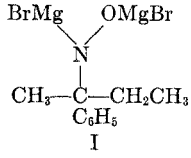
the reaction sequence proposed by Campbell *et al.*,[6] which involves (1) replacement of the active hydrogen of the oxime by MgBr, (2) addition of RMgBr to the C=N linkage, (3) elimination of Mg(OH)Br by closure of the ethyleneimine ring at an α-carbon, and (4) formation of the free imine by hydrolysis. The only modification of this sequence seemingly necessitated by the present work is some accounting for the unidirectional ring closure.

According to Campbell, the same intermediate, I, should be obtained from either of two pairs of



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reactants, acetophenone oxime and ethylmagnesium bromide or propiophenone oxime and methylmagnesium bromide. But actually, these two pairs of reactants, after mixing and hydrolysis, yield different products; in each instance the alkyl side chain of the oxime becomes incorporated into the ethyleneimine nucleus. Quite probably this directional influence is a result of steric hindrance in the intermediate product of reaction—inspection of molecular models suggests such hindrance. The results seem to be explainable on the basis that the OMgBr grouping is in close proximity to the side chain of the oxime, and are thus dependent upon the configuration of the oxime. Ring closure, therefore, is favored in a unidirectional manner; at least it appears to take place exclusively in that sense.

During the course of this investigation, hydrolysis of 2-ethyl-3-methyl-2-phenylethyleneimine was carried out and yielded 2-amino-3-phenyl-3-pentanol. The latter was described by Campbell[7] as being a liquid, but, in our experience, the once-distilled liquid crystallized slowly on standing. The solid, after repeated recrystallization from ether, melted at 98–99°. Its hydrochloride melted at 225–226°, in agreement with the melting point of 228° recorded by Campbell.

AUSTIN, TEX.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Syntheses of *N*-Substituted Isoindolines. I. Derivatives of Phthalimide

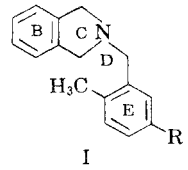
RODERICK A. BARNES AND JOHN C. GODFREY[1]

Received March 14, 1957

A series of four *N*-benzyl isoindolines has been prepared *via* alkylation of potassium phthalimide and reduction of the resulting *N*-benzylphthalimides with lithium aluminum hydride. Basic hydrolysis of the intermediate phthalimides has been shown to yield *N*-benzylphthalamic acids. A new infrared band characteristic of *N*-benzylphthalimides is reported.

Recent advances in the chemistry and pharmacology of reserpine and its derivatives have spurred interest in the synthesis of heterocycles bearing some of the structural features present in these natural products, in the hope that useful ataractics might result. The isoindolines discussed herein contain a basic tertiary amine bound to an aromatic system and to a benzyl group carrying a labile *meta*-substituent. This grouping may be considered to be roughly analogous to that found in the B, C, D, and E rings of reserpine, as shown in structure I.

It was necessary to develop an improved synthesis for the 2-methyl-5-nitrobenzyl chloride (II),[2] which was required for the Gabriel reaction. It was condensed with potassium phthalimide in refluxing ethanol-acetone. Reduction of the product, *N*-(2-methyl-5-nitrobenzyl)phthalimide, III, over Adams' catalyst afforded a high yield of *N*-(2-methyl-5-aminobenzyl)phthalimide, VI. Curiously, compound VI was bright yellow as obtained from the reaction mixture, but the crystals became colorless when suspended in dilute hydrochloric acid, presumably because of formation of a colorless, insoluble hydrochloride at the crystal surface. Basification regenerated the original yellow color. These observations suggested the possibility that the product was not VI, but was instead 3-(2′-methyl-5′-aminophenyl)-1,2,3,4-tetrahydroisoquinoline-1,4-dione. Gabriel[3] demonstrated conclusively that certain *N*-substituted-phthalimides may be rearranged to 3-substituted-1,2,3,4-tetrahydroisoquinoline 1,4-



