Electrophilic Substitution of the Pyrido[2,1-*a*]isoindole System[1]

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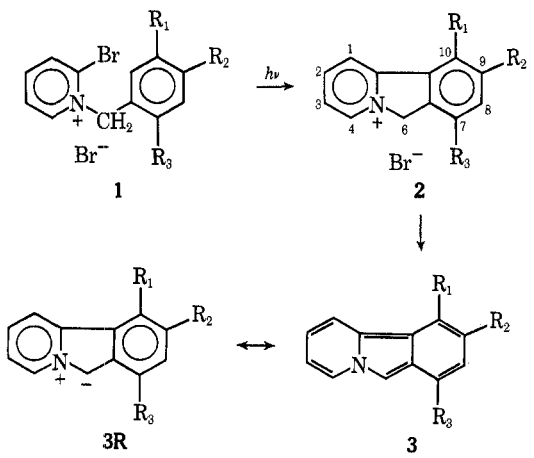
Except for those substitutions which occur in strongly acid media, electrophilic substitution of the title compound **3a** occurs at position 6. The reactions exhibiting this orientation include condensation with aromatic aldehydes, benzoylation, reaction with *p*-nitrosodimethylaniline, diazonium coupling, and reaction with an activated aryl halide. There is strong evidence that nitration of **2a** occurs at position 9 and that sulfonation does not occur at position 6.

Earlier communications[2,3] have described the photochemical cyclization of 1-benzyl-2-bromopyridinium bromide (**1a**) to pyrido[2,1-*a*]isoindolium bromide (**2a**) which on treatment with sodium carbonate afforded the base **3a**. Although the nmr spectrum of the base indicates that we are dealing with an aromatic system, analogy with indolizine[4,5] suggests that one of the many possible dipolar resonance structures, the ylide **3R**, might contribute significantly to the resonance hybrid and that with suitable electrophilic reagents attack would occur at position 6.

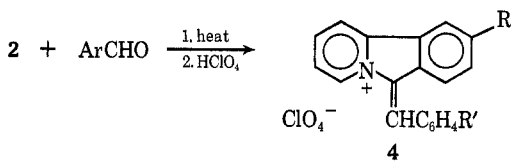


1 **2** **3R** **3**

a, $R_1 = R_2 = R_3 = H$ **d**, $R_1 = R_3 = H$; $R_2 = NO_2$
b, $R_1 = R_3 = H$; $R_2 = Br$ **e**, $R_1 = R_3 = H$; $R_2 = CN$
c, $R_1 = R_3 = Cl$; $R_2 = H$

Preliminary experiments led to the formation of intractable materials probably because of the instability of the base **3a**, and no better results were obtained by use of the somewhat more stable bases **3b** and **3c** having halogen substituted in the carbocyclic ring. Aqueous solutions of pyrido[2,1-*a*]isoindolium bromide (**2a**) are acidic (pK_a = 5.05), indicating the existence of the equilibrium **2** ⇄ **3** + HBr. This suggested that the desired electrophilic reactions might be carried out by use of the salt **2** without generating the base directly.

Refluxing the salt **2a** or its 9-bromo derivative **2b** in ethanol with aryl aldehydes led to the expected benzylidene derivatives **4** which were yellow to green in color. Nmr showed that the new products **4** had lost the two protons which had been at position 6 in the starting material, and in the case of the *p*-tolualdehyde condensation product **4b** showed that both of the possible geo-



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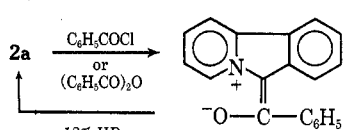
a, R = H; R′ = H **d**, R = Br; R′ = *p*-NO_2
b, R = H; R′ = *p*-CH_3 **e**, R = Br; R′ = *o*-Cl
c, R = Br; R′ = H

metrical isomers were formed. From the spectrum it would appear that 80% of the mixture had a methyl singlet at δ 2.50 and 20% had a methyl singlet at δ 2.22. It seems reasonable to assume that the isomer having the methyl group cis to the pyridinium ring would have the signal at lower field owing to the deshielding effect of the positive charge, but this is merely conjectural.

Since the arylidene condensation products **4** are in essence stilbenes, it seems possible that irradiation with ultraviolet light might lead to cyclodehydrogenation[6] or cyclodehydrohalogenation.[7] Irradiation of **4c** or **4e** for 24 hr produced no change in the uv spectrum.

Benzoylation of **2a** was readily accomplished by heating it at 100° with benzoyl chloride or benzoic anhydride. The product was not a salt but rather the betaine **5** derived from the enolate form of the 6-benzoyl derivative. The ir spectrum showed the absence of a carbonyl group and the nmr spectrum showed only aromatic protons. In deuteriochloroform there was a



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distinctive doublet at δ 10.56 corresponding to the proton at position 4 flanking the quaternary nitrogen, but at somewhat lower field than usually observed. If the measurement is carried out in trifluoroacetic acid, which is capable of protonating the oxygen, the doublet for the hydrogen at position 4 is found at the more normal value of δ 9.03. We regard the downfield shift when deuteriochloroform is substituted for trifluoroacetic acid as arising from the deshielding action of the negative charge on the enolate anion.

