

Imidazo[1,2-*a*]pyridine Anthelmintics. Synthesis of 6-Phenylaminoimidazo[1,2-*a*]pyridine-2-carbamate and 5-Acylaminopyridines by a Chapman Rearrangement

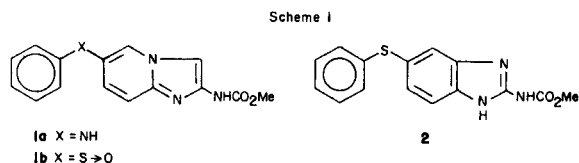
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The title compound, a potential anthelmintic agent, was prepared in seven steps from 5-hydroxy-2-picoline. The intermediate 5-(*N*-phenylbenzamido)-2-picoline was prepared by a facile Chapman rearrangement of the corresponding benzimidoyl ester. Oxidation and Curtius rearrangement of the substituted picoline gave 5-(*N*-phenylbenzamido)-2-aminopyridine which underwent ring closure and debenzoylation to furnish methyl 6-phenylaminoimidazo[1,2-*a*]pyridine-2-carbamate. Fries rearrangement of the penultimate *N*-benzoyl derivative gave a 6-(*p*-benzoylphenylamino)imidazo[1,2-*a*]pyridine derivative, whose structure was confirmed by cmr study. The title compound lacked significant anthelmintic activity.

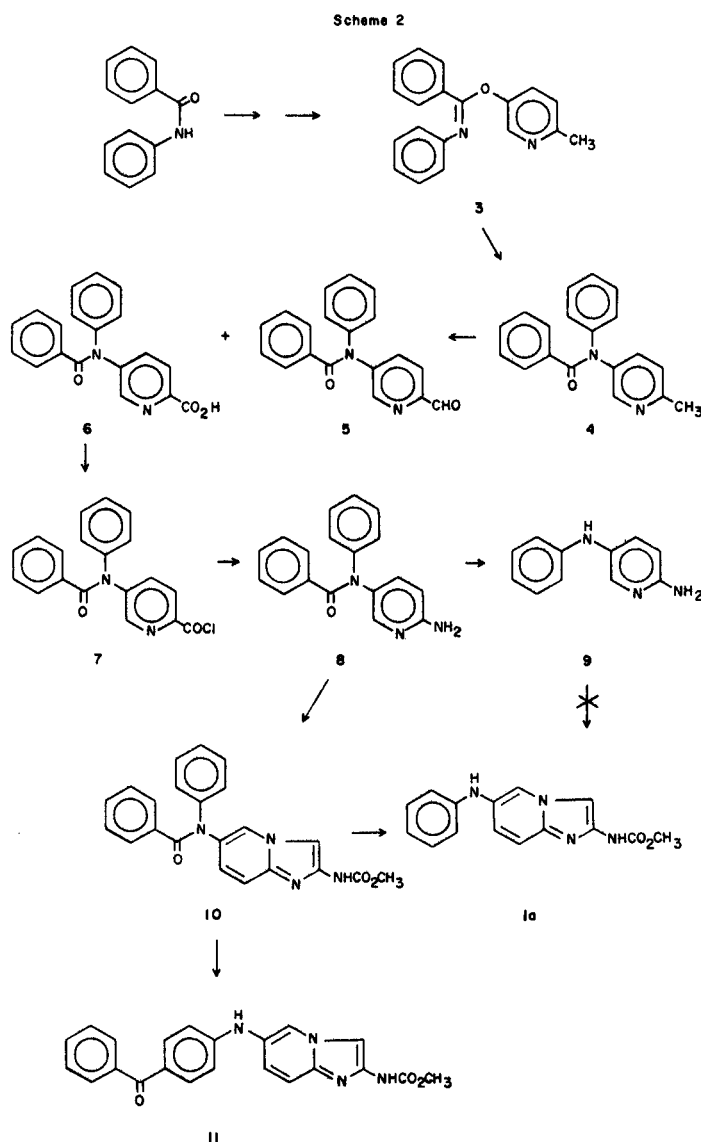
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The broad-spectrum anthelmintic activity of 6-phenylsulfinylimidazo[1,2-*a*]pyridine-2-carbamate **1b** and the benzimidazole counterpart, fenbendazole **2** is well known. The anthelmintic activity is known (1,2) to be sensitive to the functionality which bridges the aryl group and the heterocyclic ring system, *i.e.*, sulfinyl in **1b**.