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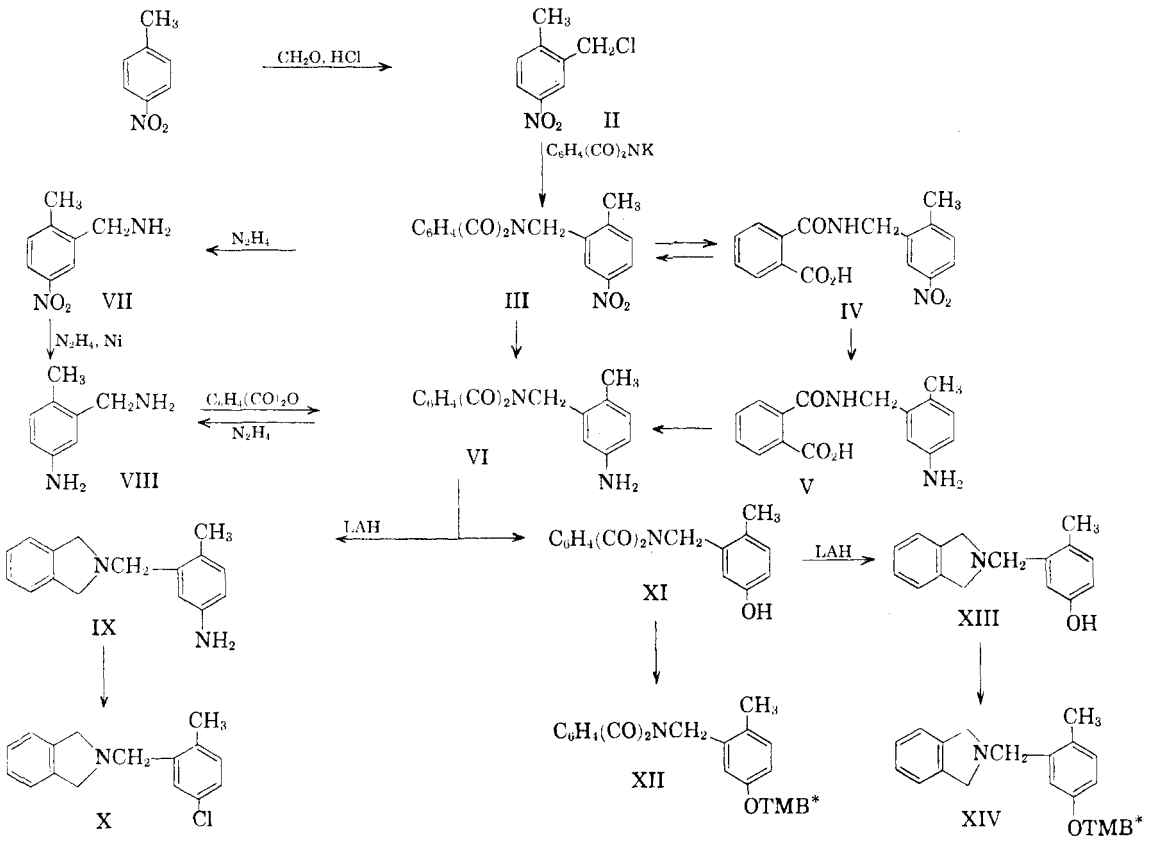
(1) Smith, Kline & French, postdoctoral fellow, 1955–1957.

(2) H. Stephen, W. F. Short, and G. Gladding, *J. Chem. Soc.*, 510 (1920).

(3) S. Gabriel and J. Coleman, *Ber.*, **33**, 980 (1900).

CHART I



* TMB = 3,4,5-trimethoxybenzoyl.

diones, which are yellow in basic solution. However, the infrared spectrum, with typical phthalimide bands at 5.66 and 5.87 μ,[4] as well as a strong band at 10.51 μ, which was found to be associated with all of the N-benzylphthalimides encountered in this study, supported structure VI. Further, the ultraviolet spectrum of VI, λ_{max} 222 mμ (log ϵ 4.63) and 298 (3.07) is very similar to that of *N*-phenylphthalimide,[5] λ_{max} 302 (3.35). Significantly, solutions of VI in benzene, ethanol, and chloroform are colorless, and their solutions do not absorb appreciably in the near-ultraviolet and visible regions. The yellow color of the crystalline solid must be a result of intermolecular resonance, or electron transfer from one molecule to another.[6]

Attempts to rearrange III to a tetrahydroisoquinoline under the conditions described by Gabriel[3] (sodium ethoxide in ethanol) or with dry sodium methoxide in refluxing benzene or xylene resulted only in decomposition.

None of the several variations in reaction conditions resulted in anything but poor recovery of starting material. Compound III dissolved readily in dilute, aqueous ethanolic potassium hydroxide. Acidification of the resulting solution with acetic acid precipitated IV, *N*-(2-methyl-5-nitrobenzyl)-phthalamic acid, in a nearly quantitative yield. Compound IV reverted to III on recrystallization or heating above its melting point. *N*-(4- and 2-Nitrobenzyl)phthalimides, compounds XV and XVI, behaved similarly, and no evidence for the expected rearrangement could be found.

