with stirring over a period of 1 hour to a boiling mixture of 65 g. (1.0 mole) of zinc dust and 300 ml. of absolute ethanol. After an additional reflux period of 1 hour the mixture was allowed to cool, the zinc dust removed by centrifugation and the ethanolic solution poured into 500 ml. of warm 5% hydrochloric acid. Upon standing a yellow solid (5.5 g.,

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[1] Support for a part of this work by contract DA-04-200-ORD-235 with the Office of Ordnance Research is gratefully acknowledged.

[2] After the present work had been completed, the dehydrogenation of acenaphthene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was reported by E. A. Braude, A. G. Brook and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954). As the quinone must be prepared separately this method is probably not superior to those described herein.

[3] R. G. Flowers, U. S. Patent 2,390,363, Dec. 4, 1945.

[4] Melting points are uncorrected.

[5] M. Blumenthal, *Ber.*, **7**, 1092 (1874).

[6] Dry tetrahydrofuran may be used as the solvent for the reaction. In this case water is added (after removal of the zinc) until the mixture is cloudy. The product separates and solidifies after several hours.