N-(2-Nitrobenzyl)phthalimide[11] (XVI) was prepared in 62% yield by the procedure developed for III, m.p. 224–225°. (Reported,[11] 219–220°).

N-(2-Methyl-5-nitrobenzyl)succinimide (XVII) was prepared in 42% yield according to the procedure for III. It was recrystallized successively from ligroin, ethyl acetate-hexane, and twice from benzene-hexane, but a sharp melting point was never obtained, the compound softening at 116° and melting at 120.0–122.0°. Its infrared spectrum shows typical 5-membered ring imide absorption at 5.66 and 5.88 μ.

Anal. Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.97; H, 4.83; N, 11.31.

N-(4-Nitrobenzyl)phthalamic acid. N-(4-Nitrobenzyl)-phthalimide, 580 mg., was stirred under nitrogen for 35 min. with 20 ml. of 5% potassium hydroxide in ethanol. Addition of 2 ml. of acetic acid and dilution to 100 ml. with water precipitated 103 mg. of starting material, which was filtered off. The filtrate slowly deposited 73 mg. (15%) of yellow crystals, m.p. 187–190° dec. Purification for analysis was effected by boiling with 7 ml. of acetone; solution in 2 ml. of dimethylformamide, filtration, and precipitation with water; and a final reflux with acetone. The product now melted at 214–215° dec.

Anal. Calcd. for $C_{15}H_{12}O_5N_2$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.96; H, 4.16; N, 9.35.

N-(2-Nitrobenzyl)phthalamic acid. To a solution of 500 mg. of N-(2-nitrobenzyl)phthalimide in 20 ml. of acetone was added 15 ml. of 2% potassium hydroxide in ethanol, and the solution was stirred with a stream of nitrogen for 3.00 min., while the color changed to light orange. Addition of 9 drops of concentrated hydrochloric acid and dilution to 220 ml. with water precipitated 372 mg. (74%) of N-(2-nitrobenzyl)phthalamic acid. The product changed from long needles to prisms at 190–200°, and then melted at 221–223°. The infrared spectrum of the product, after heating to complete conversion to prisms, proved it to be identical with starting material. The infrared spectrum of the unheated product (needles) showed absorption at 3.00, 5.90, and 6.04 μ, in agreement with the phthalamic acid structure. No further analyses were obtained.

N-(4-Aminobenzyl)phthalimide (XVIII). Reduction of N-(4-nitrobenzyl)phthalimide over Adams' catalyst in benzene produced XVIII, yellow crystals m.p. 205–207° dec., in 88% yield. It was crystallized from chloroform and ligroin for analysis, m.p. 207–208° dec.

Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.47; H, 4.84; N, 11.20.

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[Contribution from the School of Chemistry, Rutgers, The State University]

Syntheses of N-Substituted Isoindolines. II. Derivatives of Quinolinimide

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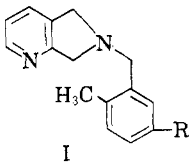
A practical synthetic approach to 2-substituted 4-azaisoindolines has been developed. The nature of the basic hydrolysis products of N-benzhydrylquinolinimide has been investigated and their structures established.

The synthesis of 2-benzylhydryl-4-azaisoindoline, IX, was undertaken as a model for the synthesis of structure I.[2] It was anticipated that IX might have some interesting pharmacological action of its own.



I

The obvious methods for preparing N-benzhydrylquinolinimide, IV, (heating quinolinic acid and benzhydrylamine together in refluxing xylene, acetic anhydride, ethylene glycol, or without a solvent, or refluxing a mixture of diethyl quinolinate and benzhydrylamine at atmospheric pressure) led only to nicotinic acid benzhydrylamide, VII, because of the ease of decarboxylation of picolinic acids. However the mixed anhydride procedure of Vaughan[3] gave an acceptable yield of 3-carbethoxypicolinic acid N-benzhydrylamide, II, accompanied by the isomeric amide III. When heated to 200° in vacuum, the mixture of II and III was converted to N-benzhydrylquinolinimide, IV, which was readily separable from unchanged III on the basis of the solubility of III in ethanol, in which IV is only slightly soluble.

