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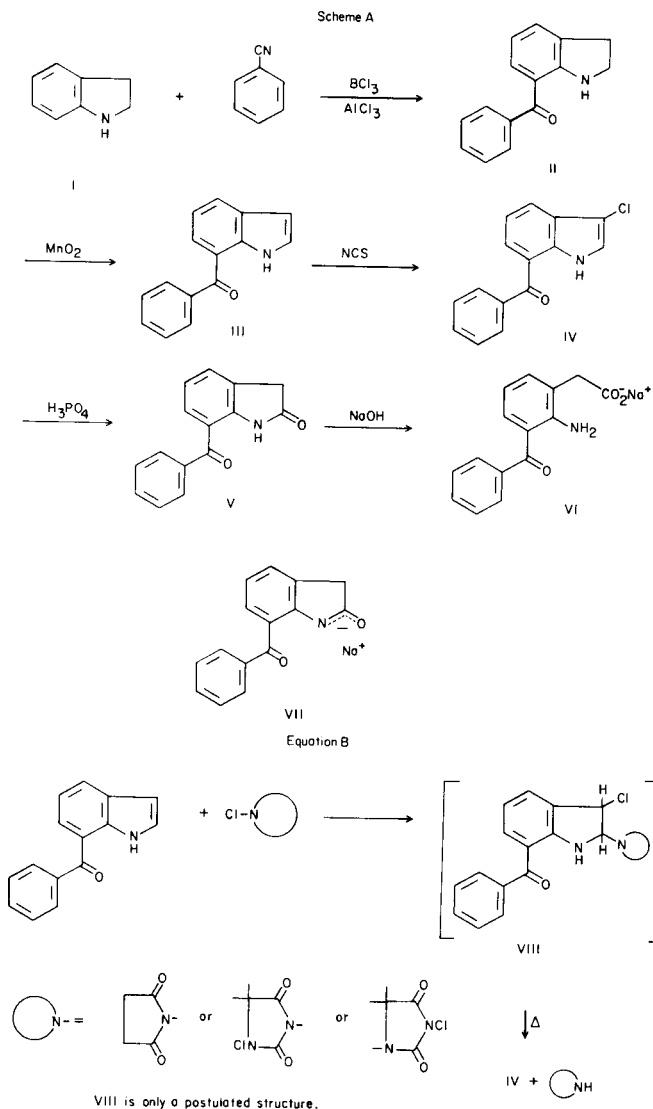
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Dedicated to Professor John C. Sheehan on the occasion of his sixty-fifth birthday.

2-Amino-3-benzoylphenylacetic acid, sodium salt was prepared from indoline through a process applicable to large scale production.

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Amfenac sodium (AHR-5850D, VI) was identified as a potent antiinflammatory agent several years ago at A. H. Robins research laboratories. A number of synthetic processes have been devised (1) for this compound and its analogs. Recently, we developed another synthetic scheme (Scheme A) which was demonstrated to work well from gram to pilot plant scale.



By modification of the method of Sugawara, *et al.* (2), *ortho*-benzoylation of indoline in the presence of boron trichloride gave an 80% yield of 7-benzoylindoline (II). Dehydrogenation of II to III, chlorination of III to IV, acid hydrolysis of IV to V, and saponification of V (86%) furnished product VI in an overall yield of 58% from indoline. In this unique sequence of reactions, we applied some well-known generic transformations (3) to our novel structures. The wealth of literature information was helpful in enabling us to develop a smooth procedure in a relatively short period of time; yet in some cases, we had to refine the existing procedure or find better reagents for the desired transformations. We wish to report here some of our experiences with this process which could be useful in other instances.

The active manganese dioxide used for dehydrogenation was supplied by Diamond Shamrock. It worked satisfactorily and remained active for at least six months. The dehydrogenation reaction can be conducted either at room temperature in toluene for less than an hour or at room temperature in methylene chloride for eighteen hours. Acetic acid was also found useful as a solvent.

