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α-PHENYLISOCINCHOMERONIC AND 4-AZAFLUORENONE 3-CARBOXYLIC ACIDS

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UDC 547.826.2'412.5'836.07

3,6-Dimethyl-6-phenylpyridine, obtained on phenylation of 2,5-lutidine, has been used in the synthesis of α-phenylisocinchomeronic acid, derivatives of it, and also for the preparation of 4-azafluorenone 3-carboxylic acid. It was established that 4-hydroxy-3,6-dimethyl-2-phenylpyridine was formed on phenylation of 2,5-lutidine.

Pyridine bases containing methyl and phenyl substituents in the ring seemed of interest for the preparation of phenyl substituted pyridine carboxylic acids and also of condensed heterocycles. Compounds of such type are the subject of numerous investigations carried out mainly with the aim of obtaining effective physiologically active compounds.

The initial subject of the present work was 3,6-dimethyl-2-phenylpyridine (I). Its preparation from the oxime 5-hydroxy-2-methyl-1-phenylhexa-1,3-diene has been described in [1], and also from 2,5-lutidine by a multistage synthesis in [2]. Various melting points were cited in these studies for the picrate of (I) base, viz., 179-180°C in [1] and 134-135°C in [2]. The data obtained by us corresponded to the second value.

Considering that the most convenient means of synthesizing 3-methyl-2-phenylpyridine (30% yield) is the phenylation of β-picoline from [3] we examined the possibility of obtaining pyridine (I) by this method. The reaction of 2,5-lutidine with phenyllithium was carried out on gentle boiling in ether. 3,6-Dimethyl-2-phenylpyridine (I), formed in 21% yield, was characterized as the picrate and iodomethylate. A special feature of its mass spectral fragmentation was the formation of a $[M - H]^+$ ion peak of maximum intensity which confirmed the presence of the phenyl substituent in the ortho position relative to the nitrogen atom. The presence in the mass spectrum of peaks with m/z 167 $[M - H - CH_3]^+$ and 152 $[M - H - CH_3 - CH_3]^+$ confirmed the presence of two methyl groups. The high intensity of the ion peak with m/z 167 indicated that a methyl group was found in the ortho position relative to the nitrogen atom.

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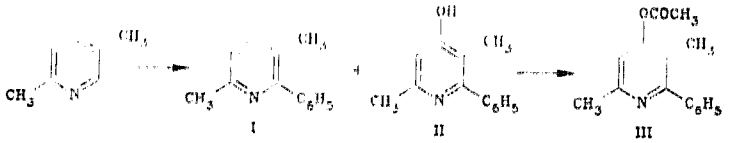
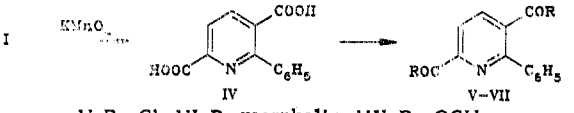


The phenylation reaction of 2,5-lutidine was accompanied by the formation of a significant amount of resinous products partially reverting to the initial lutidine. From the residue after distillation of (I) base, 4-hydroxy-3,6-dimethyl-2-phenylpyridine (II) was isolated in insignificant yield, the structure of which was confirmed by data of elemental analysis, IR, mass (presence of a molecular ion peak), and PMR spectra.

Confirmation of the structure of compound (II) was also provided by its conversion into 3,6-dimethyl-4-acetoxy-2-phenylpyridine (III). Evidently the hydroxy derivative (II) is formed by the oxidation of (I) under the conditions of the experiment.

α-Phenylisocinchomeronic acid (IV) was obtained in moderate yield on oxidation of pyridine (I) with potassium permanganate and was converted into the diacid chloride (V), dimorpholide (VI), and dimethyl ester (VII). These derivatives of acid (IV) were subjected to a study of their useful practical properties. On the other hand they served to confirm its structure.

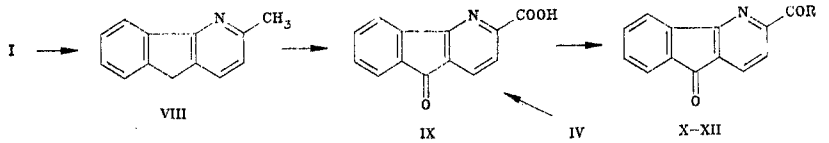


V R=Cl; VI R=morpholino VII R=OCH_3

Searches for routes of obtaining azafluorenones containing functional substituents have been conducted in our laboratory, since they may be useful in synthetic and applied respects.