Hydrogenation of IV over platinum gave a high yield of the unstable amino acid V. When heated slowly in vacuum to about 160°, V was dehydrated to VI, identical in all respects with the product obtained by direct hydrogenation of III.

Treatment of III with hydrazine in refluxing ethanol[7] produced 2-methyl-5-nitrobenzylamine, VII, which on reduction with hydrazine and Raney nickel[8] was converted to 2-methyl-5-aminobenzylamine, VIII. Diamine VIII was also obtained in good yield by treatment of VI with hydrazine.

(4) J. Chouteau, *Bull. soc. chim. France*, **20**, 1148 (1953).
(5) R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, Wiley and Sons, Inc., New York, 1951, serial no. 149.
(6) R. S. Mulliken, *J. Am. Chem. Soc.*, **72**, 600 (1950); R. S. Mulliken, *J. Am. Chem. Soc.*, **74**, 811 (1952); C. Reid and R. S. Mulliken, *J. Am. Chem. Soc.*, **76**, 3869 (1954).
(7) H. R. Ing and R. H. F. Manske, *J. Chem. Soc.*, 2356 (1926).
(8) D. Balcom and A. Furst, *J. Am. Chem. Soc.*, **75**, 4334 (1953).

When equimolar amounts of VIII and phthalic anhydride were heated to 190°, the product consisted of VI accompanied by an equal weight of colorless material which is believed to be *N*-(2-methyl-5-phthalimidobenzyl)phthalimide.

Reduction of VI was accomplished by treatment with excess lithium aluminum hydride in ether. The spectrum, analyses, and molecular weight[9] of the product were as expected for structure IX, *N*-(2-methyl-5-aminobenzyl)isoindoline, and indicated that the reduction had proceeded normally. Diazotization of IX in concentrated hydrochloric acid produced approximately equal quantities of *N*-(2-methyl-5-chlorobenzyl)isoindoline, X, and impure *N*-(2-methyl-5-hydroxybenzyl)isoindoline, XIII.

In order to more closely approximate the structure of reserpine, it was considered desirable to substitute the 3,4,5-trimethoxybenzoyl group at the 5-benzyl position, as in structures XII and XIV. To this end, VI was diazotized in 69% sulfuric acid, affording a respectable yield of *N*-(2-methyl-5-hydroxybenzyl)phthalimide, XI. A 3 to 4 molar excess of the acid chloride was required for the conversion of XI to its 3′,4′,5′-trimethoxybenzoate, XII, in dry pyridine. An equimolar quantity of the acid chloride gave an unsatisfactory yield.

Compound XI was reduced to *N*-(2-methyl-5-hydroxybenzyl)isoindoline, XIII, with lithium aluminum hydride. The pyridine procedure was found not to be suitable for the conversion of XIII to its trimethoxybenzoate, XIV, because of the sensitivity of the isoindoline nucleus. The desired ester was obtained in excellent yield as its hydrochloride by refluxing the dry sodium salt of the phenol with three equivalents of 3,4,5-trimethoxybenzoyl chloride in benzene. The free base, which was quite sensitive to light and oxygen, was readily obtained by extracting a chloroform solution of the hydrochloride with dilute potassium hydroxide.

Condensations carried out under the same conditions employed in the preparation of III yielded XV, *N*-(4-nitrobenzyl)phthalimide;[10] XVI, *N*-(2-nitrobenzyl)phthalimide;[11] and XVII, *N*-(2-methyl-5-nitrobenzyl)succinimide (Chart II). Compound XV was reduced to *N*-(4-aminobenzyl) phthalimide, XVIII. This product was only slightly less yellow than VI, and exhibited the same behavior as VI in acid, base, and organic solvents.

N-(2-Nitrobenzyl)phthalimide, XVI, is very insoluble in most organic solvents, and was therefore reduced to 12-keto isoindolino(1,2-*b*)quinazoline, XIX, according to the procedure of Gabriel.[12] The characteristic absorptions of XIX in the 6 μ region occur at 5.78 (carbonyl) and 6.05 (C=N) μ, and are of approximately equal intensity.

