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Some N-Basically Substituted Derivatives of *o*-Nitroaniline

BY ALFRED BURGER AND JAMES M. FREDERICKSEN

Some syntheses designed by us to lead to 9-(dialkylaminoalkyl)-isoalloxazine derivatives as potential metabolite antagonists to natural flavines were interrupted by the war four years ago, and the appearance of several recent articles based on similar thoughts[1,2,3,4] made resumption of this work inadvisable. We wish to report the syntheses and properties of some of the intermediates prepared in these studies.

TABLE I

Deriv. of chlorobenzene	Amine	Product	Yield, %	M. p., °C.	B. p., °C. (mm.)	Formula	% Composition	Calcd.	Found
2-Nitro-5-methoxy[a]	N-β-Aminoethylmorpholine	3-(2-Morpholinoethyl)amino-4-nitroanisole	63[b]	85–86[c]	235–245 (9–10)[d]	$C_{13}H_{19}N_3O_4$	N,	14.94	15.03
Same	1-Diethylamino-4-aminopentane	3-(1-Methyl-4-diethylaminobutyl)-amino-4-nitroanisole	51[e]		193[f] (4–5)	$C_{28}H_{33}N_9O_{17}$[g]	N,	16.43	16.83
Same	Cyclohexylamine	3-Cyclohexylamino-4-nitroanisole	36	76–77[h]	195–205 (2–3)	$C_{13}H_{18}N_2O_3$	N, OCH$_3$,	11.19 12.40	10.75 12.02
Same	Piperazine	1,4-Bis-(2-nitro-5-methoxyphenyl)-piperazine	29	240–242[i]		$C_{18}H_{20}N_4O_6$	N, OCH$_3$,	14.43 15.98	14.55 15.98
2-Nitro-	N-β-Aminoethylmorpholine	2-(2-Morpholinoethyl) aminonitrobenzene[j]	47	44–45[k]	190–195 (2)	$C_{12}H_{17}N_3O_3$	N,	16.72	16.69
2-Nitro-	2-Amino-2-methylpropanol	2-(1,1-Dimethyl-2-hydroxyethyl)-aminonitrobenzene	8		150–160[l] (1–2)	$C_{12}H_{16}N_2O_4$[m]	N,	11.11	11.33

[a] Prepared by the method of Hodgson and Handley, *J. Chem. Soc.*, 128, 543 (1926). [b] 20% of unchanged chloronitroanisole was recovered by steam distillation. [c] Yellow crystals from ethanol or benzene–ligroin. [d] Distilled at 150° (2 mm.), and collected crystalline on a cold surface. [e] 16% of unchanged chloronitroanisole recovered. [f] Yellow oil. [g] Dipicrate m. p. 112–113°. [h] Red crystals from ligroin. [i] The insoluble orange solid was washed with ether and sublimed at 1 mm. [j] Dipicrate m. p. 210–212° (dec.); $C_{24}H_{23}N_9O_{17}$: % N calcd., 17.76; found, 17.56. [k] Red crystals from dilute ethanol. [l] Red oil. [m] O-Acetyl derivative prepared with acetic anhydride in pyridine at 100°, *cf.* Karrer and Naef, *Helv. Chim. Acta*, 19, 1029 (1936), yellow crystals m. p. 64–65° from ethanol.

Experimental

Alkylaminonitrobenzenes.—Approximately equivalent amounts of 2-nitrochlorobenzene or its 5-methoxy derivative and the amine were refluxed for several hours in two equivalents of dry pyridine, 0.5 mole of the 2-nitrochlorobenzene and 0.01 to 0.05 mole of the 5-methoxy derivative being taken. Four to five hours of reaction time was used for runs of one-twentieth mole or less; eight hours for those of one-half mole. In some cases, unreacted chloronitroanisole was then removed by steam distillation. The residue was extracted with several portions of ether, and the reaction product obtained by evaporation of the solvent. Data as to the percentage composition and the physical properties of the substances prepared from the derivatives of chlorobenzene are given in Table I.