Like 3-acylindolizines which are readily deacylated by hot mineral acid,[8] our benzoylation product **6** was debenzoylated by heating it with 12% hydrobromic acid.

(1) This research was supported by Research Grant CA-05509 of the National Cancer Institute of the National Institutes of Health.

(2) A. Fozard and C. K. Bradsher, *Tetrahedron Lett.*, 3341 (1966).

(3) A. Fozard and C. K. Bradsher, *J. Org. Chem.*, **32**, 2966 (1967).

(4) E. T. Borrows and D. O. Holland, *Chem. Rev.*, **42**, 611 (1948).

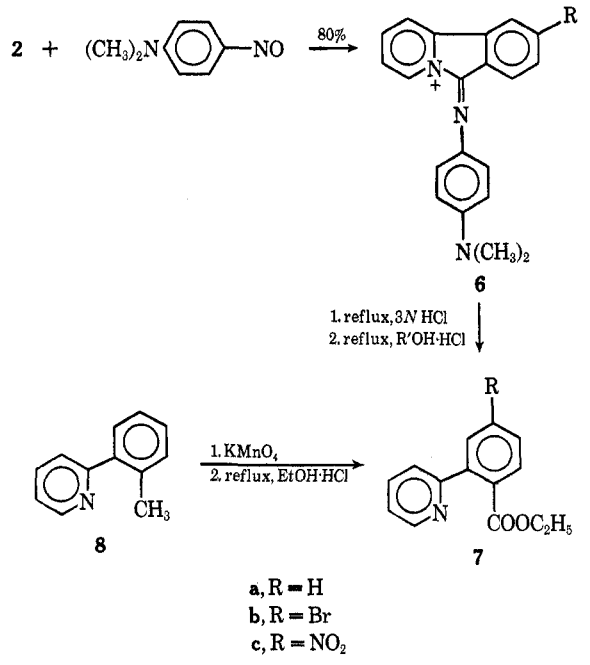
(5) H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(6) *Cf.* F. B. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964).

(7) S. M. Kupchan and H. C. Wormser, *J. Org. Chem.*, **30**, 3792 (1965).

(8) *Cf.* M. Scholtz, *Ber.*, **45**, 734 (1912); A. E. Chichibabin and E. N. Stepanow, *ibid.*, **62**, 1068 (1929).

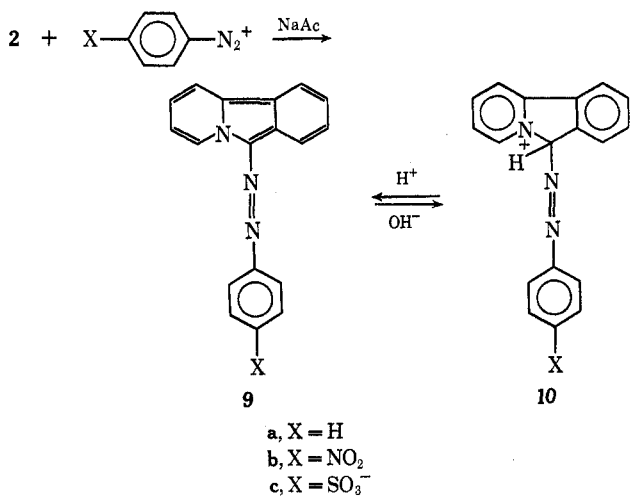
With *p*-nitroso-*N*,*N*-dimethylaniline the salt **2** was attacked at position 6, affording a dark green product **6**.



a, R = H
b, R = Br
c, R = NO_2

The structure of the condensation product **6** was demonstrated by hydrolysis to *o*-2-pyridylbenzoic acid which was isolated as its ethyl ester **7**. The structure of **7** was demonstrated by its synthesis from 2-*o*-tolylpyridine (**8**).

