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Substances Related to the Iboga Alkaloids. Synthesis and Reactions of 3-(2-Indolyl)piperidine

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In model studies directed at finding a synthetic pathway to the ibogaine ring system, a number of compounds derived from 3-(2-indolyl)piperidine (Va) have been prepared, and their conversion to IIa attempted. Ethyl 1-[3-(2-indoyl)piperidyl]acetate (IIIa) and the corresponding acid were synthesized by the reduction of the appropriate quaternary salt of 3-(2-indolyl)pyridine. The parent compound (IVa) was prepared by the sequence 3-(2-indolyl)pyridine → 1-benzyl-3-(2-indolyl)pyridinium bromide → 1-benzyl-3-(2-indolyl)-1,2,5,6-tetrahydropyridine → 3-(2-indolyl)piperidine. A number of attempts to convert IV to compounds related to II are reported.

Although the presence of an isoquinuclidine moiety in the alkaloids of the ibogaine group has been noted, and various synthetic efforts have been directed at the synthesis of substances of this type,[2] and of compounds derived from the degradative studies of the natural alkaloids,[3] there have been no reported syntheses of compounds of the 3-(2-indolyl)piperidine group which is also characteristic of these alkaloids. Some appropriately substituted compound of this type might prove to be a worthwhile starting material for a projected total synthesis of the naturally occurring compounds. The possibility also exists that such synthetic compounds might possess useful physiological properties.

The most attractive starting material for the synthesis of 3-(2-indolyl)piperidine and its derivatives appeared to be 3-(2-indolyl)pyridine (I), prepared by cyclization of 3-acetylpyridine phenylhydrazone.[4] By an appropriate reaction sequence this compound may be convertible into the tetracyclic compound (IIa), which lacks only four carbon atoms of the ibogamine molecule. Initially, the indolylpyridine was treated with ethyl bromoacetate to form the quaternary salt. This was hydrogenated to the substituted piperidine (IIIa); however, all efforts to effect the cyclization of IIIa, or the corresponding acid (IIIb) to the ketone (IIb), resulted in either recovery of the starting material or the formation of dark, resinous materials.

The attempted cyclizations included the action of polyphosphoric acid at a variety of temperatures on both the acid and its esters, and also treatment of the ester with sodium hydride in a number of solvents and at various temperatures.

An alternate approach to II was devised, employing 3-(2-indolyl)piperidine (IVa) as the starting material. It was envisioned that the remaining ring would be added *via* a gramine synthesis as employed in the synthesis of the dehydrogenation products of ibogamine[3] and in the synthesis of an indoloquinolizine.[4b] Attempted hydrogenation of I, employing platinum oxide catalyst, in either neutral or acidic solution, failed to afford the desired piperidine.

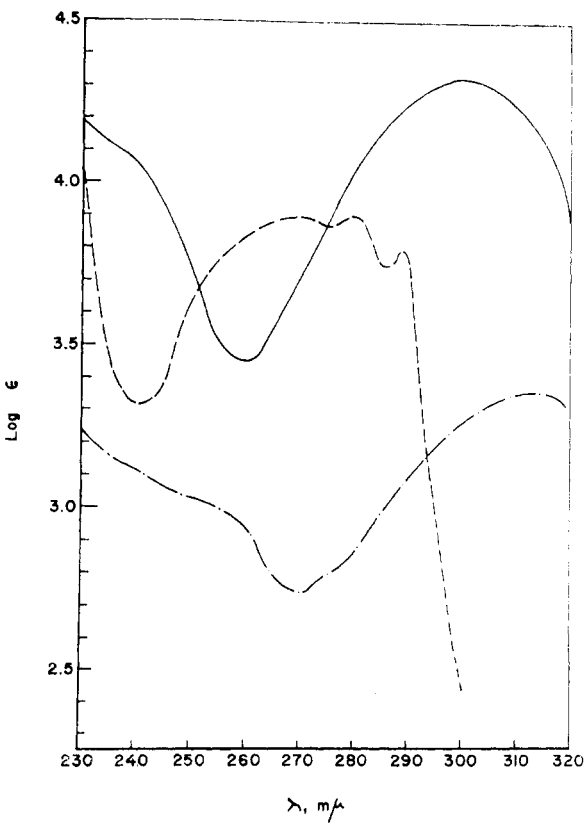

Fig. 1. Ultraviolet spectra: (———) 1-benzyl-3-(2-indolyl)-1,2,5,6-tetrahydropyridine; (– – – –) 3-(2-indolyl)-piperidine; (–·–·–·) 3-(2-indolyl)pyridine

