SYNTHESIS OF DERIVATIVES OF 2-(o-NITROBENZYL)PYRIDINE

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Diazotization of 2-(o-nitro-p-aminobenzyl)pyridine (I) in concentrated H_2SO_4 and subsequent diazo-reaction lead to the formation of 2-(o-nitro-p-halogenbenzyl)pyridines. During the acylation reaction with acetic anhydride and benzoyl chloride, the corresponding derivatives are readily formed. Compound I reacts with benzyl chloride with the formation of the corresponding mono- and dibenzyl derivatives and with p-nitrobenzaldehyde with the formation of the corresponding azomethine.

In 1949 Schofield conducted the diazotization and subsequent deamination of amine I and obtained 2-(o-nitrobenzyl)pyridine [1]. Later by means of the diazo reaction 2-(o-nitro-p-cyanobenzyl)pyridine [2] was synthesized from compound I, and from the former different derivatives of 3-nitro-4-(pyridyl-2-methyl)-benzoic acid [3] were readily obtained. Weinstein et al. [4] described the conversion of compound I into 2-(o-nitro-p-chlorobenzyl)pyridine and 2-(o-nitro-p-oxybenzyl)pyridine. Diazotization of amine I is conducted in a medium of dilute hydrochloric [1, 2, 4, 5] or sulfuric [4] acids, and the yields of the products of the reaction are equivalent to 30–50%.

The present study describes the synthesis of certain derivatives of 2-(o-nitrobenzyl)pyridine having a substitution in the n-position of the benzene ring and arising from compound I. It was found that diazotiazation of amine I in a medium of concentrated sulfuric acid at a temperature of 25–28° C proceeds quite readily. By means of the diazo reaction 2-(o-nitro-p-chlorobenzyl)pyridine (II), 2-(o-nitro-p-bromobenzyl)-pyridine (III), and 2-(o-nitro-p-iodobenzyl)pyridine (IV) were obtained with yields of 90.5, 88 and 92.5% respectively.

The amine I readily enters into the acylation reaction. On interaction with acetic anhydride 2-(o-nitro-p-acetylaminobenzyl)pyridine (V) is formed, and benzoylation leads to the formation of 2-(o-nitro-p-benzoylaminobenzyl)pyridine (VI). Alkylation of compound I with excess benzyl chloride at 100° C leads to the formation of 2-(o-nitro-p-dibenzylaminobenzyl)pyridine (VII) with an admixture of 2-(o-nitro-p-benzylaminobenzyl)pyridine (VIII). By the reaction between amine I and p-nitrobenzaldehyde 2-o-nitro-p-(p-nitrobenzylidenamino)benzyl pyridine (IX) was obtained.

The constants, yields, and data of the elementary analysis of the compounds obtained are presented in the table.

EXPERIMENTAL

2-(o-Nitro-p-chlorobenzyl)pyridine was synthesized by a previously described method [5], 118–119° C. According to data in the literature [2] 118.5° C.

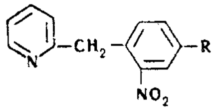
2-(o-Nitro-p-chlorobenzyl)pyridine (II). Cuprous chloride solution. A mixture of 3 g cuprous chloride, 5 g potassium chloride, 75 ml water, 6 ml conc HCl and 0.75 g powdered copper were mixed, left overnight, and filtered.

At 25–28° C 1 g (0.015 mole) sodium nitrite in 10 ml concentrated H_2SO_4 was added to a solution of 3 g (0.013 mole) amine of compound I in 20 ml concentrated sulfuric acid. The resultant diazo solution was stirred for 30 min, cooled to 0° C, and gradually added to a solution of cuprous chloride, cooled to 0°, holding at a temperature of 7–15° C. The reaction mixture was left overnight, the precipitate was removed, and the filtrate was made alkaline with a 20% solution of sodium hydroxide. The residue was removed by filtration and combined with the first precipitate. The combined precipitates were dried in the air, and then extracted with absolute ethyl alcohol. The extract was evaporated to dryness under vacuum. The residue was dissolved in several milliliters of chloroform and chromatographed on aluminum oxide, eluting the product with chloroform. The colorless fractions which produce a dark spot when a sample is transferred onto filter paper and irradiated with ultraviolet light were removed. From the eluate 1.91 g of light yellow crystals of compound II were isolated. By means of subsequent elution with chloroform the yellow band was out of the column, and, after evaporating the eluate under vacuum, 1 g (33%) of the original amine of I with a m.p. of 117–119° C was extracted. Compound II was purified by repeated chromatography on aluminum oxide using chloroform as the eluate.