As a part of a general program to prepare 6-substituted imidazo[1,2-*a*]pyridine-2-carbamates as potential anthelmintic agents, it was of interest to prepare 6-arylamino analogs, in particular **1a**. Whereas 6-arylthioimidazo[1,2-*a*]pyridines are built up from 3-arylthiopyridines, which are in turn easily prepared by nucleophilic displacement of the corresponding 3-halo derivative, the synthesis of the requisite 3-arylamino pyridines has been shown to be more formidable (3).

The Chapman rearrangement has been used with success in the preparation of various diphenylamine derivatives (4,5) and we thought to explore its utility in the preparation of these otherwise difficultly accessible 3-arylamino pyridines. Treatment of *N*-phenylbenzimidoyl chloride (6), prepared from benzanilide, with 5-hydroxy-2-picoline in the presence of sodium ethoxide gave the desired aryl imidate **3** in good yield. The Chapman rearrangement of **3** to the *N*-benzoylarylamino pyridine **4** went smoothly (75% yield) in the absence of solvent at 270°. It is likely that the Chapman rearrangement is the most versatile and efficient synthesis of 3(5)-arylamino pyridine derivatives due to the simple nature of the procedure and the ready availability of 3(5)-hydroxypyridines.



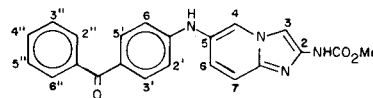
Annulation of an imidazole ring to pyridine requires conversion of the 2-methyl functionality of **4** to an amino group which could presumably be accomplished by oxidation, conversion to the acid chloride and the Curtius rearrangement. Oxidation of 2-picoline with potassium permanganate (**7**) is the method of choice for conversion to the picolinic acid, but this oxidation went very poorly in the case of **4**, even under forcing conditions. Selenium dioxide in dioxane gave the desired picolinic acid **6** in fair yield accompanied by sizable amounts of the aldehyde **5** and unreacted starting material. The aldehyde, a potentially useful intermediate for other heterocyclic ring closure reactions, required chromatographic purification from other neutral components in the reaction mixture. The acid **6** was converted to the acid chloride **7** by thionyl chloride and then by means of the acyl azide and the Curtius rearrangement to the 2-aminopyridine derivative **8**.

There remained only to take **8** through debenzoylation and ring closure reactions to give **1a**. The debenzoylation of the pyrid-5-ylbenzanilide **8** with concentrated hydrochloric acid gave 2-amino-5-phenylaminopyridine **9** in fair yield which was shown not to react with methyl chloroacetylcarbamate (**1**) to give appreciable amounts of the imidazo[1,2-*a*]pyridine **1a** under a variety of conditions. Reasoning that the secondary arylamine was interfering with the condensation and ring closure on the primary amine, we undertook the ring closure in HMPA with **8**, the protected diarylamine, to furnish the desired imidazo[1,2-*a*]pyridine-2-carbamate **10** still possessing the benzoyl protecting group.

Debenzoylation of **10** was attempted with polyphosphoric acid because of our concern that the carbamate might be labile to treatment with strong base. Instead of undergoing debenzoylation in polyphosphoric acid, rearrangement of **10** had apparently occurred as the product **11** was not identical to **10** in tlc mobility, but was isomeric by elemental analysis. Previous studies by Birchall and Thorpe (8,9) have established that treatment of *N*-aroyldiphenylamines with polyphosphoric acid gives the dearoylated derivatives as the major product plus varying amounts of *o*- and *p*-aroyl Fries rearrangement products. ^{13}C nmr studies established that **11** indeed was the product of a Fries rearrangement, in fact that the product was a 6-(*p*-benzoylphenylamino)imidazo[1,2-*a*]pyridine derivative. The key information identifying structure **11** is the appearance of ^{13}C nmr signals at 113.0 and 132.3 ppm, both due to a pair of equivalent carbon atoms (2',6' and 3',5') and of the carbonyl signal at 193.6 ppm. The latter was proof of the rearrangement where an amidic carbonyl was converted to a ketonic one while the paired signals showed the substitution to be para on the former *N*-phenyl group. Other features of the ^{13}C spectrum are fully consistent with the structure shown. The *p*-Fries rearrangement

Table 1

^{13}C -NMR Chemical Shifts from TMS of Methyl 6-(*p*-Benzoylphenylamino)imidazo[1,2-*a*]pyridine-2-carbamate (**11**) in DMSO- d_6



Chemical Shift (ppm)	Carbon Assignment
193.6	ArCOAr
153.8	Carbamate CO, C ₁ '
150.0	
142.6	C ₂
139.1	C ₉ , C ₁₁ '
138.5	
132.3	C ₃ ', C ₅ '
131.4	C ₄ '
128.9	C ₂ '', C ₆ ''
128.2	
127.1	C ₅
126.3	C ₄ '
122.8	C ₆
119.1	C ₄
115.3	C ₇
113.0	C ₂ ', C ₆ '
99.8	C ₃
51.8	OCH ₃

product was isolated chromatographically in good yield (69%) and the debenzoylated derivative or the *o*-rearrangement product was not observed in significant (>5%) amounts, although some starting material could be recovered.

