[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

α-Alkylaminopyridines and 1,5-Di-(alkyl-α-pyridylamino)-pentanes

BY F. F. BLICKE AND M. U. TSAO[1]

It has been shown that when α-aminopyridine or α-acetylaminopyridine[2] is treated with a lower alkyl halide[3] or an alkylene dihalide,[4] the pyridine compound reacts to a large extent in the tautomeric imine form, and that only a small amount of the α-alkylaminopyridine is produced. However, in spite of the unavoidable formation of N-alkyl-α-pyridoneimines, it has been stated[5] that interaction of higher alkyl halides (10–14 carbon atoms) with α-aminopyridine represents a convenient method of preparation for α-alkylaminopyridines which contain long carbon chains.

α-Methyl-,[3,6] α-ethyl-,[7] α-isopropyl-,[7,8] α-allyl-,[8] α-isoamyl-[2,7] and α-cetylaminopyridine[8] and a variety of α-basic-alkylaminopyridines[9] have been produced by reaction between sodium α-aminopyridine and the required alkyl halide, basic-alkyl halide[9] or dialkyl sulfate[6]; the propyl and butyl derivatives have been synthesized from the sodium compound and propyl and butyl *p*-toluenesulfonate,[10] respectively.

ω,ω′-Di-α-pyridylaminoalkanes [C_5H_4N—NH-$(CH_2)_x$NH—C_5H_4N; x = 6–10 incl.] have been prepared[11] in good yields from sodium 2-aminopyridine and polymethylene dihalides, however, in the case of 1,5-di-(α-pyridylamino)-pentane, a compound in which we were especially interested, the yield was only 13%. We were able to prepare the pentane in 42% yield by reaction of sodium α-formylaminopyridine with 1,5-dibromopentane, and hydrolysis of the 1,5-di-α-pyridylformylamino)-pentane; furthermore, by the use of this sodium compound and the required alkyl or substituted alkyl halide we also obtained ethyl-, butyl-, hexyl-, β-cyclohexylethyl- and β-phenylethylaminopyridine. The sodium derivatives of the three alkylaminopyridines reacted with 1,5-dibromopentane to yield the corresponding 1,5-di-(alkyl-α-pyridylamino)-pentanes.

Experimental

α-(Formylamino)-pyridine.—This compound was synthesized by the method of Tschitschibabin and Knunjanz.[12] From 94.0 g. (1 mole) of α-aminopyridine we obtained 53.5 g. (43.8%) of formylaminopyridine and 32 g. of unchanged aminopyridine. The latter was recovered by treating the lower boiling fraction (said to contain aminopyridine formate by Tschitschibabin, *et al.*) with aqueous alkali, allowing the aminopyridine to solidify, and then purifying it by distillation.

Sodium Derivative of α-(Formylamino)-pyridine.—Sixty-one grams (0.50 mole) of formylaminopyridine, dissolved in 200 cc. of warm, dry toluene, was placed in a two-necked, 500-cc. flask fitted with a reflux condenser; 22.5 g. (0.57 mole) of powdered sodium amide was added, portionwise, during a fifteen minute period, while the flask was cooled with water. A vigorous evolution of ammonia took place and a voluminous white precipitate was formed. The mixture was shaken frequently and heated on a steam-bath for one-half hour.

α-(Ethylamino)-pyridine.—To the mixture of sodium formylaminopyridine, prepared as described above from 61.0 g. of formylaminopyridine. there was added 54.5 g. (0.5 mole) of ethyl bromide, and the material was heated for seventy hours on a steam-bath. After removal of the sodium bromide, the toluene was distilled under reduced pressure and the residue fractionated. The yield of α-(ethylformylamino)-pyridine was 42 g. (56%); b. p. 114–115° (3 mm.).

In order to remove the formyl group, 35 g. of the α-(ethylformylamino)-pyridine was refluxed with a mixture of 40 cc. of hydrochloric acid and 40 cc. of water for four hours. The cold solution was made alkaline with solid sodium hydroxide, the precipitated oil was collected and dried with stick sodium hydroxide. Upon distillation the α-(ethylamino)-pyridine, a light yellow oil, boiled at 79–82° (4 mm.); yield 23 g. (81%).

Sulfuric acid, dissolved in dry ether, was added to α-(ethylamino)-pyridine dissolved in the same solvent. The precipitated, crystalline sulfate was dissolved in absolute alcohol, the solution shaken with Norite, filtered, and absolute ether added to the filtrate until a turbidity was produced. The mixture was then placed in a refrigerator. The precipitated, colorless, crystalline sulfate melted at 111–113°.

Anal. Calcd. for $C_7H_{10}N_2 \cdot H_2SO_4$: S, 14.53. Found: S, 14.32.