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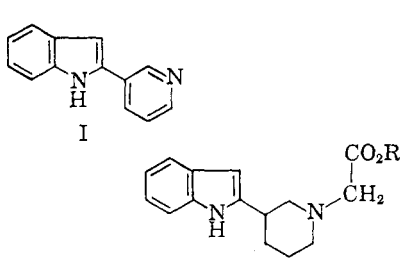
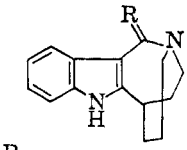
(2) L. H. Werner and S. Ricca, *J. Am. Chem. Soc.*, **80**, 2733 (1958).

(3) H. B. MacPhillamy, B. C. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Am. Chem. Soc.*, **80**, 2172 (1958).

(4)(a) A. P. Gray and W. L. Archer, *J. Am. Chem. Soc.* **79**, 3554 (1957). (b) S. Sugasawa, M. Terashima, and Y. Kanaoka, *Pharm. Bull. (Japan)*, **4**, 16 (1956). *Chem. Abstr.*, **51**, 3593 (1957).



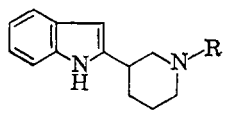
I



IIa. R = H_2
b. R = O

IIIa. R = C_2H_5
b. R = H

Accordingly, an indirect route to IVa was devised. Reaction of 3-(2-indolyl)pyridine with benzyl bromide gave the quaternary salt in excellent yield. Upon reduction with sodium borohydride, it afforded 1-benzyl-3-(2-indolyl)-1,2,5,6-tetrahydropyridine.[5]

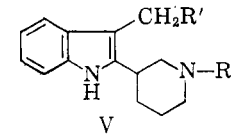


IVa. R = H
b. R = $SO_2C_7H_7$
c. R = COC_6H_5

Hydrogenation of this tetrahydropyridine was accompanied by hydrogenolysis of the benzyl group, affording the desired 3-(2-indolyl)piperidine (IVa). This indirect route may be general for reduction of a pyridine to a piperidine where direct methods fail. The over-all yield (23%) appears to be at least adequate.

The indolylpiperidine was converted to the *p*-toluenesulfonamide (IVb), which was treated with formaldehyde and dimethylamine to give the gramine (Va). With aqueous alcoholic potassium cyanide it gave a mixture of the amide (Vc) and the nitrile (Vd).

Hydrolysis of this mixture with base gave the corresponding acid (Ve). A number of attempts were made to remove the *p*-toluenesulfonamide group from this series of compounds using the hydrobromic–acetic acid–phenol method which has been used successfully in the synthesis of dehydrogenation products of the natural materials,[3]



V

a. R = $SO_2C_7H_7$	R′ = $N(CH_3)_2$
b. R = COC_6H_5	R′ = $N(CH_3)_2$
c. R = $SO_2C_7H_7$	R′ = $CONH_2$
d. R = $SO_2C_7H_7$	R′ = CN
e. R = $SO_2C_7H_7$	R′ = CO_2H
f. R = COC_6H_5	R′ = $^+N(CH_3)_3I^-$
g. R = COC_6H_5	R′ = CN

and other *p*-toluenesulfonamides.[6] However, treatment of any of these compounds under the usual conditions for cleavage of toluenesulfonamides gave only dark materials which could not be dissolved in organic solvents. Attempted cleavage of IVb to the parent indolyl piperidine also failed to yield any isolable product.[7]

Alternatively, IVa was converted to the benzamide (IVc) and thence to the gramine (Vb). Treatment of this gramine with cyanide gave a mixture of the amide and nitrile; however, we were unable to isolate the amino acid following basic hydrolysis of this mixture.

A final attempt to prepare II, involving mild reaction conditions, was carried out. The gramine (Vb) was converted to its methiodide (Vf) which on heating for a short period of time with potassium cyanide afforded the nitrile (Vg).[8]

Hydrolysis of Vf with base gave no isolable amino acid, although a small quantity of benzoic acid was obtained. In view of the difficulties encountered in preparing reasonable quantities of intermediates, and the problems associated with the cyclization to II, this approach to the ibogaine ring system appears to leave much to be desired, and has consequently been abandoned.