Dilute potassium hydroxide in aqueous ethanol rapidly hydrolyzed IV to a mixture of V and VI. The ratio of VI/V was found to increase rapidly with time. After 1 hr. the ratio was very nearly one, while VI was produced quantitatively in 24 hr. In addition, 3-carboxy-N-benzhydrylpicolinamide, V, rearranged to 2-carboxy-N-benzhydrylnicotinamide, VI, on attempted recrystallization from ethanol-water, or on heating its hydrochloride above 100°. The decarboxylation product of VI, nicotinic acid N-benzhydrylamide, VII, was synthesized independently by refluxing a mixture of nicotinic acid and benzhydrylamine briefly at atmospheric pressure.

The direct reduction of IV to 2-benzhydryl-4-

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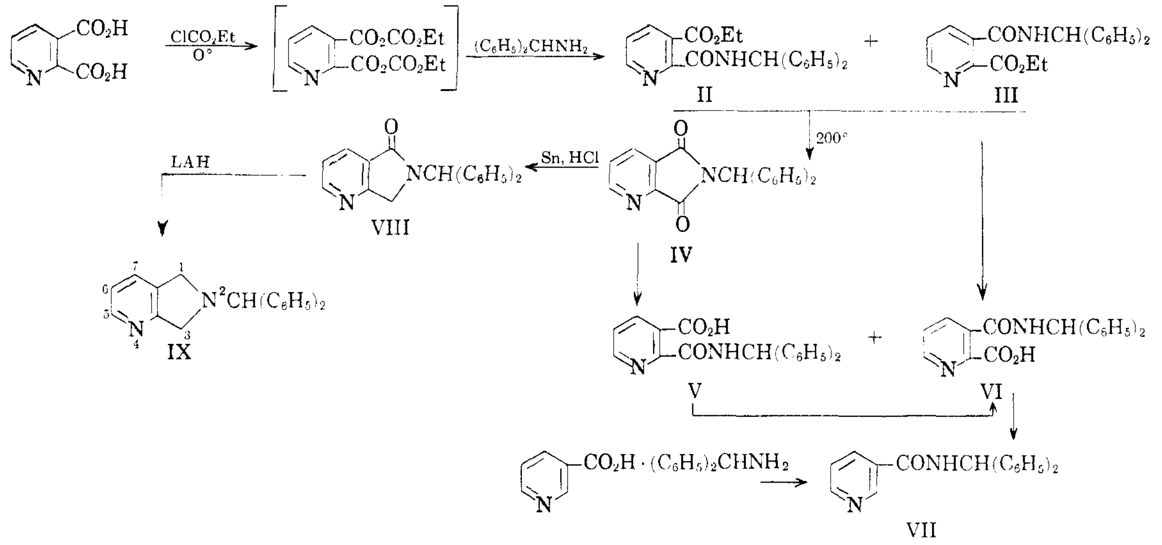
[1] Smith, Kline & French, postdoctoral fellow, 1955–1957.

[2] See paper I, R. A. Barnes and J. C. Godfrey, *J. Org. Chem.*, **22**, 1038 (1957).

[3] J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **74**, 676 (1952).



azaisoindoline, IX, with lithium aluminum hydride gave only a trace of IX, accompanied by a complex mixture of by-products. Reduction of IV with tin and hydrochloric acid in glacial acetic acid[4] led to an intermediate which is thought to be 1-keto-2-benzhydryl-4-azaisoindoline, VIII. This product was completely resistant to basic hydrolysis, and on treatment with hydrogen iodide and red phosphorous at 180°[5] yielded a colorless amino acid which gave no color with ferrous sulfate solution,[6] indicating that it was not a picolinic acid. It did not decarboxylate below 200°, but neither did it yield a picoline on fusion with potassium hydroxide. The product of the latter reaction exhibited only basic properties but could not be obtained pure with the quantity of material available. The alternative 3-keto structure for VIII could hardly be accomodated by the above observations. In addition, coordination of tin at the pyridine nitrogen atom might be expected to favor reduction at the α- rather than the β-carbonyl of *N*-benzhydrylquinolinimide.