2-(2-Morpholinoethyl)-aminoaniline.—When a solution of 7.5 g. of 2-(2-morpholinoethyl)-aminonitrobenzene in 150 cc. of hot 50% ethanol was treated with a freshly prepared solution of 20.7 g. of sodium hydrosulfite dihydrate in 100 cc. of hot water, the red color soon changed to green. After brief boiling, the mixture was acidified with 80 cc. of 10% hydrochloric acid, the solution was cleared with norite, and evaporated to dryness under reduced pressure. The residue was washed with ether, and then decomposed with a cold 20% sodium hydroxide solution under ether. The aniline derivative was extracted into ether and worked up, yielding 5.3 g. (80%) of a red oil. Its *tripicrate* crystallized from ethanol, m. p. 201–203° (dec.).

Anal. Calcd. for $C_{30}H_{28}N_{12}O_{22}$: N, 18.50. Found: 18.33, 18.75.

1,4-bis-(2-Nitro-ethylaminophenyl)-piperazine.—A mixture of 3.0 g. of *o*-(β-chloroethyl)-aminonitrobenzene, 2.8 g. of piperazine and 0.05 g. of sodium iodide reacted exothermically, and was then refluxed for six hours. It was poured into water, the small amount of precipitated solid was filtered from much red oil, and washed with water. The oil from the filtrate was treated with alcohol and deposited another crop of the same orange crystals. Recrystallization from ethanol raised the melting point to 140–141°. The yield was 0.9 g.

Anal. Calcd. for $C_{20}H_{26}N_6O_4$: N, 20.28. Found: N, 20.27.

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(1) Hall and Turner, *J. Chem. Soc.*, 699 (1945).

(2) Neeman, *ibid.*, 812 (1946).

(3) Adams, Weisel and Mosher, THIS JOURNAL, 68, 883 (1946).

(4) Kipnis, Weiner and Spoerri, *ibid.*, 69, 799 (1947).

Preparation of 2- and 4-Benzylpyridine

BY KENNETH E. CROOK

Several investigators have reported the preparation of 2- and 4-benzylpyridines by heating a mixture of benzyl chloride, pyridine and a copper catalyst.[1]

Reported yields of the mixed benzylpyridines are 40 to 50%. The isomers have usually been separated as the picrates. Yields of the pure isomers are seldom given. The article of von Braun and Pinkernelle[1b] reporting a 50% yield of the 2-isomer, is not explicit as to whether this yield is based on the starting material or on the mixture of isomers.

Need for rather large quantities of 2- and 4-benzylpyridine prompted a search for conditions giving better yields. It was found possible to obtain 75% yields of a mixture of 2- and 4-benzylpyridines, 90% of which was separated into the two isomers by fractional distillation.

Experimental

Solvent.—By using pyridine hydrochloride as a solvent, the yields of the mixed benzylpyridines were nearly double and the violence of the initial exothermal reaction between benzyl chloride and pyridine was greatly reduced. At the conclusion of the rearrangement, the pyridine hydrochloride was recovered by distillation and used for succeeding runs without purification or replenishment.

Catalyst.—Copper metal (or cuprous chloride into which the copper is assumed to be converted) has been used as the catalyst for the rearrangement of the pyridinium salt. Copper (or cuprous chloride) has been reported to cause the conversion of benzyl chloride into dibenzyl and products of unknown composition.[2] This reaction may account for most of the tarry material produced when a mixture of copper, benzyl chloride and pyridine is heated. If benzylpyridinium chloride (no catalyst) is distilled, the vapors which pass over at about 190° (liquid temperature) consist of a mixture of benzyl chloride and pyridine. Rearrangement of benzylpyridinium chloride (catalyst present) is negligible at 190°. By dissolving the catalyst in the hot pyridine–pyridine hydrochloride mixture *prior* to the addition of benzyl chloride, the amount of tar formation is negligible. Copper, equivalent quantities of copper and cupric chloride, or cupric chloride alone, may be used.

Procedure

The procedure employed was a modification of that originally used by Tschitschibabin[1a] as modified by LaForge[1a] and by Crook and McElvain.[1c] The procedure finally adopted is given in some detail since it was found to be advantageous to modify most of the steps in previously recorded procedures.