(5) Although it is known that various 3-substituted pyridinium salts are reduced by borohydride to 1,3-disubstituted 1,2,5,6-tetrahydropyridines, [K. Schenker, *Angew. Chem.*, **72**, 638 (1960)] the double bond in our reduction product could be located elsewhere in the tetrahydropyridine ring. The tetrahydropyridine has an ultraviolet spectrum very similar in shape to that of 3-(2-indolyl)pyridine; however, each maximum is shifted to a lower wave length by 4 to 18 mμ. (Fig. 1). This may be interpreted as indicating that the unsaturation in the reduction product is conjugated with the indole ring, and that it must either be the Δ^3-tetrahydropyridine, or the Δ^2-isomer. The spectra of 3-(2-indolyl)piperidine and its derivatives show normal indole absorption (Fig. 1). Since the Δ^2-tetrahydropyridine is an enamine conjugated with an aromatic system, the ultraviolet spectrum should show a shift in acid solution; however, the ultraviolet spectrum of this compound failed to show any change in acid solution. The spectrum of 3-(2-indolyl)pyridine changes markedly in acid solution (maxima at 245 and 325 mμ) and is similar to that of its quaternary salts and the spectra of the indolyl piperidines are not altered in acid. This spectral evidence, coupled with Schenker's results, indicates that the reduction product is almost certainly 1-benzyl-3-(2-indolyl)-1,2,5,6-tetrahydropyridine.

(6) (a) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, **74**, 2006 (1952). (b) H. R. Snyder and H. C. Geller, *J. Am. Chem. Soc.*, **74**, 4864 (1952). C. D. I. Weisblat, B. J. Magorlein, A. R. Hanze, E. I. Fairburn, and S. T. Rolfson, *J. Am. Chem. Soc.*, **75**, 5893 (1953).

(7) The decomposition of these compounds under strongly acid conditions is possibly due to the fact that the amines react to give a vinyl indole, which would polymerize under the conditions cited.

(8) Although the method of synthesis of this nitrile and the analytical data leave little doubt of its identity, the infrared spectrum shows medium absorption at 5.80 μ, either in chloroform solution or in potassium bromide. This unusual band is in addition to the nitrile absorption at 4.46 μ, and the amide band at 6.20 μ. The absorption at 6.20 μ is at unusually long wave length; however, the parent amide (IVc) also absorbs at 6.20 μ. Normally amides of this type show carbonyl absorption at 5.98 to 6.13 μ. (L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Methuen, London, 1958, pp. 203 ff.) The band at 5.80 μ is an unexplained anomaly.

EXPERIMENTAL[9]

3-(2-Indolyl)pyridine. This compound was prepared by a modification of the method of Gray and Archer.[4a] A mixture of 300 g. of polyphosphoric acid and 37.5 g. of once recrystallized 3-acetylpyridine phenylhydrazone (m.p. 140–143°)[10] was heated 1 hr. on the steam bath with occasional stirring, and then warmed on a hot plate to 135° for 10 min. The dark brown reaction mixture was poured into water, allowed to cool and made basic by the cautious addition of 50% potassium hydroxide. The resulting cream-colored solid was collected, washed with water, and dissolved in ethanol. The ethanol solution was filtered, heated to the boiling point and diluted with water to incipient turbidity. After cooling there was obtained 23.3 g. (68%) of 3-(2-indolyl)pyridine, m.p. 170–175°. Gray and Archer give a m.p. of 166–173° for once recrystallized material, while Sugasawa[4b] gives m.p. 174°. λ_{max}: 288 mμ, log e, 3.26; 256 mμ (Sh), log ε 3.00; 315 mμ, log ε 3.35. Shifted in acid to λ_{max} 245 mμ log ε 3.37; 325 mμ, log ε 3.42.

1-Carbethoxymethyl-3-(2-indolyl)pyridinium bromide. To a solution of 5.0 g. of 3-(2-indolyl)pyridine in 100 ml. of ethyl acetate was added 10 ml. of ethyl bromoacetate. The reaction mixture was kept overnight at room temperature, and the supernatant liquid decanted from the orange, crystalline product. Recrystallization from ethanol–ethyl acetate gave 5.4 g. (50%) of yellow-orange crystals, m.p. 128–130°. The analytical sample, m.p. 130–132°, was prepared from the same solvent pair. λ_{max}: 249 mμ, log ε 4.12; 331 mμ, log ε 4.26.