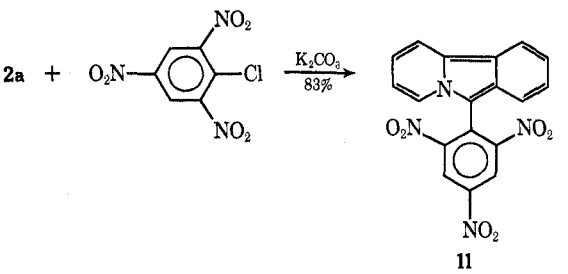
The coupling of the salt **2** or perhaps more exactly the base **3** with diazonium salts may be effected if the pH of the reaction mixture is brought to approximately 7 by addition of sodium acetate. The coupling product precipitated directly from the reaction mixture and was purified by crystallization as the hydrobromide or hydroperchlorate **10**. As can be easily seen from comparison of formulas **9** and **10**, the salts are less conjugated than the bases and understandably function as indicators.



a, X = H
b, X = NO_2
c, X = SO_3^-

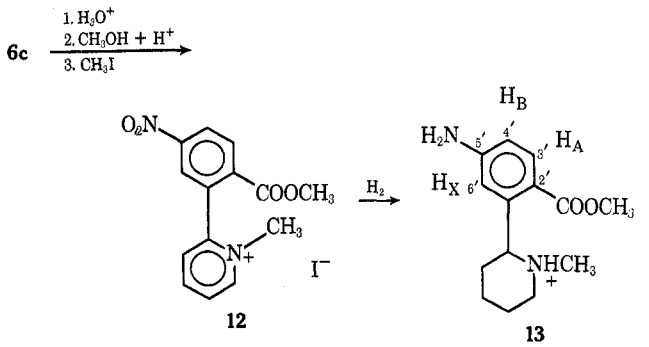
In the case of the *p*-nitro dye the color change is from yellow (**10b**) to deep purple (**9b**) and occurs at pH 5.5–6.2. The colors are very intense and easily observable below 10^{-6} *M*. The salt **10a** of the unsubstituted coupling product turned out to be very resistant to isomerization and acid hydrolysis for it was recovered unchanged after being refluxed in 12% hydrobromic acid.

Unlike indolizine[9] our salt **2** could not be alkylated with methyl iodide or benzyl bromide. We did succeed in making what is presumably the 6-picryl derivative by using picryl chloride.



The electrophilic reactions of **2a** disucssed so far were carried out in a neutral or basic solution. It seemed of interest to examine two of the more classical types of electrophilic substitution of aromatic systems, nitration and sulfonation, which are usually carried out under strongly acidic conditions. Under such conditions one is probably dealing with the salt **2** and not with an equilibrium between the salt and the base (**2** ⇄ **3**). Nitration of the salt was carried out using a mixture of concentrated nitric and sulfuric acids and, as expected, the product showed a methylene peak at δ 6.25 in the nmr, indicating that the methylene group was not substituted.

It seemed likely that substitution would occur in the terminal ring more remote from the center of charge on the quaternary nitrogen and that this could be demonstrated *via* coupling of the nitration product with *p*-nitroso-*N*,*N*-dimethylaniline followed by ring opening (**6** → **7**), quaternization to form **12**, and reduction to **13**.



Evidence that the amino group of **13** was not at the 3′ or 6′ position was afforded by the failure to observe the typical ir absorption pattern[10] due to the out-of-plane deformation of three adjacent aromatic hydrogen atoms as well as the failure to find a complex ABC pattern in the nmr. Analysis[11] of the ABX aromatic proton pattern showed that the strongly deshielded proton (hence adjacent to the carbomethoxy group) is *strongly* coupled by a proton which must be ortho. This makes it possible to eliminate the possibility that **13** could have the amino group at the 4′ position and indicates

(9) *Cf.* M. Scholtz, *Ber.*, **45**, 1718 (1912); M. Scholtz, *Arch. Pharm. (Weinheim)*, **251**, 666 (1913).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 78.

(11) We are indebted to Professor P. W. Jeffs for this analysis.

TABLE I

6-BENZYLIDENEPYRIDO[2,1-*a*]ISOINDOLIUM SALTS (4)

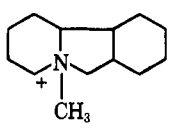
R	R′	Anion	Registry no.	Mp, °C[a]	Yield, %	Formula[b]
H	H	ClO_4	28901-40-8	196–197[c]	80[d]	$C_{19}H_{14}ClNO_4$
H	*p*-CH_3	ClO_4	28901-41-9	193–195[e]	78[d]	$C_{20}H_{16}ClNO_4$
Br	H	Br	28901-42-0	229–230[c]	90	$C_{19}H_{13}Br_2N \cdot H_2O$
Br	H	ClO_4	28901-43-1	243.5–245[c]		$C_{19}H_{13}BrClNO_4$
Br	*p*-NO_2	Br	28901-44-2	269–271[f]	72	$C_{19}H_{12}Br_2N_2O_2 \cdot H_2O$
Br	*p*-NO_2	ClO_4	28901-45-3	264–266[f]		$C_{19}H_{12}BrClN_2O_6$
Br	*o*-Cl	ClO_4	28901-46-4	255–257[c]	87[d]	$C_{19}H_{12}BrCl_2NO_4$

[a] All melting points occurred with decomposition. [b] Satisfactory analyses (C, H, N) were supplied for all of these compounds: Ed. [c] Yellow-green powder. [d] Yield of bromide. [e] Yellow microcrystals. [f] Pale green powder.

that electrophilic attack has occurred at the 9 position of the pyrido[2,1-*a*]isoindole system.