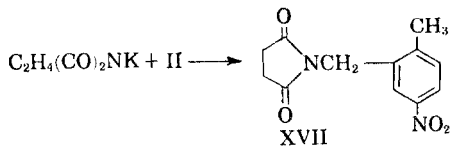
All of the *N*-substituted phthalimides encountered in this study exhibited strong absorption bands between 10.45 and 10.75 μ (Table I). Changes in the *N*-substituent did not markedly affect this band, while any alteration of the 5-membered imide ring caused its disappearance.

CHART II

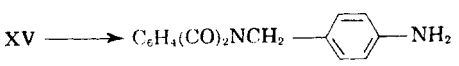
$C_6H_5(CO)_2NK + NO_2C_6H_4CH_2Cl \rightarrow C_6H_4(CO)_2NCH_2R$

XV, R = *p*-$NO_2C_6H_4$

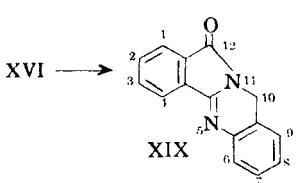
XVI, R = *o*-$NO_2C_6H_4$



XVII



XVIII



XIX

(9) K. G. Cunningham, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

TABLE I

INFRARED BANDS OF *N*-SUBSTITUTED PHTHALIMIDES

Phthalimide	λ_{max}, Microns
N-(2-methyl-5-nitrobenzyl), III	10.58
N-(2-methyl-5-aminobenzyl), VI	10.51
N-(2-methyl-5-acetamidobenzyl)	10.49
N-(2-methyl-5-hydroxybenzyl), XI	10.51
N-[2-methyl-5-(3′,4′,5′-trimethoxybenzoyl) benzyl], XII	10.48
N-(4-nitrobenzyl), XV	10.60
N-(2-nitrobenzyl), XVI	10.55
N-(4-aminobenzyl), XVIII	10.72

EXPERIMENTAL[13]

2-Methyl-5-nitrobenzyl chloride (II). In a 5-l. 3-necked flask fitted with a stirrer and reflux condenser were placed 400 g. (2.92 mole) of *p*-nitrotoluene and 225 g. of trioxane dissolved in 885 ml. of concentrated sulfuric acid. (Cooling is sential when dissolving the trioxane.) The solution was stirred, 206 g. of anhydrous zinc chloride was added, and the mixture was cooled to about 0°. Dry hydrogen chloride was passed through the solution for 4.5 hr. while the ice bath was allowed to melt. The mixture stood overnight, 2 l. of ice and water were added, the solution was cooled to 20° and filtered, removing 130 g. of starting material. The filtrate was extracted with three 700 ml. portions of ether, the solution was dried, the solvent removed, and the dark oil which remained was distilled at 0.5 mm. *p*-Nitrotoluene (156 g.) distilled at 55–65°, and the product (117 g.) came over at 104–108°. Recrystallization from *ca.* one liter of isooctane yielded 104 g. (67.5%), m.p. 62.5–64.0°. A sample was recrystallized for analysis, m.p. 63.0–64.0°.

Anal. Calcd. for $C_8H_8O_2NCl$: C, 51.76; H, 4.34. Found: C, 51.86; H, 4.41.

(10) H. Salkowski, *Ber.*, **22**, 2137 (1889).

(11) S. Gabriel, *Ber.*, **20**, 2227 (1897).

(12) S. Gabriel, *Ber.*, **45**, 713 (1912).

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

2-Methyl-5-nitrobenzyl alcohol. Prepared according to the method of Weinmayr,[14] 1.0 g. of II yielded 0.80 g. of the alcohol (89%), crystallized several times from ethanol-water, m.p. 78–79°. As this value was several degrees above previous reports, the sample was analyzed.

Anal. Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43. Found: C, 57.64; H, 5.49.

N-(2-Methyl-5-nitrobenzyl)phthalimide (III). In a 3-l. 3-necked flask fitted with a stirrer and 2 reflux condensers, 17.27 g. of 85% potassium hydroxide (0.262 mole) was dissolved in 985 ml. of absolute ethanol. To the hot solution was added 38.50 g. (0.262 mole) of phthalimide and 1060 ml. of dry acetone, and the mixture was stirred under reflux overnight. A solution of 48.50 g. (0.262 mole) of 2-methyl-5-nitrobenzyl chloride in 400 ml. of dry acetone was then added, and the mixture was refluxed for an additional 48 hr. It was filtered while hot, chilled, and the resulting precipitate, 44.2 g., colorless needles, m.p. 176–178°, was filtered off. A solid residue (28.5 g.) remained on removal of solvent from the filtrate. It was swirled with 100 ml. of cold chloroform, filtered, freed of solvents, and recrystallized from ethyl acetate and ligroin, yielding 16 g. of III, m.p. 176–178°. Total yield 77.7%. The analytical sample was recrystallized from ethyl acetate, m.p. 178.5–179.5°.[15]

Anal. Calcd. for $C_{16}H_{12}O_4N_2$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.84; H, 4.10; N, 9.44.