Either *N*-chlorosuccinimide or 1,3-dichloro-5,5-dimethylhydantoin was employed as the chlorinating agent. In aprotic solvents such as methylene chloride, an adduct of the chlorinating agent and the indole compound (Equation B) was detected by mass spectroscopy. Both of these adducts decomposed thermally, but the hydantoin derivative was more stable than the succinimide derivative. In protic solvents like acetic acid, no such adduct could be detected. Thus, *N*-chlorosuccinimide was used in methylene chloride and the hydantoin derivative was preferred in acetic acid due to its advantage of costing less and providing two positive halogens.

Hydrochloric or sulfuric acid hydrolyses of 3-haloindoles to oxindoles are classical methods, but yields are usually less than 50%. The use of phosphoric acid for this transformation is new, and it provides higher yields of oxindoles. The mechanism of the reaction is believed to involve protonation of the indole ring as the first step. Hydrochloric acid is a strong enough acid to protonate the indole ring, but its low concentration (37%) at working

conditions results in slow reaction and incomplete conversion. Sulfuric acid has the concentration required for efficient protonation and thus rapid reaction but suffers from its strong oxidizing power which causes formation of oxidation side products (e.g., isatin derivatives). Phosphoric acid was thought to be able to provide rapid protonation without any oxidation and was demonstrated to be the reagent of choice. Either methoxyethanol or acetic acid can be used as a co-solvent to increase the solubility of IV in the reaction mixture.

Saponification of V to VI in a dilute aqueous solution was impractical due to the solubility of VI in water. Saponification in a concentrated alcoholic solution was also a problem because the sodium salt (VII) of oxindole, formed in the initial phase of the reaction, was insoluble and caused the mixture to form a non-stirrable solid cake. Toluene was used for the purpose of increasing the volume of the mixture so that the solid cake would become a stirrable suspension. Since toluene is not a good solvent for VI, the solvent system dissolves less product and thus facilitates isolation. It was also found that toluene as a co-solvent helped to minimize the formation of some undesirable side-products.

#### EXPERIMENTAL

##### 7-Benzoylindoline (II).

A solution of indoline (99%, 120 g., 1.0 mole) and benzonitrile (124 g., 1.2 moles) in toluene (555 ml.) was heated to reflux, and 90 ml. of toluene distilled to remove any moisture present. A separate reaction vessel was charged with toluene (745 ml.) and after chilling to 5°, boron trichloride (130 g., 1.1 moles). The boron trichloride solution was kept at 5-10° while the dried indoline-benzonitrile solution was added over a period of 2.5 hours. While cooling was maintained, aluminum chloride (147 g., 1.1 moles) was added portion-wise over a period of 45 minutes at 5-10°. The reaction mixture was then heated to reflux for 16 hours. The reaction was cooled to 8°, and water (188 ml.) was added. A heavy gum precipitated but stirring was continued. After the addition of 800 ml. of 2*N* hydrochloric acid, the reaction mixture was heated to reflux again for 2.5 hours. During the reflux period, the mixture changed to a tan, granular suspension. This solid was collected by filtration after the mixture was cooled to room temperature, washed several times with ice water, and compressed with rubber sheeting. The damp solid was resuspended in 1.1 liter of water, and the suspension was basified with 25% sodium hydroxide at a temperature below 20°. The suspension changed to a yellow, granular consistency and stirring was continued for 4 hours, during which time the mixture became milky, and the solid lost its granular appearance. The yellow solid was collected and washed with water. The dry solid weighed 179 g., 80% yield, m.p. 121-125° [lit. (4) m.p. 124-125°]; nmr (deuteriochloroform): ppm 7.90-6.85 (M, 8H), 6.55 (t, J = 7.5 Hz, 1H), 4.05-2.90 (M, 4H).