Sulfonation of **2** occurs in fuming sulfuric acid, affording a purple betaine presumably with the sulfo group at position 9, although it can be said definitely only that it has no substituent at position 6.

Attempts to carry out catalytic reduction of pyrido[2,1-*a*]isoindolium bromide (**2a**) over 10% palladium/charcoal at atmospheric pressure failed, but over platinum oxide in the presence of hydrobromic acid the aromatic rings were completely reduced, affording the dodecahydro derivative which was isolated as the methiodide **14**.



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Experimental Section

Analyses were carried out by Janssen Pharmaceutica, Beerse, Belgium, and by Galbraith Laboratories, Knoxville, Tenn. Melting points were taken with the Hoover melting point apparatus and are uncorrected. All nmr data were obtained with 60-MHz instruments.

Pyrido[2,1-*a*]isoindolium Bromide (2a).[3]—A Hanovia 450-W water-cooled ultraviolet source was used as before, but the procedure was modified to permit preparation of **2a** on a larger scale. A Vycor rather than Pyrex filter and a more concentrated solution of **1a**, 5 g in 400 ml of 5% HBr, was used while a stream of nitrogen was bubbled through the solution during irradiation. The gray product crystallized once from ethanol–acetone (92% yield), mp 199–203° dec (lit.[3] 207.5–209.5°), was pure enough for subsequent reactions.

2-Bromo-1-(2,5-dichlorobenzyl)pyridinium Bromide (1c).—The quaternization of 2-bromopyridine with 2,5-dichlorobenzyl bromide was carried out as usual[3] except that it was at 60° for 12 days, mp 150–152° (30% yield). The colorless microcrystalline analytical sample, mp 153–154.5°, was crystallized from methanol–ethyl acetate.

Anal. Calcd for $C_{12}H_8Br_2Cl_2N$: C, 36.22; H, 2.28; N, 3.52. Found: C, 35.93; H, 2.25; N, 3.54.

7,10-Dichloropyrido[2,1-*a*]isoindolium Bromide (2c).—The photocyclization of **1c** was carried out (75% yield) by the general procedure[3] except that 5% hydrobromic acid was solvent. It crystallized from methanol–ethyl acetate as a tan powder with decomposition at about 275°.

Anal. Calcd for $C_{12}H_8BrCl_2N$: C, 45.46; H, 2.54; N, 4.42. Found: C, 45.03; H, 2.54; N, 4.19.

7,10-Dichloropyrido[2,1-*a*]isoindole (3c).—This base (mp 100–102°) was obtained (93% yield) from **2c** by addition of sodium carbonate and on sublimation at 90° (0.35 mm) afforded yellow needles: mp 102.5–104° dec; uv max (95% EtOH) 446 mμ (log ε 2.54), 420 (2.80), 395 (2.90), 370 (3.59), 354 (3.51), 281 (3.49), 246 (4.14), 213 (4.28).

Anal. Calcd for $C_{12}H_7Cl_2N$: C, 61.04; H, 2.99; N, 5.93. Found: C, 60.96; H, 2.96; N, 5.78.

6-Benzylidenepyrido[2,1-*a*]isoindolium Bromide (4).—One gram of the salt **2** was placed in about 25 ml of absolute ethanol with 1 g (excess) of the aryl carboxaldehyde. The mixture was refluxed for about 20 hr and then the solvent was removed by vacuum evaporation. The benzylidene derivatives **4** were crystallized from methanol–ethyl acetate to which, in the case of the 9-bromo derivatives **4c–e**, a trace of hydrobromic acid was added.

The **perchlorates** were prepared by addition of excess 35% perchloric acid to the aqueous solution of the bromides and crystallized from ethanol. The results are summarized in Table I.

Betaine of 6-Benzoylpyrido[2,1-*a*]isoindole (5) by Benzoylation of 2a. A. With Benzoyl Chloride.—A suspension of 0.5 g of **2a** in 5 ml of benzoyl chloride was heated on a steam bath for 4 hr. The mixture was poured into dry ether and the solid residue collected and washed with dry ether. The residue was crystallized from ethanol–water, affording 0.3 g (55%) of fluffy yellow needles: mp 135–137° (pure, mp 136–138°); uv max (95% ethanol) 419 (log ε 4.40), 405 sh (4.21), 295 sh (4.11), 286 (4.17), 272 sh (4.18), 268 (4.20), 248 (4.53), 240 (4.54), 219 (4.34), 206 (4.33).

B. With Benzoic Anhydride.—A mixture of 1 g of **2a** and 5 g of benzoic anhydride was heated for 19 hr at 100° in a stoppered flask. The solution was cooled and poured into anhydrous ether. The ether was decanted and the dark colored product taken up in chloroform; the washed and dried chloroform solution was chromatographed over alumina. The chloroform was removed and the residue crystallized from ethanol–water, affording 0.56 g (52%) of orange needles, mp 135–137°, identical (ir) with the product of procedure A.

Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.74; H, 4.83; N, 5.16.

Hyrolysis of the Betaine 5.—A suspension of 0.25 g of the betaine **5** in 10 ml of 12% hydrobromic acid was refluxed for 18 hr. The small quantity of colorless precipitate obtained on cooling the solution proved to be benzoic acid (ir). The filtered solution was made basic with sodium carbonate and the resulting base converted to the bromide by dissolving it in hydrobromic acid. The excess acid was removed by vacuum evaporation and the residue crystallized from ethanol–ethyl acetate. The gray-brown solid (0.11 g, 49% yield) was shown (ir) to be pyrido[2,1-*a*]isoindolium bromide (**2a**), mp 200–204°.

6-{[*p*-(Dimethylamino)phenyl]imino}pyrido[2,1-*a*]isoindolium Bromide (6a).—To a hot solution of 2 g of pyrido[2,1-*a*]isoindolium bromide in 20 ml of ethanol was added a hot solution of 1.2 g of *p*-nitroso-*N*,*N*-dimethylaniline in 10 ml of ethanol. The dark mixture was refluxed for 30 sec and allowed to stand for several hours at room temperature before it was cooled and the long, dark green needles, mp 213–216°, collected, yield 2.5 g (83%). After recrystallization from methanol–ethyl acetate, the product melted at 222.5–224° dec.

Anal. Calcd for $C_{20}H_{18}BrN_3 \cdot H_2O$: C, 60.31; H, 5.06; N, 10.55. Found: C, 60.17; H, 5.11; N, 10.15.

The **perchlorate** was dark blue, mp 228–229.5° dec.

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.81; H, 4.71; N, 10.16.

9-Bromo-6-{[*p*-(dimethylamino)phenyl]imino}pyrido[2,1-*a*]isoindolium Bromide (6b).—This was prepared essentially as was **6a**, affording (82%) a dark blue solid, mp 208–210° dec (after crystallization from methanol–ethyl acetate).

Anal. Calcd for $C_{20}H_{17}Br_2N_3 \cdot H_2O$: C, 50.34; H, 4.01; N, 8.81. Found: C, 50.72; H, 4.32; N, 8.37.

The **perchlorate** crystallized from dimethylformamide–ether as a deep purple solid, mp 250.5–252° dec.

Anal. Calcd for $C_{20}H_{17}BrClN_3O_4$: C, 50.18; H, 3.58; N, 8.78. Found: C, 50.12; H, 3.76; N, 8.86.

Ethyl *o*-2-Pyridylbenzoate (7a). A. From 6a.—A solution of 1 g of **6a** bromide in 15 ml of 3 *N* hydrochloric acid was refluxed for 3 hr. The solution was made basic by addition of sodium hydroxide and the alkaline solution washed with ether.

The aqueous solution was acidified and the water removed under reduced pressure. The residual salts were extracted several times with hot absolute ethanol which dissolved the organic salt but not the sodium chloride. The residue obtained by evaporating the ethanol was esterified by refluxing for 4 hr with 5% hydrogen chloride in absolute ethanol. After removal of the solvent under reduced pressure, the product was taken up in water which was then made basic by addition of sodium carbonate. The product was extracted with ether and the solution was washed, dried (Na_2SO_4), and concentrated. The residue was crystallized from petroleum ether (30–60°), affording 0.5 g (85%) of tan solid, mp 68–70°. A colorless analytical sample, mp 69.5–71°, was obtained by vacuum sublimation.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.65; H, 6.09; N, 6.00.

B. From 2-*o*-Tolypyridine (8).—To a refluxing suspension of 1 g of 2-*o*-tolylpyridine[12] (**8**) in 50 ml of 10% sodium hydroxide, 2.82 g of powdered potassium permanganate was added slowly over 1 hr. The mixture was stirred and refluxed for a total of 5 hr, after which the excess permanganate was destroyed by addition of ethanol. The manganese dioxide was removed by filtration and unreacted tolypyridine removed by extraction with ether. Acidification of the aqueous solution with hydrochloric acid followed by vacuum evaporation left a mixture of salts which was treated with absolute ethanol, and the procedure was continued essentially as in part A. The product, mp 69–72° (32.5% yield), was identical (mixture melting point, ir) with that obtained in part A.

2-(5′-Bromo-2′-carbethoxyphenyl)pyridine (7b).—Starting with **6b** and using the procedure for conversion of **6a** to **7a**, **7b** was produced in 50% yield, mp (after sublimation) 50–51.5°.

Anal. Calcd for $C_{14}H_{12}BrNO_2$: C, 54.92; H, 3.95; N, 4.58. Found: C, 55.09; H, 3.92; N, 4.47.