Four moles (462 g.) of pyridine hydrochloride was distilled into a one-liter flask and allowed to solidify while the flask lay on its side. This flask was fitted with a Claisen adapter carrying a dropping funnel and a water reflux condenser bearing a tube containing calcium chloride, 5 g. of anhydrous cupric chloride and 80 cc. (1 mole) of pyridine were added, and the flask heated until all the pyridine hydrochloride had melted and the cupric chloride dissolved. Heating was discontinued and 115 cc. (1 mole) of benzyl chloride (b. p. 90–91° at 40 mm.) was added during ten-fifteen minutes while the flask was shaken continuously. The mixture was then refluxed gently for twelve hours. The pyridine hydrochloride was distilled off through a 45-cm. Vigreux column at 90 mm. pressure. Distillation was stopped when the vapor temperature reached 195°. This pyridine hydrochloride was used without purification for the next run. There was a slight gain in quantity of pyridine hydrochloride with succeeding runs.

The black residue was cooled, 200 cc. of water and 15 cc. of hydrochloric acid (sp. gr. 1.2) added, and the mixture warmed until it appeared homogeneous. The brown to black liquid was made basic with ammonium hydroxide, 100 cc. of a 1-1 mixture of benzene and ligroin added and the organic layer washed with 100-cc. portions of 1-10 ammonium hydroxide until the aqueous layer ceased to acquire a blue color (2–4 times), then washed once with water.

The organic layer was dried by placing it, together with stock potassium hydroxide, in a separatory funnel and withdrawing the aqueous layer periodically until no more formed.

After removing the solvent at atmospheric pressure, the residue was distilled through a 45-cm. Vigreux column and gave 123.5–128.5 g. of a mixture of 2- and 4-benzylpyridines boiling at 175–190° (40 mm.) and a higher boiling residue of 16–20 g.

By using 0, 1 and 2 moles of pyridine hydrochloride as the solvent, the quantities of benzylpyridines and of higher boiling material were 60 and 56 g., 88 and 30 g., and 103 and 28 g., respectively. Decreasing the time of heating to six hours gave erratic results. Other modifications which did not increase yields were: heating for twenty-four hours, heating in a carbon dioxide atmosphere, stirring, continuous addition of cupric chloride during the heating period, and the use of equivalent amounts of copper and cupric chloride as the catalyst.

The isomers were separated by fractional distillation through a 1.2 × 115-cm. column packed with 0.32-cm. glass helices. In order to minimize losses of the less abundant 4-isomer, as much as possible of the 2-isomer was removed at 276.5–277° and two intermediate fractions of 277–280.5 and 280.5–289° were collected. The residue in the still was then set aside while the intermediate fractions were put through the column a second time. All material boiling at 289° and above was then returned to the still and the fraction boiling at 289–289.5° collected as 4-benzylpyridine. From 1 kg. lots, 640–680 g. of 2-benzylpyridine (b. p. 276.5–277° cor. (730 mm.)) and 245–255 g. of 4-benzylpyridine (b. p. 289–289.5° cor. (730 mm.)) were obtained.

As an indication of purity the 2- and 4-isomer gave picrates which melted without purification at 139.5–140° and 138.5–139°, respectively. Reported melting points of the picrates of the 2- and 4-isomer are 140° and 136–138°.[1a]

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(1) (a) Maier-Bode u. Altpeter, "Pyridin u. Seine Derivate in Wissenschaft u. technik," Edwards Brothers, Ann Arbor, Michigan, 1943; (b) J. von Braun and W. Pinkernelle, *Ber.*, **64**, 1871 (1931); (c) J. Overhoff and J. P. Wibaut, *Rec. chim.*, **50**, 957 (1931); K. E. Crook and S. M. McElvain, THIS JOURNAL, **53**, 4006 (1931); P. C. Teague, *ibid.*, **69**, 714 (1947).

(2) A. Onufrowies, *Ber.*, **17**, 836 (1884); T. Zincke, *ibid.*, **2**, 739 (1869).

Brominations with Pyridine Hydrobromide Perbromide

BY CARL DJERASSI AND CAESAR R. SCHOLZ

In connection with another problem, we had occasion to investigate the action of pyridine hydrobromide perbromide on some steroid ketones. Although pyridine and quinoline hydrobromide perbromides have been used occasionally as brominating agents, particularly with phenols and for the addition of bromine to double bonds,[1] no examples of the bromination of ketones with these reagents seem to have been recorded.

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(1) *Cf.* Rosenmund, Kuhnhenn and Lesch, *Ber.*, **56**, 1262, 2042 (1923).