N-(2-Methyl-5-nitrobenzyl)phthalamic acid (IV). One gram of finely-ground *N*-(2-methyl-5-nitrobenzyl)phthalimide was suspended in 25 ml. of ethanol, a cooled solution of 2 g. of potassium hydroxide in 25 ml. of water was added, and the mixture was shaken for 30 min. It was filtered into a solution of 2 ml. of glacial acetic acid in 75 ml. of water and the flask was rinsed with 50 ml. of water. The precipitate which formed in the filtrate was filtered and washed with 100 ml. of water. The product was dried over phosphorus pentoxide at room temperature, 1.0 g. (94%), m.p. 190.1–190.9° dec.

Anal. Calcd. for $C_{16}H_{14}O_5N_2$: C, 61.14; H, 4.49; N, 8.92. Found: C, 61.49; H, 4.71; N, 8.87.

N-(2-Methyl-5-aminobenzyl)phthalamic acid (V). A mixture of 461 mg. (1.47 mmole) of IV, 40 mg. of Adams' catalyst, and 50 ml. of ethanol was hydrogenated in a Parr shaker, the theoretical amount of hydrogen being absorbed in 22 min. A yellow precipitate, which proved to be 43 mg. of VI, was filtered off. Removal of solvent from the filtrate left 351 mg. of the semi-crystalline amino acid V. Attempts to purify V were not successful, so the crude product was used for conversion to VI.

N-(2-Methyl-5-aminobenzyl)phthalimide VI. (*a*) *By reduction of III.* A mixture of 6.79 g. of *N*-(2-methyl-5-nitrobenzyl)phthalimide, 244 mg. of Adams' catalyst, and 300 ml. of glacial acetic acid was shaken at 25° and *ca.* 4 atmospheres of hydrogen pressure until a definite break in the hydrogen consumption curve occurred, which required 50 min. and *ca.* four molar equivalents of hydrogen. The catalyst was filtered off, solvent was immediately removed under vacuum at 100°, and the yellow residue boiled with 35 ml. of chloroform. Cooling produced VI, m.p. 241–242° dec., in 92% yield.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.16; H, 5.13; N, 10.47.

The same product was obtained on hydrogenation of III over Raney nickel or Adams' catalyst in benzene (83%), or by the treatment of III with ferrous ion in concentrated ammonium hydroxide (35%), according to the procedure of Eder and Widmer.[16]

Removal of solvent from the chloroform crystallization liquor yielded 4-xylidine, identified as its picrate m.p. 218–219° dec.[17] It must have arisen through hydrogenolysis of the benzyl C—N bond of *N*-(2-methyl-5-aminobenzyl) phthalimide.[18]

(*b*) *By dehydration of phthalic acid mono N-(2-methyl-5-aminobenzyl)amide* (V). One gram of V was heated under vacuum at 160° for 1 hr. Conversion to VI, m.p. 238–240°, was quantitative.

(*c*) *From 2-methyl-5-aminobenzylamine* (VIII). To 10 ml. of dry xylene were added 168 mg. (1.23 mmole) of 2-methyl-5-aminobenzylamine and 183 mg. (1.23 mmoles) of phthalic anhydride. The xylene was distilled off, the solid residue heated to 190°, dissolved in 50 ml. of chloroform, and the insoluble hydrochloride of VI was precipitated by the addition of 3*N* hydrochloric acid. Neutralization of the hydrochloride yielded 64 mg. of VI, m.p. 234–236°.

The chloroform solution was neutralized, washed with water, and dried. The 72 mg. of white needles obtained were recrystallized from ethanol-chloroform, m.p. 294°. This material is probably *N*-(2-methyl-5-phthalimidobenzyl)phthalimide as it exhibits rather broad carbonyl absorption at 5.66 and 5.80–5.85 μ, as well as *N*-benzylphthalimide absorption at 10.58 μ.

Anal. Calcd. for $C_{24}H_{16}O_4N_2$: N, 7.07. Found: N, 6.95.

The *picrate* of *N*-(2-methyl-5-aminobenzyl)phthalimide was prepared in chloroform, m.p. 218–219° dec.