Anal. Calcd. for $C_{17}H_{17}BrN_2O_7$: C, 56.52; H, 4.74; N, 7.76. Found: C, 56.30; H, 4.91; N, 7.60.

1-Benzyl-3-(2-indolyl)pyridinium bromide. To a solution of 20 g. of 3-(2-indolyl)pyridine in 350 ml. of ethyl acetate was added 36 ml. of benzyl bromide. After three days the crystals were collected and washed well with ethyl acetate and ether to give 37.4 g. (99%) of orange solid, m.p. 232–235°, which could be used without additional purification. The analytical sample was recrystallized from ethanol, and had m.p. 233–235° dec., λ_{max}: 247 mμ, log ε, 4.14.

Anal. Calcd. for $C_{20}H_{17}BrN_2$: C, 65.76; H, 4.69; N, 7.67. Found: C, 65.84; H, 4.80; N, 7.57.

Ethyl 1-[3-(2-indolyl)piperidyl]acetate. A solution of 4.5 g. of the quaternary salt from ethyl bromoacetate and the indolylpyridine in 50 ml. of ethanol was hydrogenated at 50 p.s.i., and room temperature, using 0.5 g. of platinum oxide catalyst.[11]

The catalyst was filtered out and the solvent removed at reduced pressure, leaving a dark brown glass. This material was dissolved in water, made basic with 5% sodium bicarbonate and extracted with chloroform. The chloroform extract was washed with water, dried, and the solvent removed at reduced pressure, leaving a pale brown oil which crystallized on trituration with hexane. Recrystallization from hexane gave 1.1 g. (30%) of white crystals, m.p. 102–104°. The analytical sample, m.p. 107–108°, was crystallized from the same solvent.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.25; H, 7.57; N, 9.86. λ_{max}: 271 mμ, log ε 3.86; 280 mμ, log ε 3.88; 288 mμ, log ε 3.78.

1-[3-(2-Indolyl)piperidyl]acetic acid. A suspension of 1.61 g. of ethyl [3-(2-indolyl)-1-piperidyl] acetate in 10 ml. of 10% potassium hydroxide was heated 3 hr. under reflux, the reaction mixture was cooled, extracted with two portions of ether, warmed to drive off excess ether and then acidified to *p*H 4 with a mixture of acetic acid and hydrochloric acid. The resulting solid was collected to give 1.51 g. (99% if a dihydrate is assumed) of material which appeared to lose water at 175° and finally decomposed at 213–215°. The analytical sample was prepared by dissolving a small quantity of the amino acid in 10% hydrochloric acid, treating with charcoal, filtering, and adding aqueous ammonia to *p*H 5. The cream colored solid was collected and recrystallized several times from aqueous methanol to give white crystals which lost solvent at 180–185°, and finally decomposed at 220–222°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2 \cdot CH_3OH$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.33; H, 7.53; N, 9.54 λ_{max}: 270 mμ, log ε 4.00; 278 mμ, log ε, 3.99; 288 mμ, log ε, 3.92.

1-Benzyl-3-(2-indolyl)-1,2,5,6-tetrahydropyridine. To a solution of 4.5 g. of the benzyl quaternary salt in 200 ml. of ethanol was added 6 g. of sodium borohydride. The reaction mixture was stirred 2 hr. under reflux, cooled, cautiously acidified with 5% hydrochloric acid, made basic with 5% sodium hydroxide, and diluted with water. The resulting crystals were collected and recrystallized from cyclohexane–ethyl acetate to give 2.13 g. (60%) of green-brown plates, m.p. 153–157°. For analysis a small sample of the compound was dissolved in methylene chloride and filtered through an alumina column. Recrystallization of the material obtained in this manner gave cream colored plates, m.p. 166–167°.

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.72. Found: C, 83.32; H, 7.20; N, 9.73. λ_{max}: 224 mμ, log ε 4.27; 238 mμ, log ε 4.10; 302 mμ; log ε 4.33.