2-(o-Nitro-p-bromobenzyl)pyridine (III). Solution of cuprous bromide. A mixture of 3 g cuprous bromide, 15 g potassium bromide, 75 ml water, 6 ml concentrated HBr, and 0.75 g powdered copper was mixed, left overnight, and filtered.

A 3 g (0.013 mole) quantity of the amine of compound I was dissolved in 20 ml conc H_2SO_4 at 0° C, and 1 g (0.015 mole) of sodium nitrite in 10 ml H_2SO_4 at 5–7° C was added. The mixture was stirred for 30 minutes at 5° C and excess nitrous acid was dissociated by addition of sulfamic acid. The resultant diazo solution was added to a solution of cuprous bromide and the temperature was maintained below 12° C. The latter solution was left overnight and then stirred at room temperature until the evolution of nitrogen was complete. The residue was separated, washed many times with iced water, dried in air, and extracted with absolute ethyl alcohol. The alcohol was removed by distillation under vacuum, and the residue was dissolved in a small quantity of dimethylformamide and chromatographed in a column containing aluminum oxide eluting with a mixture of benzene and chloroform (1 : 2). As described above 1.86 g of compound III with mp of 35–37° C and 1.35 g (35%) of the original amine of compound I with a mp 117–119° C were extracted. Compound III was purified by repeated chromatography in aluminum oxide using a mixture of benzene and chloroform (1 : 2) as eluent.

2-(o-Nitro-iodobenzyl)pyridine (IV). A 3 g (0.013 mole) quantity of amine of compound I was dissolved in 20 ml of conc H_2SO_4 at 0° C, 1 g (0.015 mole) sodium nitrite in 10 ml conc H_2SO_4 was added at 4–5° C, and the mixture was stirred for 30 min at this temperature. The obtained diazo solution was slowly added to a solution of 2.5 g (0.015 mole) potassium iodide and 3 g (0.012 mole) iodine in 5 ml water cooled to 0° C at a temperature lower than 10° C. The mixture was left overnight and stirred at room temperature until evolution of nitrogen was complete (approximately 3 hr). The residue was separated and treated twice with 100 ml of a 15% solution of sodium hyposulfite, washed with cold water, dried in air, and extracted with absolute ethyl alcohol. The extract was evaporated to half volume and water was added until the precipitate ceased to form. A 1.92 g quantity of impure compound IV was obtained. The original amine of I (1.6 g, 53.5%) was isolated when the filtrate which remained after



Compound	R	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
II	Cl	45—45.5[a]	$C_{12}H_9N_2O_2Cl$[b]	57.84 57.68	3.85 3.81	11.22 10.99	57.94	3.65	11.27	90.5
III	Br	41—42	$C_{12}H_9N_2O_2Br$[c]	49.15 49.22	3.20 3.31	9.34 9.09	49.17	3.10	9.64	88.0
IV	I	85—87	$C_{12}H_9N_2O_2I$[d]	42.83 43.04	2.71 2.81	8.00 7.91	42.37	2.67	8.24	92.5
V	$NHCOCH_3$	160.5—161	$C_{14}H_{13}N_3O_3$	62.02 62.08	4.92 4.93	15.46 15.42	61.97	4.83	15.49	90.0
VI	$NHCOC_6H_5$	158.5—160	$C_{19}H_{15}N_3O_3$	68.46 68.52	4.61 4.59	12.53 12.24	68.45	4.63	12.61	99.0
VII	$N(CH_2C_6H_5)_2$	117	$C_{26}H_{23}N_3O_2$	76.46 76.64	5.59 5.87	10.02 9.88	76.26	5.66	10.27	35.4
VIII	$NHCH_2C_6H_5$	53.5—55	$C_{19}H_{17}N_3O_2$	71.52 71.70	5.86 5.87	12.80 12.60	71.44	5.36	13.15	11.8
IX	$N{=}CHC_6H_4NO_2$-*n*	156—157	$C_{19}H_{14}N_4O_4$	62.69 62.67	3.66 3.81	15.50 15.80	62.98	3.90	15.46	96.0