Reduction of VIII to 2-benzhydryl-4-azaisoindoline (IX) proceeded smoothly with lithium aluminum hydride in ether only when the reaction was carried out at 0°. At higher temperatures further reactions of IX in the presence of the reducing agent produced colored products which were too unstable to be characterized.

EXPERIMENTAL[7]

3-Carbethoxypicolinic acid benzhydrylamide (II). Quinolinic acid 1.00 g. (6.00 mmole) was suspended in a mixture of 20 ml. dry chloroform and 15 ml. dry benzene, and treated with 1.20 g. (12.0 mmole) of triethylamine, resulting in the formation of two liquid phases. The mixture was cooled to 0° and 1.30 g. (12.0 mmole) of ethyl chlorocarbonate dissolved in 5 ml. of chloroform was added. After standing 20 min. at 0°, a solution containing 1.32 g. (6.00 mmoles) of benzhydrylamine hydrochloride and 0.60 g. (6.0 mmoles) of triethylamine in 16 ml. of dry chloroform was added, accompanied by evolution of gas. The mixture stood at 25° overnight. Removal of solvent left a crystalline mass which was washed with 100 ml. of water and 2 × 60 ml. of 10:1 ammonium hydroxide, leaving 1.620 g. (75%) of white crystals, m.p. 150–170°. It was treated with charcoal and crystallized 5 times from ethanol-hexane, m.p. 172.0–173.0°. The infrared spectrum shows absorption at 3.09 (N—H), 5.75 (ester carbonyl), and 6.08 (amide carbonyl) μ.

Anal. Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; N, 7.77. Found: C, 73.16; H, 5.49; N, 7.77.

2-Carbethoxynicotinic acid benzhydrylamide (II). Exhaustive dilution with water of the first recrystallization liquor from the preparation of II precipitated tan needles which, after 20 recrystallizations from ethanol-water, yielded colorless needles, m.p. 110.0–111.0°. It was air-dried for analysis, since vacuum drying over phosphorus pentoxide was found to depress the melting point and the carbon value obtained. Even with these precautions, the sample gave a consistently low carbon value, probably because of the ready loss of ethanol to form IV.

Anal. Calcd. for $C_{22}H_{20}O_3N_2$: C, 73.31; H, 5.59; N, 7.77. Found: C, 72.18; H, 5.52; N, 7.93.

When 2-carbethoxynicotinic acid benzhydrylamide was heated at 100° for 0.5 hr. with 10% aqueous potassium hydroxide, a mixture of 2-carboxynicotinic acid benzhydrylamide (VI) and *N*-benzhydrylnicotinamide (VII) was produced.

N-Benzylhydrylquinolinimide (IV). The crude mixture of II + III, 33.0 g., was heated under aspirator vacuum at 180–195° for 1 hr. The glass obtained on cooling was boiled with 200 ml. of absolute ethanol. Cooling gave 27.2 g. (93%) of IV, m.p. 159.7–161.0°. It was dissolved in 200 ml. of chloroform, treated with charcoal at room temperature, and the solvent replaced with ethanol by distilling off the chloroform through a short column while adding ethanol. The purified product melted at 160.3–161.8°.

Anal. Calcd. for $C_{20}H_{14}O_2N_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.49; H, 4.41; N, 8.98.

3-Carboxypicolinic acid benzhydrylamide (V). A solution of 1.40 g. (4.46 mmole) of *N*-benzhydrylquinolinimide (IV), 184 ml. of 95% ethanol, 176 ml. of water, and 3.50 g. (6.25 mmole) of potassium hydroxide was shaken at 25° for 50 min. The solution was acidified with 3 ml. of 6*N*

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(4) A. Hafner, *Ber.*, **23**, 337 (1890).