The chloroaurate melted at 125–126°.

Anal. Calcd. for $C_7H_{10}N_2 \cdot HAuCl_4$: Au, 42.66. Found: Au, 42.50.

α-(Butylamino)-pyridine.—To the sodium derivative of α-(formylamino)-pyridine, prepared from 28.5 g. of α-(formylamino)-pyridine, 32 g. of butyl bromide was added, and the mixture was heated on a steam-bath for thirty-six hours. After removal of the sodium bromide and distillation of the solvent from the filtrate a dark brown liquid residue, α-(butylformylamino)-pyridine, was obtained. The latter was not distilled but was hydrolyzed immediately by boiling it with 14 g. of potassium hydroxide, dissolved in 150 cc. of 95% alcohol, for four hours.[13] The alcohol was removed, and water was added to the residue. The oily, organic layer was separated and distilled. After a small amount of water had distilled, the product was collected; b. p. 106–107° (4 mm.); yield 12.5 g. (34%). The product gradually solidified; picrate m. p. 133–134°. Slotta and Franke[10] reported b. p. 124–126° (16 mm.); m. p. 45°; picrate m. p. 138°.

α-(Hexylamino)-pyridine.—This compound, as well as the two following ones, was prepared in the same manner as the corresponding ethylamino derivative.

The yield of the product, by the use of 0.50 mole of

---

(1) This investigation was made possible by a grant from the Wm. S. Merrell Company.

(2) Magidson and Menschikoff, *Ber.*, **59**, 1209 (1926).

(3) (a) Tschitschibabin and Seide, *J. Russ. Phys.-Chem. Soc.*, **46**, 1216 (1914); *Chem. Zentr.*, **86**, I, 1064 (1915); (b) Tschitschibabin, Konowalowa and Konowalowa, *Ber.*, **54**, 814 (1920).

(4) Scherlin and Welitschkin, *J. Gen. Chem. U. S. S. R.*, **5**, 1586 (1935); *Chem. Zentr.*, **107**, II, 2373 (1936).

(5) Sharp, *J. Chem. Soc.*, 1855 (1939).

(6) Tschitschibabin and Knunjanz, *Ber.*, **61**, 2215 (1928).

(7) British Patent 264,508; *C. A.*, **22**, 91 (1928).

(8) British Patent 265,167; *C. A.*, **22**, 244 (1928).

(9) Whitmore, Mosher, Goldsmith and Rytina, THIS JOURNAL, **67**, 393 (1945).

(10) Slotta and Franke, *Ber.*, **63**, 678 (1930)

(11) Sharp, *J. Chem. Soc.*, 1191 (1938).

(12) Tschitschibabin and Knunyanz, *Ber.*, **64**, 2841 (1931). The yield was not reported.

(13) The acid hydrolysis, described under α-(ethylamino)-pyridine, is a better procedure.

α-(formylamino)-pyridine, was 50%; b. p. 135–137° (2 mm.). The hydrochloride melted at 112–114°.

Anal. Calcd. for $C_{11}H_{18}N_2{\cdot}HCl$: Cl, 16.53. Found: Cl, 16.66.

α-(β′-Cyclohexylethylamino)-pyridine.—Since the crude product was obtained in a solid state it was recrystallized from ether; m. p. 97–98°; yield 38%. The hydrochloride, purified as described for the ethylamino derivatives, melted at 124–126°.

Anal. Calcd. for $C_{13}H_{20}N_2{\cdot}HCl$: Cl, 14.74. Found: Cl, 14.74.

α-(β′-Phenylethylamino)-pyridine.—The base, obtained in 31.5% yield, boiled at 145–148° (2 mm.). The chloroplatinate melted at 175–176°.

Anal. Calcd. for $2\ (C_{13}H_{14}N_2){\cdot}H_2PtCl_6$: Pt, 24.2. Found: Pt, 24.6.

1,5-Di-(α-pyridylamino)-pentane.—The sodium derivative, obtained from 27 g. (0.22 mole) of formylaminopyridine, 10 g. (0.25 mole) of sodium amide and 100 cc. of toluene, was heated with 26 g. (0.11 mole) of 1,5-dibromopentane for twenty hours on a steam-bath. The precipitated sodium bromide was removed, the toluene distilled from the filtrate under reduced pressure, and the dark brown, liquid residue, 1,5-di-(α-pyridylformylamino)-pentane, hydrolyzed by heating it with 14 g. of potassium hydroxide, dissolved in 150 cc. of 95% alcohol, for twelve hours. The alcohol was distilled under reduced pressure, water added to the crystalline residue to dissolve inorganic compounds and aminopyridine, the product filtered, washed thoroughly with water, dried and washed with ether. The light yellow pentane weighed 12.5 g. (42%). After recrystallization from methyl alcohol it melted at 147–148°; Sharp[11] reported 150°.