Anal. Calcd. for $C_{16}H_{14}O_2N_2 + C_6H_3O_7N_3$: C, 53.34; H, 3.46; N, 14.14. Found: C, 53.41; H, 3.53; N, 14.21.

N-(2-Methyl-5-acetylaminobenzyl)phthalimide. A mixture of 162 mg. of *N*-(2-methyl-5-aminobenzyl)phthalimide, 20 ml. of acetic anhydride, and a trace of sodium acetate was heated at 136° for 48 hr. The solvent was removed, and the residue was refluxed for 24 hr. with 40 ml. of water containing enough ethanol to solubilize the organic material. The precipitate which formed on cooling was recrystallized from ethanol-water to constant m.p. 218.7–219.5°.

Anal. Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.11; H, 5.23; N, 9.09; $COCH_3$, 13.97. Found: C, 69.72; H, 5.14; N, 9.09; $COCH_3$, 13.45.

2-Methyl-5-nitrobenzylamine (VII). A mixture of 1.160 g. (3.92 mmoles) of N-(2-methyl-5-nitrobenzyl)phthalimide, 10 ml. of ethanol, and 23 drops of 85% hydrazine hydrate was refluxed for 20 min. The mixture, containing a voluminous precipitate, was cooled, acidified with 6*N* hydrochloric acid, warmed to decompose the salt completely, cooled, filtered, diluted to 50 ml. with water, and filtered again. The filtrate was made basic with 10% potassium hydroxide, extracted three times with 30 ml. of chloroform, and the combined extracts dried. Removal of the solvent left 543 mg. (83%) of oil which rapidly crystallized, m.p. 35–40°. It was crystallized several times from ligroin for analysis, m.p. 42.5–43.5°.

Anal. Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.85; H, 6.13; N, 16.66.

The *picrate* of 2-methyl-5-nitrobenzylamine formed readily in ethanol and was recrystallized from ethanol-chloroform, yellow rhombohedral prisms, m.p. 208° dec.

Anal. Calcd. for $C_8H_{10}O_2N_2 + C_6H_3O_7N_3$: C, 42.54; H, 3.31; N, 17.72. Found: C, 42.97; H, 3.32; H, 17.64.

2-Methyl-5-aminobenzylamine (VIII). (*a*) *From N-(2-methyl-5-aminobenzyl)phthalimide* (VI). When subjected to the same treatment employed in the preparation of 2-methyl-5-nitrobenzylamine, 336 mg. of VI yielded 110 mg. (71%) of 2-methyl-5-aminobenzylamine. The crude diamine melted at 99–100°, but absorbed carbon dioxide rapidly during

(14) V. Weinmayr, U. S. Patent **2,373,438**, April 10, 1945 [*Chem. Abstr.*, **39**, (3793)].

(15) J. Tscherniac, German Patent **134,979** [*Chem. Zentr.*, **76**, 1084 (1902)] obtained a product $C_{16}H_{12}O_4N_2$, m.p. 176°, from the condensation of *p*-nitrotoluene with *N*-hydroxymethylphthalimide, but was unable to distinguish between structure III and *N*-(2-nitro-5-methylbenzyl)-phthalimide. It seems probable that his product was III.

(16) R. Eder and C. Widmer, *Helv. Chim. Acta*, **5**, 1 (1922).

(17) Beilstein, 2nd Ed., **XII**, p. 602.

(18) For comparison, see H. Adkins and B. Wojcik, *J. Am. Chem. Soc.*, **56**, 2419 (1934).

crystallization from ethanol-ligroin. It was therefore converted to the dipicrate, which was shown by comparison of the infrared spectra to be identical with the product obtained by procedure *b*.

(*b*) *From 2-methyl-5-nitrobenzylamine* (VII). A solution of 716 mg. (4.31 mmoles) of VII and 16 drops of 85% hydrazine hydrate (*ca.* 13 mmoles) in 8 ml. of ethanol was warmed on a steam bath and Raney nickel was slowly added over a period of 50 min. When no more gas was evolved, the solution was boiled briefly, cooled, filtered, combined with 15 ml. of ethanol saturated with picric acid, and again brought to a boil. Cooling precipitated 2.01 g. (78.5%) of the dipicrate. It was crystallized several times from ethanol, m.p. 225–226° dec.

Anal. Calcd. for $C_8H_{12}N_2 + 2\ C_6H_3O_7N$: C, 40.45; H, 3.03; N, 18.89. Found: C, 41.20; H, 3.32; N, 18.84.