(5) S. Gabriel and J. Coleman, *Ber.*, **35**, 2831 (1902).

(6) H. S. Mosher and R. C. Elderfield, *Heterocyclic Compounds*, J. Wiley and Sons, Inc., New York, 1950, Vol. I, p. 569.

(7) Microanalyses by W. Manser, Zurich, Switzerland. All melting points are corrected.

hydrochloric acid, concentrated to 120 ml., and diluted with 60 g. of ice, which precipitated white crystals, m.p. 160–175° with evolution of gas. It was recrystalized from 25 ml. of ethanol-water, needles, m.p. 195–200°, and finally purified for analysis by solution in 5% ammonium hydroxide, treatment with charcoal, and precipitation with 5% acetic acid, m.p. 205–206°. The sample gave no color when dissolved in ethanol containing ferrous sulfate. Its infrared spectrum (Nujol mull) exhibited strong absorptions at 3.05, 5.92, and 6.03 μ.

Anal. Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.54; H, 4.91; N, 8.67.

2-Carboxynicotinic acid benzhydrylamide (VI). Dilution of the original 180 ml. aqueous filtrate from V to one liter with water slowly precipitated VI, which was filtered off after 5 days and purified in the same manner as V. The product decarboxylated above *ca.* 152°, to form *N*-benzhydrylnicotinamide, m.p. 184°. It gave a bright orange color with ferrous sulfate in ethanol, and exhibited strong absorptions (Nujol mull) at 3.02, 5.85, and 6.12 μ.

Anal. Calcd. for $C_{20}H_{16}O_3N_2$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.36; H, 4.91; N, 8.51.

The relative amounts of V and VI obtained were found to depend upon duration of reaction, long reaction times favoring production of VI. In no experiment did the yield of V exceed 50%, while nearly quantitative yields of VI were obtained if the reaction was allowed to proceed for a day or more.

N-Benzhydrylnicotinamide (VII). (*a*) *From quinolinic acid and benzhydrylamine.* A mixture of 424 mg. (2.33 mmoles) of benzhydrylamine, 393 mg. (2.35 mmoles) of quinolinic acid, and 7.5 ml. of ethylene glycol was refluxed for 1 hr. Dilution with 45 ml. of water yielded a product which was crystallized from ethanol-water and ethanol-ligroin for analysis, m.p. 178.0–178.5°.

Anal. Calcd. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.08; H, 5.58; N, 9.76.

(*b*) *From 3-carboxypicolinic acid benzhydrylamide* (V). The hydrochloride of V was quantitatively converted to VII by heating to 200° in vacuum. It was recrystallized several times from ethanol-water, m.p. 183.2–184.2°.

Anal. Found: C, 79.04; H, 5.54; N, 9.84.

(*c*) *From 2-carboxynicotinic acid benzhydrylamide* (VI). When heated to 190° under vacuum, 14 mg. of VI yielded 13 mg. of VII, m.p. 182–184°.

(*d*) *From nicotinic acid and benzhydrylamine.* Nicotinic acid, 1.14 g. (0.0062 mole), and 919 mg. (0.0075 mole) of benzhydrylamine was heated to 230° in a wax bath, and then at reflux over a small flame for 2.5 min. The cooled mass was boiled with 15 ml. of water, filtered, and the precipitate which separated on cooling was crystallized twice from ethanol and 4 times from ethyl acetate to a final m.p. 182–184°. Purified yield, 320 mg. (18%).

The samples of *N*-benzhydrylnicotinamide from all sources were shown to be identical by comparison of their infrared spectra.