Debenzoylation could be accomplished successfully with excess sodium methoxide at reflux to furnish **1a** in excellent yield. Anthelmintic evaluation (10) of the phenylamino derivative **1a** showed it to possess mediocre activity, very much inferior to the activity of the phenylsulfanyl analog **1b** (1).

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. Pmr spectra were determined with a Varian T60 (proton) with tetramethylsilane as an internal standard. ^{13}C Nmr spectra were obtained with a Varian CFT-20 on a saturated solution (4% w/v) in DMSO- d_6 with tetramethylsilane as internal reference. Chromatographic separations were performed on silica gel (E. Merck 7734) using a ratio of 20:1, absorbent to fractionable material.

2-Methylpyrid-5-yl *N*-Phenylbenzimidate (**3**).

A mixture of benzanilide (60 g., 304 mmoles) and phosphorus pentachloride (63.4 g., 304 mmoles) was heated on a steam bath to maintain the evolution of hydrogen chloride. Heating was continued until gas evolution had ceased, and the resultant liquid was concentrated under aspirator vacuum to remove phosphorus oxychloride. The residue was dissolved in ether (500 ml.), the small amount of insoluble material was filtered and discarded, and the solvent was evaporated *in vacuo*. The residue, *N*-phenylbenzimidoyl chloride, crystallized, m.p. 38-39.5° [lit. (4b) m.p. 38-40°].

Sodium metal (7.0 g., 304 mmoles) in small pieces was added to ethanol (400 ml.) and after complete solution had been achieved, 5-hydroxy-2-methylpyridine (48 g., 442 mmoles) was added. To this solution was added the benzimidoyl chloride which had been dissolved in dioxane (200 ml.), maintaining the temperature at 30-35° with a cold water bath during the addition. The reaction was complete within 30 minutes by tlc (3% methanol in dichloromethane on silica gel). Addition of ether and hexane caused precipitation of solids which were filtered and discarded. Volume reduction *in vacuo* to an oily residue and addition of ether produced a second insoluble material which was filtered and shown by tlc to be mostly picoline starting material. Evaporation of the filtrate to a residue and chromatography on silica gel (2% methanol in dichloromethane) gave 42.9 g. of **3** (49%), m.p. 73-74°, after product fractions were pooled, concentrated to a residue, and recrystallized from ether-light petroleum ether; pmr (deuteriochloroform): δ 2.47 (s, 3H, CH₃), 5.8-6.9 (m, 12H, aromatic protons), 7.45 (d, 1H, pyridine H-6).

Anal. Calcd. for C₁₁H₁₆N₂O: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.07; H, 5.73; N, 9.61.

5-(*N*-Benzoylphenylamino)-2-methylpyridine (**4**).

The picolinyl imidate (**3**, 20 g., 69 mmoles) was melted in a 100 ml. round bottom flask and covered with a nitrogen atmosphere by repeated evacuation and flushing with nitrogen. The flask was immersed in a Wood's metal bath at 270° for an hour and then removed and allowed to cool. The reaction mixture was covered with ether, scratched to induce crystallization, and the resultant crystals were filtered. A second crop was obtained from the mother liquor by addition of hexane. Both crops were homogeneous by tlc (3% methanol in dichloromethane), 15.0 g. (75%), m.p. 129-130°; pmr (deuteriochloroform): δ 2.52 (s, 3H, CH₃), 6.0-6.6 (m, 12H, aromatic protons), 7.35 (d, 1H, pyridine H-6).

Anal. Calcd. for C₁₉H₁₆N₂O: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.21; H, 5.73; N, 9.61.

5-(*N*-Benzoylphenylamino)-2-pyridinecarboxaldehyde (**5**) and 5-(*N*-Benzoylphenylamino)-2-pyridinecarboxylic Acid (**6**).