1,5-Di-(ethyl-α-pyridylamino)-pentane.—Twenty-one grams (0.166 mole) of α-(ethylamino)-pyridine, dissolved in 150 cc. of dry toluene, was heated with 8 g. (0.205 mole) of powdered sodium amide on a steam-bath for one hour. Ammonia was evolved, and a clear solution was obtained. Twenty grams (0.083 mole) of pentamethylene bromide was added, whereupon a vigorous reaction took place, and sodium bromide began to precipitate. After the mixture had been heated on a steam-bath for twenty-four hours, the precipitate was filtered and the solvent removed; b. p. 185–195° (0.02 mm.); most of the pentane boiled at 194–195° (0.02 mm.); yield 9.5 g. (34.5%).

The base (9.5 g.) was dissolved in dry ether and the solution treated with hydrogen chloride. When the precipitated, gummy hydrochloride was rubbed under ether it became solid. It was dissolved in absolute alcohol, the solution shaken with Norite, filtered, and dry ether added to the filtrate until it became turbid. The mixture was then placed in a refrigerator. The precipitated, crystalline dihydrochloride weighed 6 g.; m. p. 177–179°.

Anal. Calcd. for $C_{19}H_{28}N_4{\cdot}2HCl$: Cl, 18.42. Found: Cl, 18.45.

1,5-Di-(butyl-α-pyridylamino)-pentane.—This compound and the following one were prepared in the same manner as the corresponding ethyl derivative. From 24 g. of α-(butylamino)-pyridine there was obtained 10.6 g. (36%) of the pentane; b. p. 225–228° (0.02 mm.).

The sulfate separated as a gum when sulfuric acid, dissolved in absolute ether, was added to the base dissolved in the same solvent. The gum became solid when rubbed under ether. The salt was purified by the use of alcohol and ether in the manner described above; m. p. 170–171°.

Anal. Calcd. for $C_{23}H_{36}N_4{\cdot}2H_2SO_4$: S, 11.35. Found: S, 11.22.

1,5-Di-(hexyl-α-pyridylamino)-pentane.—The dihydrochloride melted at 93–94°.

Anal. Calcd. for $C_{27}H_{44}N_4{\cdot}2HCl$: Cl, 14.26. Found: Cl, 14.15.

Summary

α-Ethylamino-, α-butylamino-, α-hexylamino-, α-(β′-cyclohexylethylamino)-, α-(β′-phenylethylamino)-pyridine and 1,5-di-(α-pyridylamino)-pentane have been obtained by interaction of sodium α-formylaminopyridine and the required alkyl halide or alkylene dihalide.

The sodium derivatives of the alkylaminopyridines reacted with 1,5-dibromopentane to yield 1,5-di-(alkyl-α-pyridylamino)-pentanes.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 20, 1946

NOTES

The Identification of Trimesic Acid from the Oxidation of *s*-Trialkyl Aromatic Hydrocarbons

BY J. V. KARABINOS, J. I. WRIGHT AND H. F. HIPSHER

Since permanganate oxidation of *s*-trialkyl aromatic hydrocarbons gives the water soluble trimesic acid, we have found it convenient to isolate two derivatives with good melting points by the following procedure.

Two grams of hydrocarbon was refluxed with stirring for twelve hours in 500 cc. of water containing 20 g. of potassium permanganate. After filtration and acidification of the filtrate with hydrochloric acid the solution was evaporated to dryness on a steam-bath. After several dryings with absolute ethanol the crystalline residue was divided into two portions and one refluxed with 100 cc. of methanol containing 5% of dry hydrogen chloride for six hours and the other with ethanol-hydrogen chloride. Each was cooled and a small portion of the solvent removed *in vacuo* and the respective esters crystallized on further cooling. In some cases recrystallization of the esters from their respective alcohols was unnecessary. The m. p.'s of the esters from several *s*-trialkyl benzenes as well as literature values are listed below.

Hydrocarbon	M. p. of trimesates, °C. Trimethyl	 Triethyl
Mesitylene	144–144.5	
1,3-Dimethyl-5-ethylbenzene	143–145	134
3,5-Diethyltoluene	143–144.5	
1,3,5-Triethylbenzene	144–144.5	133–134
Literature values	143–144[a]	132–133[b]

[a] Pechmann, *Ann*, **264**, 296 (1891). [b] Shorger, THIS JOURNAL, **39**, 2677 (1917).

AIRCRAFT ENGINE RESEARCH LABORATORY
NATIONAL ADVISORY COMMITTEE FOR AERONAUTICS
CLEVELAND, OHIO

RECEIVED JANUARY 23, 1946