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CHANGES UNDERGONE BY 2-AMINO-N-(PYRIDYL-3')ANILINES UNDER PSCHORR REACTION CONDITIONS

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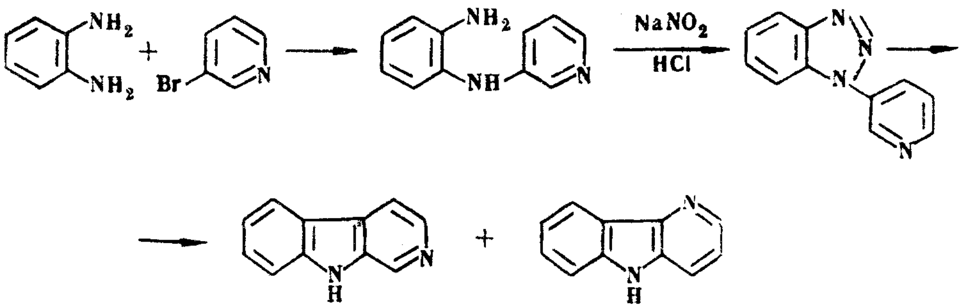
Reaction of 2-nitroaniline with 3-bromopyridine, 3-iodo-5-methylpyridine, and 3-iodo-6-methylpyridine gives 54-73% yield of the hitherto unknown 2-nitro-N-(pyridyl-3') aniline, 2-nitro-N-(5'-methylpyridyl-3') aniline, and 2-nitro-N-(6'-methylpyridyl-3') aniline. The nitro compounds prepared can easily be reduced to the corresponding amino-N-pyridylanilines. The amino compounds do not form carbolines under Pschorr reaction conditions, but are converted to triazoles or N-(pyridyl-3')-aniline.

In 1930 Spath and coworkers [1] reported that it was possible to prepare mixed β and δ carbolines from aminopyridylanilines according to the equation:



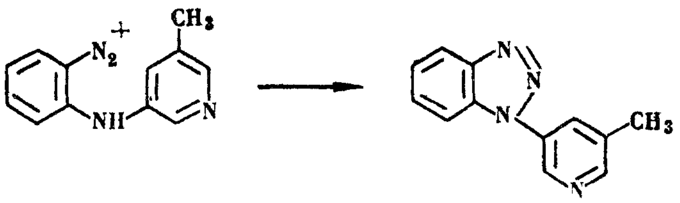
Reaction of an aqueous solution of 2-phenylenediamine with 3-bromopyridine in a sealed tube (150°) gives an aminopyridylaniline which is further converted to a triazole, and zinc chloride fusion of the latter at 320° gives mixed β- and δ-carbolines. The reaction conditions are drastic and give rise to extensive resinification. Later the synthesis of carboline compounds from aminopyridylanilines was described [2]. This eliminates the stage of preparing a triazole, and involves less drastic conditions [2].

This method is based on the Pschorr cyclization reaction. The pyridine ring is deactivated for an electrophilic substitution and less open to attack than the benzene one. An amino group in the pyridine ring facilitates electrophilic attack, and the aromatic substituent still further enhances the activating effect of that group. Reaction occurs at room temperature in the presence of copper powder, or with the same yield on boiling without the catalyst.

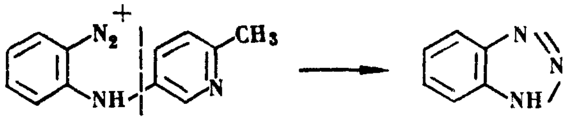
In the present case, reaction of 3-bromopyridine, 3-iodo-5-methylpyridine, and 3-iodo-6-methylpyridine with 2-nitroaniline at 160-170° gave, respectively, 2-nitro-N-(pyridyl-3') aniline, 2-nitro-N-(5'-methylpyridyl-3'), and 2-nitro-N-(6' methylpyridyl-3') aniline, in 54-73% yield.

The nitro compounds were readily reduced by hydrazine hydrate and Raney nickel to aminopyridylanilines. However, these amino compounds could not be cyclized to carbolines by the Pschorr method. Under Pschorr reaction conditions 2-amino-N-(pyridyl-3') aniline eliminated nitrogen to give N-(pyridyl-3') aniline:

Under the same conditions 2-amino-N-(5'-methylpyridyl-3') aniline was converted to 1-(5'-methylpyridyl-3') benzotriazole:



When the diazo compound prepared from 2-amino-N-(6' methylpyridyl-3') aniline was boiled for two hours, N–C bond breaking was observed with benzotriazole formation:



Experimental

2-Nitro-N-(pyridyl-3') aniline. 26.7 g (0.17 mole) 3-bromopyridine, 17.7 g (0.13 mole) o-nitroaniline, 16.7 g (0.12 mole) anhydrous potassium carbonate were placed in a two-necked flask fitted with reflux condenser and stirrer, along with 840 mg copper bronze and 110 ml nitrobenzene, the whole refluxed for 24 hr, the nitrobenzene steam distilled off, and the residue extracted with chloroform. The extract was dried over sodium sulfate, the solvent distilled off under reduced pressure, the residue dissolved in benzene, and run on to a column of activity grade 2 alumina, from which it was eluted with ether. After removing the ether from the eluate, the residue was recrystallized from aqueous ethanol, to give 21.2 g (76.1%) yellow product mp 95-96°. Found: C 61.51; H 4.20; N 19.79%. Calculated for $C_{11}H_9N_3O_2$: C 61.39; H 4.22; N 19.52%.