The benzoylated anilinicpicoline (**4**, 20 g., 70 mmoles) was dissolved in dioxane (140 ml.) and selenium dioxide (15.5 g., 140 mmoles) and water (2.5 ml., 140 mmoles) were added. The mixture was heated at reflux with stirring for 18 hours, cooled, and filtered through a filter aid. The filter cake was washed with ethyl acetate (4 x 150 ml.) and the filtrate and washings were combined and extracted with water. After separation of the aqueous phase and filtration of the organic phase again, the ethyl acetate layer was then extracted with 10% sodium bicarbonate solution (3 x 100 ml.). The bicarbonate extracts were backwashed with ethyl acetate, acidified with acetic acid, and reextracted with ethyl acetate. Both the acidic and neutral ethyl acetate extracts were dried and evaporated to residue (finally under high vacuum). The acidic fraction crystallized and was recrystallized from ether to furnish pure **6**, 7.51 g., (34%), m.p. 177-178°; pmr (deuteriochloroform): δ 7.0-7.6 (m, 13H, aromatic protons), 10.1 (bs, 1H, COOH).

Anal. Calcd. for C₁₉H₁₄N₂O₃: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.53; H, 3.99; N, 8.56.

The neutral fraction (51%) was chromatographed with 1% methanol in dichloromethane as the eluant and recrystallized from ether to furnish unreacted starting material (27%) and the aldehyde **5**, 3.98 g. (19%), m.p. 119-120°; pmr (deuteriochloroform): δ 7.0-8.0 (m, 12H, aromatic protons), 8.58 (d, 1H, pyridine H-6), 9.98 (s, 1H, CHO).

Anal. Calcd. for C₁₉H₁₄N₂O₂: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.40; H, 4.73; N, 9.35.

5-(*N*-Benzoylphenylamino)-2-pyridinecarbonyl Chloride (**7**).

A mixture of the acid **6** (5.85 g., 18.4 mmoles), benzene (70 ml.) and thionyl chloride (10 ml., 138 mmoles), containing one drop of dimethylformamide was heated at reflux for an hour. The solution was cooled and evaporated to a residue *in vacuo*. Benzene was successively added and evaporated *in vacuo* twice to yield a hard gum which was dissolved in ether (20 ml.) and filtered to remove a small amount of insoluble material. Addition of hexane and scratching the sides of the vessel induc-

ed crystallization to give the product **7**, 6.0 g. (97%), m.p. 121-125°; pmr (deuteriochloroform): δ 7.0-8.1 (m, 12H, aromatic protons), 8.56 (d, 1H, pyridine H-2).

Anal. Calcd. for C₁₉H₁₃ClN₂O₂: C, 67.76; H, 3.89; N, 8.32. Found: C, 67.81; H, 4.05; N, 8.23.

2-Amino-5-(*N*-benzoylphenylamino)pyridine (**8**).

The acid chloride **7** (60 g., 17.8 mmoles) in acetone (250 ml.) was added to an aqueous solution of sodium azide (1.5 g., 22.5 mmoles in 4.2 ml. water). The solution, which became cloudy at once, was stirred for 30 minutes, diluted with water (250 ml.), and stirring was continued. After 15 minutes the solids were filtered, washed with water and hexane, and dried for 18 hours in a vacuum desiccator (5.85 g., 90%), p. 83-86° dec. The azide was suspended in 50% aqueous acetic (40 ml.) in a 250 ml. round bottomed flask. The mixture was stirred and heated to 85-90° when decomposition began. The temperature was maintained for 15-20 minutes and then the flask was cooled, diluted with water and extracted with dichloromethane (2 x 50 ml.). The aqueous phase was made alkaline with 50% sodium hydroxide solution (20 ml.) and extracted with ethyl acetate (3 x 100 ml.). The organic phase was washed with water, dried (magnesium sulfate) and treated with charcoal. Tlc [dichloromethane/methanol (19:1)] showed one major spot. The volume of the ethyl acetate was reduced by boiling and hexane was added. Two crops of homogeneous material (tlc) were collected, 3.75 g. (70% yield from acid chloride), m.p. 157-158°; pmr (deuteriochloroform): δ 4.50 (bs, 2H, NH₂), 6.40 (d, 1H, pyridine H-3), 7.0-7.6 (m, 11H, aromatic protons), 7.87 (d, 1H, pyridine H-2).

Anal. Calcd. for C₁₈H₁₅N₃O: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.55; H, 5.06; N, 14.38.

2-Amino-5-phenylaminopyridine (**9**).