6-(Phenylazo)pyrido[2,1-*a*]isoindolium Bromide (10a).—A solution containing 0.8 g of aniline in 10 ml of 12% hydrobromic acid was cooled in an ice bath while a solution containing 0.6 g of a solution of 2 g of **2a** in 25 ml of water was added slowly. Next 8 g of sodium acetate in 25 ml of water was added slowly and the red azo compound began to precipitate. The mixture was stirred for an additional hour before collecting the precipitate, 2.25 g (80%) of dark red solid, mp 201–205° dec. The analytical sample crystallized from methanol–ethyl acetate as red needles, mp 222–223° dec.

Anal. Calcd for $C_{18}H_{14}BrN_3 \cdot 0.75H_2O$: C, 59.11; H, 4.27; N, 10.49. Found: C, 59.36; H, 4.61; N, 10.91.

The **perchlorate** crystallized from dimethylformamide–methanol as dark red needles, decomposition at 230°.

Anal. Calcd for $C_{18}H_{14}ClN_3O_4$: C, 58.15; H, 3.80; N, 11.30. Found: C, 58.13; H, 3.92; N, 10.93.

6-[(*p*-Nitrophenyl)azo]pyrido[2,1-*a*]isoindolium Perchlorate (10b).—The coupling of **2a** with diazotized *p*-nitroaniline was carried out as in the preparation of **10a**. A notable difference is that the product which separated during the sodium acetate addition because of its dark blue color appeared to be the base **9b** (100%, mp 240–248° dec) rather than the salt **10b**. The salt **10b** was formed by heating the base with dilute perchloric acid and was recrystallized from dimethylformamide as a yellow brown solid, mp 313–314° dec.

Anal. Calcd for $C_{18}H_{13}ClN_4O_6$: C, 51.87; H, 3.14; N, 13.44. Found: C, 51.70; H, 3.28; N, 13.16.

Betaine of 6-[(*p*-Sulfophenyl)azo]pyrido[2,1-*a*]isoindolium Hydroxide (10c).—The coupling reaction between **2a** and diazotized sulfanilic acid was carried out essentially as in the preparation of **10a**. The product (89% yield) was an orange powder, mp 325–326° dec, which was very insoluble and was purified only by washing with hot dimethylformamide.

Anal. Calcd for $C_{18}H_{13}N_3O_3S \cdot 0.5H_2O$: C, 59.99; H, 3.92; N, 11.66. Found: C, 59.94; H, 3.57; N, 11.78.

6-Picrylpyrido[2,1-*a*]isoindole (11).—Solutions containing 1 g of **2a** in 30 ml of water, 1 g of picryl chloride in 30 ml of chloroform, and 1.1 g of potassium carbonate in 15 ml of water were mixed in the stated order with vigorous stirring. After 1 hr of stirring at room temperature the mixture was cooled and the product collected. The resulting black powder was washed with methanol–ether (1:4) affording 1.25 g (83%), mp 147–154° with violent decomposition. The analytical sample crystallized from dioxane–ether as a very dark blue powder, exploding at 150°: uv max (EtOH–CH_3CN, 3:2) 460 mμ (log ε 3.96), 358 (3.95), 344 (3.99), 241 (4.65).

Anal. Calcd for $C_{18}H_{10}N_4O_6$: C, 57.17; H, 2.66; N, 14.81. Found: C, 57.12; H, 2.99; N, 14.87.

9-Nitropyrido[2,1-*a*]isoindole (3d).—A mixture of 10 ml of concentrated nitric acid and 10 ml of concentrated sulfuric acid was maintained below 5°, while 2 g of **2a** was added slowly. After the mixture had stood an additional 2 hr at 0° it was poured on 100 g of ice and a small quantity of bisulfite was added to destroy any free bromine. After the ice had melted the mixture was filtered and the product precipitated by addition of a solution of 100 g of sodium acetate in 200 ml of water. The product was collected and dried under vacuum, yielding 1.50 g (88%) of a burgundy powder, mp 146–148° dec. The analytical sample, purified by vacuum sublimation, had mp 149–151° dec; uv max (95% EtOH) 482 mμ (log ε 3.30), 393 (3.18), 325 sh (3.40), 295 (4.09), 270 sh (4.04), and 209 (4.25); ir (KBr) 1325 and 1515 cm^{-1} (NO_2); nmr (CF_3COOH) δ 6.25 (s, 2, CH_2), 8.00–8.90 (m, 6, aromatic), 9.27 (d, 1, H at C-4).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.10; H, 3.62; N, 13.23.

9-Nitropyrido[2,1-*a*]isoindolium Perchlorate (2d).—The salt crystallized from acidic ethanol as a dark violet solid, with decomposition at 235–237° (darkens at 180°): uv max (95% EtOH) 325 mμ (log ε 3.90), 312 (3.99), 274 sh (3.67), 264 (3.70), 255 sh (3.66), 233 sh (3.69), and 207 (3.93).