1-Keto-2-benzhydryl-4-azaisoindoline (VIII). Twenty grams (0.064 mole) of *N*-benzhydrylquinolinimide (IV), 400 ml. of glacial acetic acid, and 15.3 g. (0.129 mole) of mossy tin were placed in a 1 liter flask fitted with a stirrer, reflux condenser, and dropping funnel, and heated to 100°. To this stirred mixture was added 26 ml. of concentrated hydrochloric acid, which caused rapid development of a yellow color. After 10 min. an additional 24 ml. of concentrated acid was added and the mixture was stirred at 100° for 50 min., then at reflux for 10 min. Removal of solvent under vacuum left a gummy solid which was washed *in situ* with 4 × 50 ml. of water. The product was dissolved in 750 ml. of ethanol, made basic with concentrated ammonium hydroxide to precipitate the oxides of tin, and filtered with the aid of "Filtercel". The resulting deep blue filtrate was diluted to 5 liters with water and allowed to stand for 36 hr. The resulting precipitate was filtered off, dissolved in 200 ml. of benzene, dried over magnesium sulfate, and treated with charcoal in the cold. The yellow solution thus obtained was freed of solvent under vacuum, and the remaining gum taken up in 120 ml. ethanol, acidified with dilute hydrochloric acid, and treated twice with charcoal. Removal of most of the solvent and neutralization with 500 ml. of 10:1 ammonium hydroxide yielded 10.5 g. (55%) of prisms, m.p. 121–123°. The product was recrystallized from 500 ml. of hexane containing a little ethyl acetate, 9.7 g. (50%), m.p. 124.5–125.8°.

Anal. Calcd. for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33. Found: C, 79.97; H, 5.44; N, 9.30.

The *picrate* was prepared in and recrystallized from ethanol, m.p. 161.0–162.0°.

Anal. Calcd. for $C_{20}H_{16}ON_2 + C_6H_3O_7N_3$: C, 58.98; H, 3.62; N, 13.23. Found: C, 58.36; H, 3.64; N, 12.90.

2-Benzhydryl-4-azaisoindoline (IX). To a solution of 11.9 g. (0.031 mole) of lithium aluminum hydride dissolved in 1 liter of dry ether and cooled to 0° was added 14.0 g. (0.047 mole) of finely ground 1-keto-2-benzhydryl-4-azaisoindoline, and the mixture was stirred at 0° for 30 hr. It was then allowed to warm to 20° during 8 hr., and the excess reagent was decomposed by the successive addition of 120 ml. of 1:1 ethanol-ether and 60 ml. of saturated sodium sulfate in water. The yellow-green solvent layer which separated was evaporated to 400 ml. and extracted with 3 × 75 ml. of 1*N* hydrochloric acid. An orange solid separated at this point and was removed by filtration. Basification of the aqueous extract with sodium carbonate precipitated an off-white solid, m.p. 160–163°. The product was dissolved in 200 ml. of benzene, thoroughly dried over magnesium sulfate, and passed over a 0.5 × 8.5 in. column of 80/200 mesh activated alumina. The column was eluted with 500 ml. of benzene. Removal of solvent from the eluate under vacuum left off-white crystals, from which the color was removed by boiling with 50 ml. of freshly-distilled dry ether. Cooling to 0° and filtration yielded 5.40 g. (40.5%) of prisms, m.p. 161–162° sl. dec. This material was shown by comparison of the infrared spectra to be identical with a sample previously obtained in trace amount by direct reduction of *N*-benzhydryquinolinimide. It was crystallized from hexane for analysis, m.p. 162.0–162.2° dec.

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.72; H, 6.36; N, 9.86.

The *dipicrate* formed in ethanol and was crystallized from the same solvent, m.p. 197.0–197.5° dec.

Anal. Calcd. for $C_{20}H_{18}N_2 + 2C_6H_3O_7N_3$: C, 51.62; H, 3.25; N, 15.05; mol. wt., 744.6. Found: C, 52.11; H, 3.26; N, 14.67; mol. wt., 745.8.

NEW BRUNSWICK, N. J.