The benzamido compound **8** (0.578 g., 2 mmoles) was heated at reflux for three hours in a mixture of water (15 ml.) and concentrated hydrochloric acid (6 ml., 72 mmoles). The solution was then cooled, diluted with ice water and extracted with ethyl acetate (2 x 50 ml.). The aqueous layer was separated, made alkaline with 2.5*N* sodium hydroxide solution and reextracted with ethyl acetate (3 x 50 ml.). The organic extracts were backwashed with water, dried (magnesium sulfate) and evaporated to a residue *in vacuo*. Trituration of the residue with ether induced crystallization. The product was recrystallized from hot ether-hexane to afford 0.148 g. (40%), m.p. 118-119°; pmr (deuteriochloroform): δ 4.40 (bs, 2H, NH₂), 5.44 (bs, 1H, NH), 6.50 (d, 1H, pyridine H-3), 7.4-6.6 (m, 6H, other aromatic protons), 7.95 (d, 1H, pyridine H-6).

Anal. Calcd. for C₁₁H₁₁N₃: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.58; H, 5.85; N, 22.82.

Methyl 6-(*N*-Benzoylphenylamino)imidazo[1,2-*a*]pyridine-2-carbamate (**10**).

A round-bottomed flask was charged with the amine **8** (0.365 g., 1.25 mmole), methyl chloroacetylcarbamate (**1**) (0.229 g., 1.5 mmole) and hexamethylphosphoramide (1.5 ml.) and heated at 100° with stirring in an oil bath. Tlc showed the reaction to be complete after two hours [dichloromethane/methanol (19:1)]. The mixture was diluted with cold water and extracted with ethyl acetate (3 x 50 ml.). The extracts were washed with water, dried (magnesium sulfate) and evaporated to a residue. Trituration of the resultant syrup with ether gave a non-crystalline solid which was filtered and reprecipitated from hot dichloromethane-hexane with charcoal treatment, 0.184 g. (38%), m.p. 170-176°. A second precipitation or chromatography [dichloromethane/methanol (19:1)] was occasionally necessary to remove a small amount of starting material; pmr (DMSO-*d*₆): δ 3.70 (s, 3H, CO₂CH₃), 7.2-7.7 (m, 12H, aromatic protons), 7.82 (s, 1H, H-3), 8.68 (s, 1H, H-5), 10.35 (bs, 1H, NH).

Anal. Calcd. for C₂₂H₁₈N₄O₃: C, 68.38; H, 4.70; N, 14.30. Found: C, 68.47; H, 4.49; N, 13.92.

Methyl 6-(4'-Benzoylphenylamino)imidazo[1,2-*a*]pyridine-2-carbamate (**11**).

The *N*-benzoylated derivative **10** (0.75 g., 1.94 mmoles) was mixed with polyphosphoric acid (4.5 g.) and heated with occasional stirring at 100°. The solid slowly dissolved. After 75 minutes the mixture was cooled and diluted with water. Ether was added and the acid was cautiously neutralized with solid potassium carbonate with stirring. The precipitate which formed was filtered and washed with water and ether. Two reprecipitations from warm dimethylformamide with water gave an off-white solid that was essentially one spot on tlc [dichloromethane/methanol (19:1), double development], 0.52 g. (69%), m.p. 233-241° dec.; pmr (DMSO- d_6): δ 3.72 (s, 3H, CO₂CH₃), 6.9-8.0 (m, 11H, aromatic protons), 8.56, 8.74 (2s, 2H, H-3,5), 10.36 (bs, 1H, NH).

Anal. Calcd. for C₂₂H₁₈N₄O₅: C, 68.38; H, 4.70; N, 14.30. Found: C, 68.11; H, 4.59; N, 14.66.

Methyl 6-Phenylaminoimidazo[1,2-*a*]pyridine-2-carbamate (**1a**).

To a solution of sodium methoxide (1.62 g., 30 mmoles) in methanol (60 ml.) was added the benzamido compound **10** (1.0 g., 2.6 mmoles) and the mixture was stirred and heated to reflux. Solution occurred within 5 minutes and a solid began to crystallize out within another 5 minutes. After 1 hour reflux was discontinued and the reaction mixture was cooled and filtered. The solid was washed with methanol and ether and dried *in vacuo*. The product was homogeneous on tlc [dichloromethane/methanol (19:1), two developments], 0.63 g. (86%), m.p. 251-253°; pmr (DMSO- d_6): δ 3.72 (s, 3H, CO₂CH₃), 6.8-7.4 (m, 7H, aromatic protons), 7.84, 7.90 (s, 2H, H-3,5), 8.38 (bs, 1H, NHCO), 10.34 (bs, 1H, NHAr).

Anal. Calcd. for C₁₃H₁₄N₄O₂: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.47; H, 5.03; N, 19.62.

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