Anal. Calcd for $C_{12}H_9ClN_2O_6$: C, 46.10; H, 2.90; N, 8.96. Found: C, 46.26; H, 2.91; N, 8.92.

6-{[*p*-(Dimethylamino)phenyl]imino}-9-nitropyrido[2,1-*a*]isoindolium Perchlorate (6c).—The crude perchlorate **2d** from 1 g of the nitro base **3d** was allowed to react with *p*-nitroso-*N*,*N*-dimethylaniline essentially as in the preparation of **6a**, affording 1.8 g (81%) of very deep purple solid, mp 244–246° dec. The analytical sample, mp 252–253° dec, was crystallized from dimethylformamide–ethyl acetate: uv max (95% EtOH) 396 mμ (log ε 4.03), 300 sh (4.12), 256 (4.37).

Anal. Calcd for $C_{20}H_{17}ClN_4O_6$: C, 54.00; H, 3.85; N, 12.60. Found: C, 54.21; H, 3.80; N, 12.61.

1-Methyl-2-(2-carbomethoxy-5-nitrophenyl)pyridinium Iodide (12).—The hydrolysis and esterification of a suspension of 1.5 g of the dimethylaminophenylimino derivative **6c** were carried out as in the preparation of **7a** except that methanol instead of ethanol was used for the esterification step. The product, unlike **7a** and **7b**, could not be recrystallized and was taken up in 40 ml of acetone containing 3 ml of methyl iodide, and the mixture was refluxed for 19 hr. The salt **12** was isolated by addition of ether, 0.75 g (55%), and recrystallized from methanol–ethyl acetate as a yellow microcrystalline solid: mp 218–220° dec; ir (KBr) 1350, 1525 cm^{-1} (NO_2); nmr (deuteriodimethyl sulfoxide) δ 3.75 (s, 3, $COOCH_3$), 4.02 (s, 3, NCH_3), 7.90–8.43 (m, 3, Ar), 8.55–9.00 (m, 3, Ar), 9.30 (d, 1, H at C-6).

Anal. Calcd for $C_{14}H_{13}IN_2O_4$: C, 42.02; H, 3.27; N, 7.00. Found: C, 42.51; H, 3.21; N, 6.98.

1-Methyl-2-(5-amino-2-carbomethoxyphenyl)piperidine Hydriodide (13).—A solution of 0.339 g of **12** in 100 ml of ethanol was stirred with 0.21 g of platinum oxide at room temperature and under hydrogen at 1-atm pressure. The theoretical quantity of hydrogen was absorbed in 1.5 hr. After filtration and concentration of the solution the residue was made to crystallize by addition of ether. The yellow microcrystals, 0.15 g (47%), mp 183–185° dec, were quite pure: ir (KBr) 835, insignificant 680–750 cm^{-1} (two adjacent H atoms); nmr (deuteriodimethyl sulfoxide, aromatic only) δ 7.00 (d of d, 1, J_{AB} = 8 Hz, J_{BX} = 2 Hz), 7.20 (d, 1, J_{BX} = 2 Hz), 7.55 (d, 1, J_{AB} = 8 Hz).

Anal. Calcd for $C_{14}H_{21}IN_2O_2$: C, 44.69; H, 5.63; N, 7.45. Found: C, 44.54; H, 5.56; N, 7.48.

Sulfonation of Pyrido[2,1-*a*]isoindolium Bromide (2a).—To 15 ml of 20% fuming sulfuric acid cooled in an ice bath 2 g of **2a** was added with stirring. When addition was complete the reaction was allowed to continue at 0° for 2 hr, after which the mixture was slowly poured into 100 ml of cold anhydrous ether. The solid was collected, washed with ether, and then crystallized from water as purple solid. Concentration of the aqueous solution and addition of ethanol caused additional precipitation.

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A total of 1.2 g (60%) of product, mp >400°, was obtained. The product appeared to be the betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide: uv max (H_2O) 306 mμ (log ε 4.08), 252 (4.19), 244 (4.21); nmr (CF_3COOH) δ 6.10 (s, 2, CH_2), 7.87–9.05 (m, 6 Ar), 9.15 (d, 1, C-4 H).

Anal. Calcd for $C_{12}H_9NO_3S$: C, 58.29; H, 3.67; N, 5.66. Found: C, 58.20; H, 3.77; N, 5.56.