2-Nitro-N-(6'-methylpyridyl-3') aniline. Similarly 15 g (0.066 mole) 6-methyl-3-iodopyridine, 6.3 g (0.046 mole) o-nitroaniline, 7 g (0.051 mole) anhydrous potassium carbonate, 350 mg copper bronze, and 45 ml nitrobenzene were reacted at 150-160° for 15 hr to give 6.5 g (53.7%) yellow crystals mp 123-125°. Found, C 62.96; H 4.82; N 18.29%. Calculated for $C_{12}H_{11}N_3O_2$: C 62.87; H 4.84; N 18.33%.

2-Nitro-N-(5'-methylpyridyl-3')aniline. Prepared similarly to the above, using 5.8 g (0.025 mole) 5-methyl-3-iodopyridine, 2.8 g (0.02 mole) o-nitroaniline, 2.8 g (0.02 mole) anhydrous potassium carbonate, 0.14 g copper bronze in 20 ml nitrobenzene, reaction temperature 150-160° reaction time 9 hr, yield 3.5 g (75.4%), red crystals, mp 126-126.5°. Found: C 63.01; H4.81; N 18.27%. Calculated for $C_{12}H_{11}N_3O_2$: C 62.87; H 4.84; N 18.33%.

2-Amino-N-(pyridyl-3') aniline. 5.2 g (0.024 mole) 2-nitro-N-(pyridyl-3') aniline, 2 g Raney nickel, and 20 ml 100% hydrazine hydrate in 100 ml ethanol were refluxed together for 15 min. After cooling the catalyst was filtered off from the reaction products, the ethanol distilled off from the filtrate under reduced pressure, and the residue recrystallized from benzene-petrol ether. Yield, 3.5 g (78.5%) amine mp 125.5-126° (the literature [1] gives mp 125-126°).

2-Amino-N-(6'-methylpyridyl-3') aniline. In the same way 1.3 g (0.0057 mole) 2-nitro-N-(6'-methylpyridyl-3') aniline was reduced with 0.55 g Raney nickel and 6 ml 100% hydrazine hydrate in 30 ml dry ethanol, in 30 min, to give 0.9 g (81.8%) compound mp 102-103°. Found: C 72.21; H 6.56; N 20.91%. Calculated for $C_{12}H_{13}N_3$: C 72.34; H 6.58; N 21.09%.

2-Amino-N-(5'-methylpyridyl-3') aniline. In the same way, from 1.5 g (0.0065 mole) 2-nitro-N-(5'-methylpyridyl-3') aniline, 0.56 g Raney nickel, and 5.6 ml hydrazine hydrate in 30 ml dry ethanol gave 0.8 g (62.4%) compound mp 126-126.5°. Found: C 72.28; H 6.57; N 20.89%. Calculated for $C_{12}H_{13}N_3$: C 72.34; H 6.58; N 21.09%.

Cyclizing 2-amino-N-(pyridyl-3') aniline. 1.6 g (0.008 mole) 2-amino-N-(pyridyl-3') aniline in 3.5 ml conc. H_2SO_4 plus 50 ml water was diazotized at 0-5° with 1.7 g $NaNO_2$ in 20 ml water, the mixture stirred for 20 min, 1.26 g urea and 1.7 g Cu powder added, the mixture stirred for 30 min. at 0.5° and then for 30 min. at room temperature. The catalyst was filtered off, the filtrate made alkaline with 25% aqueous ammonia, extracted with $CHCl_3$, and dried over Na_2SO_4. After distilling off the $CHCl_3$, the residue was dissolved in benzene, and chromatographed on 60 g activity III alumina, to give N-(pyridyl-3') aniline mp 139-141° (the literature gives [1] mp 142°).

Cyclizing 2-amino-N-(6'-methylpyridyl-3') aniline. 0.7 g (0.0036 mole) amino compound in 1.8 ml conc. H_2SO_4 plus 20 ml water was diazotized as described above with 0.73 g $NaNO_2$ in 10 ml water, 0.57 g urea added, and the whole refluxed for 2 hr. After cooling the reaction products were worked up in the way previously described, but using 35 g alumina for chromatographing, to give 0.6 g benzotriazole mp 99-100° [3]. Found: C 60.22; H 4.20; N 35.55%. Calculated for $C_6H_5N_3$: C 60.49; H 4.23; N 35.27%.

Cyclizing 2-amino-N-(5'-methylpyridyl-3') aniline. This was run exactly as for 2-amino-N-(pyridyl-3') aniline, using 0.35 g of the amino compound, 0.9 ml H_2SO_4, 10 ml water, 0.37 g $NaNO_2$ in 5 ml water, 0.28 g urea, 0.35 g Cu powder, but with 18 g activity III alumina for the chromatographing, to give 0.3 g 1-(5'-methylpyridyl-3') benzotriazole mp 112-114°. Found: C 68.65; H 4.79; N 26.55%. Calculated for $C_{12}H_{10}N_4$: C 68.55; H 4.79; N 26.65%

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