N-(2-Methyl-5-aminobenzyl)isoindoline (IX). To a solution of 0.56 g. (14 mmole) of lithium aluminum hydride in 100 ml. of ether contained in a 200 ml. 3-necked flask fitted with a gas inlet, stirrer, and reflux condenser was added 1.630 g. (6.14 mmole) of *N*-(2-methyl-5-aminobenzyl)-phthalimide (VI). The solution was stirred and refluxed for 30 hr., an additional 0.5 g. of lithium aluminum hydride added, and the reaction continued for another 42 hr. Then 8 ml. of ethanol in 8 ml. of ether was added, followed by 50 ml. of water. Separation of the ethereal layer and removal of solvent left 1.05 g. (72%) of pink crystals, m.p. 66–68°. The product was dissolved in 1*N* hydrochloric acid, heated with charcoal, filtered, and precipitated with sodium bicarbonate. Repetition of this procedure three times gave a colorless analytical sample, m.p. 73.5–74.5°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.60; H, 7.74; N, 11.66.

The *monopicrate* of *N*-(2-methyl-5-aminobenzyl)isoindoline formed readily in ethanol. Red plates recrystallized from ethanol, m.p. 171–172° dec.

Anal. Calcd. for $C_{16}H_{18}N_2 + C_6H_3O_7N_3$: C, 56.53; H, 4.53; N, 14.98; mol. wt., 467.4. Found: C, 57.15; H, 4.33; N, 14.05; mol. wt., 470.7.

N-(2-Methyl-5-chlorobenzyl)isoindoline (X). A solution of 5.062 g. (0.0171 mole) of *N*-(2-methyl-5-aminobenzyl)isoindoline in 100 ml. of concentrated hydrochloric acid was cooled to −20°, with stirring. To this solution was added 1.182 g. (0.0171 mole) of dry sodium nitrite, and after stirring for 5 min. at −20°, the mixture was rapidly heated to 100° and stirred for 10 min. Removal of solvent under vacuum left a red oil which was dissolved in 100 ml. of ether. Extraction of the ethereal solution with 3 × 15 ml. of 10% potassium hydroxide removed 600 mg. of crude *N*-(2-methyl-5-hydroxybenzyl)isoindoline (XIII). The ethereal solution was dried, the solvent was removed, and the remaining red oil was taken up in 20 ml. of dry benzene and passed over a 20 g. column of silica gel. Elution with 250 ml. of benzene removed nearly all of the *N*-(2-methyl-5-chlorobenzyl)isoindoline, contaminated with red dye. Successive elutions with 100 ml. of 10% ether in benzene, and 200 ml. of ether alone produced a mixed center fraction and a final fraction of 500 mg. of *N*-(2-methyl-5-hydroxybenzyl)isoindoline. The benzene eluate was freed of solvent and distilled in a molecular still at 190–195° and 2 mm., yielding 1.8 g. (33%) of a straw-yellow oil. It was converted to the hydrochloride in anhydrous ether and purified by treating with several portions of charcoal in dry chloroform at 25°. Precipitation from the latter solution by the addition of ether yielded colorless platelets, m.p. 211–213° dec. The infrared spectrum of this substance exhibited a strong tertiary amine hydrochloride doublet at 4.12 and 4.27 μ.

Anal. Calcd. for $C_{16}H_{18}NCl{\cdot}HCl$: C, 65.31; H, 5.83; N, 4.76. Found: C, 65.42; H, 5.79; N, 4.79.

N-(2-Methyl-5-hydroxybenzyl)phthalimide (XI). *N*-(2-Methyl-5-aminobenzyl)phthalimide, 17.796 g. (0.0669 mole), was dissolved in 125 ml. concentrated sulfuric acid, and 97 g. of ice was added, forming a thick slurry of the bisulfate salt. The slurry was cooled to −10°, and 4.62 g. (0.0671 mole) of sodium nitrite was added rapidly with good agitation. Stirring and cooling were continued for 10 min. The flask was then immersed in a steam bath for 10 min. with rapid stirring. Nitrogen was evolved, and the product precipitated. Cooling to 25° and dilution to 1100 ml. with water gave a 91% yield of yellow crystals, m.p. 164–168°. Treatment with charcoal and recrystallization from benzene gave 14.32 g. (79.5%) of XI, m.p. 180–181°.

Anal. Calcd. for $C_{16}H_{13}O_3N_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.78; H, 4.74; N, 5.07.