Dodecahydropyrido[2,1-*a*]isoindole Methiodide (14).—A solution of 1 g of **2a** in 100 ml of ethanol containing 2 ml of 48% hydrobromic acid was stirred with 0.5 g of platinum oxide for 4.5 hr under 1 atm of hydrogen. The calculated volume of hydrogen was absorbed. The filtered solution was concentrated, dilute sodium hydroxide added, and the amine extracted with ether. The dried ($MgSO_4$) ethereal solution was concentrated and the oily residue taken up in acetone containing 3 ml of methyl iodide. The mixture was refluxed for 18 hr and then concentrated and ether added, affording 0.85 g (66%) of colorless powder, mp 192–195° dec. It was recrystallized from methanol–ethyl acetate as microcrystals: mp 197–199° dec; nmr (D_2O) δ 2.22 (d, 14), 2.92–3.55 (m, 2), 3.67 (s, 3), 3.88–4.45 (m, 5).

Anal. Calcd for $C_{13}H_{24}IN$: C, 48.60; H, 7.53; N, 4.36. Found: C, 48.23; H, 7.36; N, 4.24.

Registry No.—**1c**, 28901-35-1; **2c**, 28901-36-2; **2d** perchlorate, 28901-37-3; **3c**, 28901-38-4; **3d**, 28901-39-5; **5**, 28901-47-5; **6a** bromide, 28901-48-6; **6a** perchlorate, 28841-17-0; **6b** bromide, 28901-49-7; **6b** perchlorate, 28901-50-0; **6c** perchlorate, 28901-51-1; **7a**, 28901-52-2; **7b**, 28901-53-3; **10a** bromide, 28901-54-4; **10a** perchlorate, 28901-55-5; **10b** perchlorate, 28901-56-6; **10c**, 28901-57-7; **11**, 28901-58-8; **12**, 28901-59-9; **13**, 28901-60-2; **14**, 28901-61-3; betaine of sulfopyrido[2,1-*a*]isoindolium hydroxide, 28883-86-5.

The Effect of Tetramethylethylenediamine on the Metalation of *N*-Methyl- and *N*-Phenylbenzylamine with *n*-Butyllithium. Deuteration and Electrophilic Condensations of Intermediate Lithioamines. Cyclodehydrations to Give N-Substituted Isoindolines[1]

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N-Methylbenzylamine underwent dimetalation with *n*-butyllithium–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine-(TMEDA) predominantly at the nitrogen and the *o*-benzyl positions as evidenced by deuteration studies. The intermediate dilithioamine (**2**) was condensed with benzophenone, benzaldehyde, cyclohexanone, acetophenone, and propiophenone. The resulting *o*-carbinolamines from the benzophenone and benzaldehyde condensations underwent acid-catalyzed cyclodehydration to form *N*-methylisoindoline derivatives, while the ortho condensation products from the latter three ketones underwent acid-catalyzed linear dehydration reactions, rather than cyclodehydration to form isoindolines. *N*-Phenylbenzylamine was similarly dimetalated at the nitrogen and *o*-benzyl positions with TMEDA-activated *n*-butyllithium. *o*-Carbonyl addition reactions of the dilithioamine intermediate with carbon dioxide, benzophenone, benzaldehyde, and 9-fluorenone resulted in an acid and *o*-carbinolamines, which were readily cyclodehydrated to *N*-phenylphthalimidine and *N*-phenylisoindoline derivatives.

Many aromatic compounds having a nitrogen attached either on or α to the aromatic nucleus have been shown to undergo selective ortho[3] or lateral[4] metalation with *n*-butyllithium. However, there are relatively few instances of successful ring metalation of secondary amines[5] with the exception of the dilithiation of phenothiazine[6] and its benzo derivatives[7] which proceeded in good to excellent yields. Thus, the discovery that certain tertiary amines greatly increase the activity of *n*-butyllithium offers a new approach in the investigation of the metalation of secondary amines.[8–10]

In the present investigation the metalation of *N*-methyl- and *N*-phenylbenzylamine was studied. First, the sites of dimetalation in the respective amines were determined by quenching the intermediate lithioamines with deuterium oxide. Secondly, the extent of dimetalation in these two amines using *n*-butyllithium *vs.* metalations using *n*-butyllithium–TMEDA was compared by condensing the dilithio intermediates with various electrophilic compounds. Finally, the transformations of the *o*-benzyl addition products to N-substituted isoindolines was investigated.

Metalation of N-Substituted Benzylamines. Deuteration with Deuterium Oxide.—The metalation of *N*-methylbenzylamine (**1**) and *N*-phenylbenzylamine (**3**) was attempted using *n*-butyllithium and/or *n*-butyllithium–TMEDA. Determination of the sites and qualitative estimation of the extent of dimetalation in amines **1** and **3** under the various metalating conditions were accomplished by observing the positions of deuterium incorporation on quenching with deuterium oxide and examining the ir and nmr spectra of the deuterated samples.

This method of analysis indicates that dimetalation of amine **1** must occur predominantly at the nitrogen and in the ring, ortho to the *N*-methylamino group, because each ir spectrum of deuterated amine **1**, which was shown by integration of the corresponding nmr spectrum to have 0.8–1.2 D in the aromatic ring, ex-

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