##### 7-Benzoylindole (III).

7-Benzoylindoline (II, 223 g., 1.0 mole) was dissolved in 2.23 liters of methylene chloride. Manganese dioxide (Diamond-Shamrock's M grade, 261 g., 3.0 moles) was added, and the reaction was agitated under reflux for 18 hours. The reaction mixture was filtered to remove the manganese dioxide. The filter cake was rinsed with 200 ml. of hot methylene chloride. The filtrate and washing were used for the next step. For isolation of compound III, methylene chloride was evaporated and the residue crystallized from toluene; m.p. 103-104° [lit. (1) m.p. 103-104°]; nmr (deuteriochloroform): ppm 10.43 (br, 1H), 7.85-8.86 (M, 9H), 6.52

(M, 1H).

##### 3-Chloro-7-benzoylindole (IV).

The methylene chloride solution of 7-benzoylindole (III) prepared from one mole of 7-benzoylindoline (II) was chlorinated with *N*-chlorosuccinimide (119.0 g., 0.87 moles) at 15° to 20° in a nitrogen atmosphere. The *N*-chlorosuccinimide was divided into four equal portions and added to the reaction at one-half hour intervals. The reaction was washed twice with 2.5 liters of water one hour after the final NCS addition. The combined aqueous washings were extracted with 200 ml. of methylene chloride. This methylene chloride solution was washed with an equal volume of water. The two methylene chloride solutions were combined and distilled at reduced pressure to a liquid temperature of about 80°. This residue was used to make compound V. Compound IV was crystallized from methanol, m.p. 148-149.5°; nmr (deuteriochloroform): 10.42 (br, 1H), 7.98-7.05 (M, 9H).

Anal. Calcd. for C<sub>13</sub>H<sub>10</sub>ClNO: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.40; H, 4.08; N, 5.55.

##### 7-Benzoyloxindole (V).

Compound IV as a residue from the chlorination reaction was dissolved in 2-methoxyethanol (1.8 l.) and heated to 100° with stirring. Phosphoric acid (70%, 1.3 l.) was added in a steady stream. The indole phosphate salt separated at this point but stirring was continued. The reaction mixture was kept at reflux for 4-8 hours. Tlc (silica gel, 1% methanol in chloroform) was used to monitor the reaction. Upon completion of the reaction, the mixture was treated with charcoal (20-40 g.) at reflux temperature for fifteen minutes and then filtered. The filtrate was maintained at a temperature of approximately 70° while 2.3 liters of water at 65-70° were added with stirring. The product began crystallizing during the water addition. The slurry was slowly cooled to about 5° and held there for 12 hours. The crystals were collected and dried to give 199 g. of V, 84% yield from 7-benzoylindoline, m.p. 146-151° [lit. (1) m.p. 154°]; nmr (deuteriochloroform + DMSO-d<sub>6</sub>): 9.78 (br, 1H), 7.85-7.35 (M, 7H), 6.99 (t, J = 7.5 Hz, 1H), 3.55 (S, 2H).

Sodium (2-Amino-3-benzoylphenyl)acetate Monohydrate (Amfenac Sodium, AHR-5850D, VI).

7-Benzoyloxindole (237 g., 1.0 mole) was dissolved in toluene (711 ml.) and 95% ethanol (711 ml.) with stirring at 70°. With the heating source turned off, 50% sodium hydroxide (160 g., 2.0 mole) was added to the stirred solution in a steady stream. After about three-quarters of the sodium hydroxide had been added, the sodium salt (VII) of the oxindole came out of solution as a heavy precipitate, but stirring was maintained. After all the sodium hydroxide was added, the mixture was heated to reflux for 4-5 hours. When tlc indicated all of the starting material had reacted, the mixture was treated with 15 g. of charcoal at reflux temperature for 15 minutes and then filtered. The filtrate was stirred while diisopropyl ether (1.42 liters) was added. The product began crystallizing immediately. The slurry was chilled to 5° and kept for 7-8 hours. The product was collected by filtration and washed with 50 ml. of cold dimethoxyethane. The dried product weighed 254 g., yield 86%; m.p. 248-252° dec. [lit. (1) m.p. 254-255° dec.]; nmr (deuterium oxide): 7.42-6.88 (M, 7H), 6.39 (t, J = 7 Hz, 1H), 4.88 (S, 6.5 H), 3.60 (S, 2H).

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