N-(2-Methyl-5-hydroxybenzyl)phthalimide 3′,4′,5′-trimethoxybenzoate (XII). To the dried acid chloride prepared from 14.6 g. (0.069 mole) of 3,4,5-trimethoxybenzoic acid was added 4.90 g. (0.0183 mole) of *N*-(2-methyl-5-hydroxybenzyl)phthalimide and 200 ml. of dry pyridine. The solution was heated at 100° for 10 hr. and poured into 1500 ml. of water. The precipitate was filtered off after 15 min., boiled with 200 ml. of ethanol, cooled, and filtered, yielding 6.85 g. (80.8%) of colorless needles, m.p. 179–180° (shrinkage at 165°). The analytical sample was recrystallized three times from ethyl acetate, m.p. 181.7–182.2°.

Anal. Calcd. for $C_{26}H_{23}O_7N$: C, 67.67; H, 5.02; N, 3.04. Found: C, 67.46; H, 5.08; N, 2.88.

N-(2-Methyl-5-hydroxybenzyl)isoindoline (XIII). In a 1-l. flask fitted with a Soxhlet extractor was placed 10.0 g. (0.26 mole) of lithium aluminum hydride and 500 ml. of dry ether. *N*-(2-Methyl-5-hydroxybenzyl)phthalimide, (14.32 g., 0.0536 mole), was placed in the thimble and extracted for 11 hrs. The excess reagent was decomposed with 58 ml. of ethanol in 58 ml. of ether and enough saturated sodium sulfate solution was added to clear the ether lyer, followed by 40 g. of dry sodium sulfate. The ether layer was filtered off and the remaining solids washed thoroughly with ether. Removal of solvent from the filtrate left a white solid which was washed with 100 ml. of water, dried, and recrystallized from benzene to give 4.373 g. (34%) of XIII, m.p. 136.5–137.5° dec.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.25; H, 7.13; N, 5.77.

N-(2-Methyl-5-hydroxybenzyl)isoindoline 3′,4′,5′-trimethoxybenzoate (XIV). To 1.948 g. (0.0371 mole) of sodium methoxide dissolved in 100 ml. of absolute ethanol was added 4.038 g. (0.0169 mole) of *N*-(2-methyl-5-hydroxybenzyl) isoindoline. As soon as all of the solid dissolved, the solvent was removed under vacuum at 60°, and dry benzene was added and removed twice under oil pump vacuum at 75° for 0.5 hr. To the resulting off-white solid was added 3,4,5-trimethoxybenzoyl chloride, freshly prepared from 14.0 g. (0.066 mole) of trimethoxybenzoic acid, in 100 ml. of dry benzene. An exothermic reaction occurred, and the solution was refluxed under nitrogen for 40 min. Removal of solvent under vacuum at 80° and addition of 100 ml. of 0.8*N* hydrochloric acid produced a gum which rapidly crystallized. The aqueous solution was decanted and the remaining solid was extracted *in situ* with 3 × 100 ml. of boiling ether, which removed the excess trimethoxybenzoic acid and most of the colored impurities. The solid crystal cake was washed with dilute hydrochloric acid and dried, yielding 7.80 g. (98.4%) of the hydrochloride of XIV. A sample was crystallized several times from ethyl acetate for analysis, m.p. 214.5–215.5° dec.

Anal. Calcd. for $C_{26}H_{27}O_5N{\cdot}HCl$: C, 66.45; H, 6.01; N, 2.98. Found: C, 66.42; H, 6.15; N, 2.97.

The *free base* was obtained by dissolving a sample of the hydrochloride in chloroform and extracting several times with dilute potassium hydroxide. The base remaining in the chloroform was crystallized 5 times from hexane, with charcoal treatment each time, to a constant melting point of 96.2–97.2°.

Anal. Calcd. for $C_{26}H_{27}O_5N$: C, 72.04; H, 6.28; N, 3.23. Found: C, 71.94; H, 6.36; N, 3.26.

N-(4-Nitrobenzyl)phthalimide[10] (XV) was prepared by the same method used for III, in 50% yield of flat, colorless needles, m.p. 74.5–75.5°.

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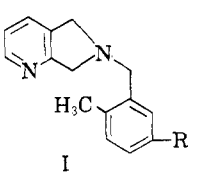
A practical synthetic approach to 2-substituted 4-azaisoindolines has been developed. The nature of the basic hydrolysis products of *N*-benzhydrylquinolinimide has been investigated and their structures established.

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*-benzhydryl-quinolinimide, 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-

(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).