SUBSTITUTED PYRIDINES

5-METHYL-4-PHENYL-2-(AMINOALKOXY, AROXYMETHYL)PYRIDINES

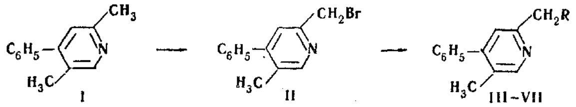
N. S. Prostakov and O. B. Baktibaev

UDC 547.821.07:542.944.1

5-Methyl-4-phenyl-2-bromomethylpyridine, obtained from 2,5-dimethyl-4-phenylpyridine via the Wohl–Ziegler reaction, was used in the syntheses of substituted 2-aminomethyl-, 2-ethoxymethyl-, and 2-phenoxymethylpyridines.

The 2,5-dimethyl-4-phenylpyridine (I) that we previously described in [1] was used in the syntheses of α-aminomethyl and α-alkoxy(aroxy)methyl derivatives of this pyridine system. The first of these compounds may be of interest as complexing agents. The transition from pyridine base I to its derivatives was accomplished via 5-methyl-4-phenyl-2-bromomethylpyridine (II). The bromination of I was accomplished with N-bromosuccinimide via the Wohl–Ziegler reaction in the presence of benzoyl peroxide. Similar transformations were previously examined in the case of some α-alkylpyridines [2,3]. Bromo derivative II could not be isolated in the free base form.

After removal of the succinimide liberated in the bromination, the reaction mass was treated with secondary amines – diethylamine, piperidine, and 2,5-dimethyl-4-piperidone – to give amines III-V.



III R = $(C_2H_5)_2N$; IV R = piperidino ; V R = 4-oxo-2,5-dimethylpiperidino
VI R = C_2H_5O; VII R = C_6H_5O

A similar method was also used to obtain derivatives VI and VII, which contain a simple ether grouping in the α-position.

EXPERIMENTAL

5-Methyl-4-phenyl-2-(diethylaminomethyl)pyridine (III). A mixture of 10.67 g (0.058 mole) of pyridine I, 16.6 g (0.093 mole) of N-bromosuccinimide, 0.51 g of benzoyl peroxide, and 400 ml of anhydrous carbon tetrachloride was placed in a quartz glass flask and irradiated for 2.5 h with a UV lamp until the N-bromosuccinimide had dissolved completely and bromine vapors had vanished. The mixture was then cooled to room temperature. The succinimide was removed by filtration and washed with three portions of carbon tetrachloride. Diethylamine [17.6 g (0.24 mole)] was added to the solution, and the mixture was refluxed for 6 h. The diethylamine hydrobromide was removed by filtration, and excess diethylamine and solvent were removed by distillation. Water (30 ml) was added to the residue, and the mixture was treated with potassium hydroxide. The organic bases were extracted with ether, and the extracts were dried with magnesium sulfate and distilled to give 6.28 g (41%) of amine III with bp 170-175° (5 mm) and R_f 0.56 [on silica gel with ether–methanol (10 : 1)]. The product was a mobile liquid that darkened rapidly in air. Found %: C 80.0, 79.5; H 8.6, 8.7; N 10.8, 11.0. $C_{17}H_{22}N_2$. Calculated %: C 80.3; H 8.7; N 11.0. The dipicrate melted at 188-189° (from alcohol–acetone). Found %: N 15.5, 15.6. $C_{17}H_{22}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: N 15.7.

5-Methyl-4-phenyl-2-(piperidinomethyl)pyridine (IV). This was similarly obtained from 10 g (0.054 mole) of I, 15.4 g (0.087 mole) of N-bromosuccinimide, 0.5 g of benzoyl peroxide, 400 ml of carbon tetra-

---

Patrice Lumumba University, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1211-1212, September, 1971. Original article submitted June 27, 1969.

chloride, and 10 g (0.117 mole) of freshly distilled piperidine. The yield of amine IV was 5.7 g (38%), and it was obtained as a viscous, greenish liquid with a characteristic sharp odor and bp 175-177° (2.5 mm) and R_f 0.70 [on silica gel with ether–methanol (10 : 1)]. The dipicrate melted at 200.5-201.5° (from alcohol–acetone). Found %: N 15.6, 15.2. $C_{18}H_{22}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: N 15.5. The dihydrochloride melted at 196-198° (from alcohol–acetone). Found %: Cl 20.6, 20.7; N 8.0, 8.0. $C_{18}H_{22}N_2 \cdot 2HCl$. Calculated %: Cl 20.9; N 8.2.