3-(2-Indolyl)piperidine. A solution of 5.08 g. of the tetrahydropyridine in 350 ml. of ethanol was hydrogenated at 35 p.s.i. for 12 hr., using 2.5 g. of 10% palladium-on-carbon. After separation from the catalyst, the solvent was removed *in vacuo*, leaving a tan solid, which on recrystallization from cyclohexane–ethyl acetate gave 1.42 g. (40%) of white crystals, m.p. 175–177° with sublimation. The analytical sample, m.p. 178–179°, was prepared by sublimation at 135° and 0.1 mm., and recrystallization from cyclohexane–ethyl acetate.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.96; H, 8.05; N, 13.99. Found: C, 78.15; H, 8.17; N, 14.20. λ_{max}: 270 mμ; log ε, 3.89; 278 mμ, log ε 3.89; 288 mμ, log ε 3.79.

1-p-Toluenesulfonamido-3-(2-indolyl)piperidine. To a solution of 0.35 g. of the indolyl piperidine in 6 ml. of dry pyridine was added 0.35 g. of *p*-toluenesulfonyl chloride. The dark red reaction mixture was allowed to stand for 1 hr., heated on the steam bath for 1 hr. and then poured into water. The brown solid was collected, washed well with water, and recrystallized from alcohol to give 0.49 g. (82%) of pale brown crystals, m.p. 188–191°. Recrystallization from alcohol gave the analytical sample, m.p. 192–193°.

Anal. Calcd. for $C_{20}H_{22}N_2SO_2$: C, 67.76; H, 6.26; N, 7.90. Found: C, 67.92; H, 6.39; N, 7.99.

1-p-Toluenesulfonamido-3-(3-dimethylaminomethyl-2-indolyl)piperidine. To a solution of 0.8 g. of the *p*-toluenesulfonamide in 4 ml. of acetic acid was added 2 ml. of 25% aqueous dimethylamine and 0.8 ml. of formalin. The reaction mixture was allowed to stand at room temperature 48 hr., poured into 40 ml. of 30% aqueous acetic acid, filtered, and made basic with concentrated ammonium hydroxide. The resulting granular precipitate was collected, washed with water, and dried overnight in a vacuum desiccator to give 0.92 g. (99%) of tan powder. All efforts to recrystallize this material were unsatisfactory, and consequently it was converted to the picrate, m.p. 183–184 dec. from aqueous acetone, for analysis.

Anal. Calcd. for $C_{23}H_{32}N_6SO_9$: C, 54.36; H, 5.03; N, 13.12. Found: C, 54.77; H, 5.34; N, 12.87.

(9) Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were carried out in chloroform solution, as liquid films, or as KBr disks on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were carried out in 95% ethanol on a Perkin-Elmer Model 4000A spectrophotometer. Melting points were determined on a Fisher-Johns block and are uncorrected.

(10) The crude phenylhydrazone gives decidedly inferior yields.

(11) This hydrogenation could also be carried out at atmospheric pressure and room temperature. A solution of 0.50 g. of salt in 25 ml. of ethanol with 0.05 g. of platinum oxide readily absorbed 92.6 ml. (99%) of hydrogen.

Cyanide treatment of Va. To a solution of 0.75 g. of the gramine in 25 ml. of ethanol and 5 ml. of water was added 2 g. of potassium cyanide. The reaction mixture was heated under reflux 48 hr., cooled, diluted with water, and the precipitated solid collected. Recrystallization from aqueous alcohol gave 0.45 g. (60%) of white solid m.p. 208–210°. Several additional recrystallizations from the same solvent gave white crystals, m.p. 215–217°.

Anal. Calcd. for $C_{22}H_{25}N_3SO_3$: C, 64.21; H, 6.12; N, 10.21. Calcd. for $C_{22}H_{23}N_3SO_2$: C, 67.15; H, 5.89; N, 10.68. Found: C, 65.37, 65.41; H, 6.11, 5.71; N, 10.12. These figures correspond to a 1:1 mixture of amide and nitrile (Calcd.: C, 65.68; H, 6.00; N, 10.45). This is confirmed by the infrared spectrum (KBr) which shows absorption at 4.45 μ and 6.00 μ.

1-p-Toluenesulfonamido-3-(3-carboxymethyl-2-indolyl)piperidine. A suspension of 0.2 g. of the amide-nitrile mixture in 5 ml. of ethanol and 5 ml. of 20% potassium hydroxide was heated 22 hr. at reflux. The reaction mixture was cooled, diluted with water, washed with methylene chloride, and acidified giving 0.14 g. (70%) of gelatinous solid. Recrystallization from aqueous alcohol gave pale tan crystals, m.p. 177–180°, dec. Several recrystallizations from aqueous-alcohol gave the analytical sample, m.p. 180–183° dec.