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[a] In a previous study this compound was described in the form of an oil. b) Found, %: Cl 14.41; 14.61. Calculated, %: 14.26. c) Found, %: Br 27.52, 27.74. Calculated, %: Br 27.27. d) Found, %: I 37.80. Calculated, %: I 37.32.

removal of the precipitate from the reaction mixture was made alkaline. Compound IV was purified by crystallization from aqueous ethyl alcohol in the presence of activated carbon and by subsequent chromatography in aluminum oxide using a mixture of benzene and chloroform (1 : 4) as the eluent.

2-(o-Nitro-p-acetylaminobenzyl)pyridine (V). A 0.8 g (0.0080 mole) quantity of acetic anhydride was added dropwise to 1 g (0.0043 mole) of the amine of I. From the yellow solution a greyish-yellow precipitate of compound V rapidly separated, which was removed and washed with iced water until a neutral reaction was obtained. A 1.07 g quantity of impure compound with a mp of 159° C was obtained which was recrystallized from ethyl alcohol.

2-(o-Nitro-p-benzolaminobenzyl)pyridine(VI). A mixture of 0.5 g (0.0021 mole) of the amine of I and 3.65 g (0.2500 mole) of benzoyl chloride was heated for 15 min to 125° C, after which 7 ml of a 10% solution of sodium hydroxide was added. Immediately a yellow oil separated out. The reaction mixture was heated for 10 minutes at 150° C, poured onto ice left overnight. The precipitate was filtered by suction and washed with iced water until a neutral reaction was obtained. A 0.72 g quantity of impure compound VI with a mp of 156° C was obtained which was recrystallized from ethyl alcohol.

2-(o-Nitro-p-dibenzylaminobenzyl)pyridine(VII) and 2-(o-Nitro-p-benzylaminobenzyl)pyridine(VIII). A mixture of 2 g (0.008 mole) of amine of I and 25.3 g (0.100 mole) of benzyl chloride was heated for 18 hr in a boiling water bath and then cooled to 0° C. The precipitate was chromatographed twice in aluminum oxide, eluting with a mixture of benzene and chloroform (1 : 4). From the initial fractions 1.98 g of compound VII was separated. From the subsequent fractions 0.33 g of compound VIII was separated in the form of yellow oil which crystallized on standing.

2-(o-Nitro-p-(p-nitrobenzilidenamino)benzyl pyridinel (IX). A mixture of 0.45 g (0.003 mole) of p-nitrobenzaldehyde and 0.69 g (0.003 mole) of the amine of I was heated for 1.5 hr at 125–140° C, cooled, and the product of the reaction was recrystallized several times from a mixture of benzene and petroleum ether.

REFERENCES

1. K. S. Schofield, J. Chem. Soc., 2408, 1949.
2. J. A. Sousa and I. Weinstein, J. Org. Chem., 27, 3155, 1962.
3. A. L. Bluhm, I. Weinstein, and J. A. Sousa, J. Org. Chem., 28, 1989, 1963.
4. I. Weinstein, A. L. Bluhm, and J. A. Sousa, J. Org. Chem., 31, 1983, 1966.
5. A. I. Nunn and K. S. Schofield, J. Chem. Soc., 583, 1952.

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