5-Methyl-4-phenyl-2-[(2,5-dimethyl-4-oxopiperidino)methyl]pyridine (V). Amine V [3.4 g (15%)] with bp 191-214° (3 mm), mp 93-96° (after several recrystallizations from petroleum ether), and R_f 0.17 [on activity II aluminum oxide with ether–heptane (3 : 1)] was obtained via the same method from 14 g (0.076 mole) of I, 21.84 g (0.122 mole) of N-bromosuccinimide, 0.7 g of benzoyl peroxide, 400 ml of carbon tetrachloride, and 24.16 g (0.19 mole) of 2,5-dimethyl-4-piperidone. Found %: C 77.7, 77.8; H 7.6, 7.6; N 9.2, 8.9. $C_{20}H_{24}N_2O$. Calculated %: C 77.9; H 7.8; N 9.1. The dihydrobromide melted at 197-198° (dec., precipitated from alcohol by ether). Found %: Br 34.1, 34.1; N 5.9, 5.7. $C_{20}H_{24}N_2O \cdot 2HBr$. Calculated %: Br 34.0; N 5.9.

5-Methyl-4-phenyl-2-(ethoxymethyl)pyridine (VI). Bromo derivative II was obtained as in the preceding experiments from 10 g (0.054 mole) of I, 15.4 g (0.87 mole) of N-bromosuccinimide, and 0.5 g of benzoyl peroxide in 400 ml of carbon tetrachloride. An alcohol solution of sodium ethoxide obtained from 2.48 g (0.108 g-atom) of sodium and 100 ml of anhydrous alcohol was added to the mixture at 0°. The mixture was initially stirred at room temperature and then refluxed for 5 h. The sodium bromide was removed by filtration, and the alcohol was removed by distillation. Water (30 ml) was added to the residue, and the mixture was treated with potassium hydroxide until it was strongly alkaline. The organic bases were extracted with ether, and the extract was dried with potassium hydroxide to give 3.5 g (28%) of VI as a viscous liquid that solidified on cooling (although crystals could not be isolated) with bp 149-150° (2.5 mm) and R_f 0.40 [on activity II aluminum oxide with ether–heptane (3 : 1)]. Found %: C 79.6, 79.7; H 7.5, 7.4; N 6.3, 6.1. $C_{15}H_{17}NO$. Calculated %: C 79.3; H 7.5; N 6.2. The picrate melted at 144.5-146.5° (from alcohol). Found %: N 12.3, 12.2. $C_{15}H_{17}NO \cdot C_6H_3N_3O_7$. Calculated %: N 12.3.

5-Methyl-4-phenyl-2-(phenoxymethyl)pyridine (VII). This compound [9 g (40%)] was similarly obtained from 15 g (0.081 mole) of base I, 23.1 g (0.13 mole) of N-bromosuccinimide, 0.75 g of benzoyl peroxide, 400 ml of carbon tetrachloride, and sodium phenoxide obtained from 3.75 g (0.113 g-atom) of sodium and 20 g (0.2 mole) of phenol in 150 ml of anhydrous alcohol. It boiled at 200-203° (2.5 mm). Found %: C 82.5, 82.6; H 6.0, 5.9; N 5.0, 4.9. $C_{19}H_{17}NO$. Calculated %: C 82.9; H 6.2; N 5.1. The hydrochloride melted at 203-205° (from acetone). Found %: Cl 11.6, 11.6; N 4.5, 4.9. $C_{19}H_{17}NO \cdot HCl$. Calculated %: Cl 11.4, N 4.5.

In the same experiment, we isolated 0.13 g of a substance which, on the basis of analytical data, can be assigned the 5-methyl-4-phenyl-2-(diphenoxymethyl)pyridine (VIII) structure, with mp 106.5-108° (from petroleum ether). Found %: C 81.4, 81.4; H 5.4, 5.8; N 3.9, 3.7. $C_{25}H_{21}NO_2$. Calculated %: C 81.7; H 5.8; N 3.8. Two spots (R_f 0.46 and 0.51) were obtained during thin-layer chromatography [activity II Al_2O_3 with ether–heptane (3 : 1)] of VII and VIII.

LITERATURE CITED

1. N. S. Prostakov and N. N. Mikheeva, Med. Prom., No. 2, 11 (1960).
2. M. Hasegawa, Chem. Pharm. Bull. (Tokyo), 1, 293 (1953).
3. B. H. Walker, J. Org. Chem., 25, 1047 (1960).