Anal. Calcd. for $C_{22}H_{24}N_2SO_4$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.24; H, 5.95; N, 6.62.

1-Benzoyl-3-(2-indolyl)piperidine. A solution of 0.8 g. of the indolylpiperidine in 5 ml. of acetone was shaken with 20 ml. of 5% sodium hydroxide and 2 ml. of benzoyl chloride until no odor of the chloride remained. The slightly gummy solid was collected and recrystallized from ethanol to give 1.07 g. (87%) of white crystals, m.p. 204–207°. Several additional recrystallizations from ethanol gave the analytical sample, m.p. 207–208°.

Anal. Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.82; N, 9.02. Found: C, 78.88; H, 6.82; N, 9.02.

1-Benzoyl-3-(3-dimethylaminomethyl-2-indolyl)piperidine. To a solution of 0.3 g. of the benzoyl derivative in 2 ml. of acetic acid was added 1 ml. of 25% aqueous dimethylamine and 0.5 ml. of formalin. After 48 hr. at room temperature the brown reaction mixture was poured into 15 ml. of 30% aqueous acetic acid, filtered, and then made basic with concentrated aqueous ammonia. The precipitate was collected and dried, affording 0.3 g. (85%) of amorphous solid. The picrate formed yellow needles, m.p. 178–180° dec., from aqueous acetone. *Anal.* Calcd. $C_{29}H_{30}N_6O_8$: C, 58.97; H, 5.12; N, 13.98. Found: C, 59.00; H, 5.29; N, 14.23.

Reaction of 1-benzoyl-3-(3-dimethylaminomethyl-2-indolyl)-piperidine with potassium cyanide. To a solution of 0.2 g. of the gramine in 7 ml. of ethanol and 2 ml. of water was added 0.6 g. of potassium cyanide. The reaction was heated 48 hr. under reflux, cooled, poured into water, and the 0.14 g. of precipitated solid collected. Attempted recrystallization of this material gave an oil, and the infrared spectrum showed absorption at 4.45, 6.00, and 6.20 μ indicating that a mixture of the amide and nitrile had been obtained. Efforts to effect the hydrolysis of this material to the amino acid failed to give any isolable product.

1-Benzoyl-3-(3-cyanomethyl-2-indolyl)piperidine. The total crude product from the reaction of 0.98 of 1-benzoyl-3(2-indolyl)piperidine with formalin and dimethylamine was dissolved in 5 ml. of acetone to which was added 3 ml. of methyl iodide. Following the initial exothermic reaction the mixture was allowed to stand for 2 hr., and the liquid decanted from the gummy residue. An attempt was made to obtain a crystalline sample of the methiodide; however, on warming in alcohol an odor of trimethylamine was obtained and upon cooling a solid was deposited which did not melt below 300°.

Due to the instability of this methiodide, the balance of the material was dissolved in 30 ml. of ethanol, to which was added a solution of 2.5 g. potassium cyanide in 5 ml. of water. The reaction mixture was heated under reflux for 3 hr., cooled, and poured into water. The resulting solid was collected, and recrystallized from cyclohexane–ethyl acetate to give 0.35 g. (34%) of crystals, m.p. 178–181°. The analytical sample was crystallized from the same solvent pair and had m.p. 180–181°.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 77.25; H, 6.21; N, 12.01.

Basic hydrolysis of Vg: A suspension of 0.25 g. of the nitrile in 5 ml. of 10% sodium hydroxide was heated overnight under reflux. After cooling, the reaction mixture was adjusted to *p*H 5 with an acetic acid–hydrochloric acid mixture and 0.02 g. of pink solid, which decomposed slowly above 200°, was collected. Acidifying the mother liquors with concentrated hydrochloric acid gave a voluminous white precipitate, most of which did not melt below 300°. This material was slurried with water, and the undissolved material collected, giving 0.02 g. (23%) of benzoic acid (m.p. and mixed m.p. 121–122°). Concentration of the acidic mother liquors to dryness *in vacuo* gave a dark brown solid, from which no organic material could be obtained.

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