Pyridine (I) seemed of interest in this project. It was established that 3-methyl-4-azafluorene (VIII) was obtained from it by the catalytic dehydrocyclization method for methylphenyl substituted pyridines developed in our laboratory [4]. Compound (VIII) has active methyl and methylene groups. However azafluorene (VII) was formed in a mixture with starting pyridine (I), separable with difficulty, consequently when obtaining 4-azafluorenone 3-carboxylic acid (XI) the mixture of compounds (I) and (VIII) was subjected to oxidation.

A more convenient method of obtaining ketoacid (IX) was the cyclodehydration of α-phenylisocinchomeronic acid (IV) with polyphosphoric acid. In this case acid (IX) was isolated (80% yield) as high melting yellow crystals. A peak was present in its mass spectrum at M^+ 225. The formation of a maximum intensity ion peak with m/z 181 $[M - CO_2]^+$ confirmed the presence of a carboxyl group. Subsequent fragmentation of this ion was accompanied by fission of the molecular ion of 4-azafluorenone [5].



X R= OCH_3; XI R=Cl; XII R=morpholino

The methyl ester (X), acid chloride (XI), and morpholide (XII) were obtained from acid (IX).

EXPERIMENTAL

Mass spectra were taken on a MX-1303 instrument with direct insertion of samples into the ion source at an ionizing voltage of 70 eV and various temperatures of admission. PMR spectra were obtained on a BS-467 (60 MHz) instrument (TMS was internal standard) and IR spectra on a Specord UR-20 spectrometer.

3,6-Dimethyl-2-phenylpyridine (I) and 4-Hydroxy-3,6-dimethyl-2-phenylpyridine (II). 2,5-Lutidine (68.5 g: 0.64 mole) was added gradually to phenyllithium obtained from lithium (9 g: 1.3 moles) and bromobenzene (100 g: 0.64 mole) in ether (300 ml). The mixture was stirred for 4 h with the ether boiling gently, then water (230 ml) was poured in. The ether solution was dried over magnesium sulfate. On distilling the residue from the ether extract

the initial lutidine (18.5 g: 27%) was obtained also and pyridine (I) (18 g: 21% on the reacted lutidine) as a yellow liquid bp 130-139°C (5 mm). Found: N 7.5%. M^+ 183. $C_{13}H_{13}N$. Calculated: N 7.6%. Picrate: mp 133-134°C (from acetone). Iodomethylate: mp 187-188°C. Found: N 3.8%. $[M - CH_3I]^+$ 183. $C_{13}H_{13}N \cdot CH_3I$. Calculated: N 4.3%.

The fraction with bp 198-207°C (5 mm) crystallized from heptane. Compound (II) (1.3 g: 1.4%) was isolated as colorless crystals, mp 222-223°C. PMR spectrum (acetone-d_6): 2.25 (s, 3 H, 3-CH_3), 2.46 (s, 3 H, 6-CH_3), 8.43 (s, 1 H, OH), 7.5 ppm (m, 6 H, 5-H and C_6H_5). IR spectrum (in chloroform): 3600 cm^{-1} (OH). Found: N 7.4%; M^+ 199. $C_{13}H_{13}NO$. Calculated: N 7.5%. Hydrochloride: mp 229-230°C (with decomposition, from alcohol). Found: 5.6%. $C_{13}H_{13}NO \cdot HCl$. Calculated: N 5.9%.

4-Acetoxy-3,6-dimethyl-2-phenylpyridine (III) was obtained in 60% yield on boiling compound (II) with acetic anhydride in benzene as colorless crystals of mp 78-79°C (from heptane). Found: 5.4%; M^+ 241. $C_{15}H_{15}NO_2$. Calculated: 5.8%.

α-Phenylisocinchomeronic Acid (IV). Potassium permanganate (23 g: 0.16 mole) was added in portions to a suspension of pyridine (I) (4 g: 0.21 mole) in water (350 ml) at 100°C. The mixture was stirred for 8 h at 100°C. The manganese dioxide was filtered off and washed with water. The combined aqueous filtrate was evaporated to 25 ml and treated with 18% hydrochloric acid to pH 5. The solid was filtered off, washed with water, and with ether. Acid (IV) (1.3 g: 24%) was obtained as colorless crystals of mp 205-207°C. IR spectrum: 3290 (OH), 1745 cm^{-1} (CO); M^+ 243. The value for the analysis of nitrogen content was underestimated by 1.2% in comparison with the calculated value.

α-Phenylisocinchomeronic acid diacid chloride (V) was obtained from acid (IV) and thionyl chloride in 90% yield as pale orange crystals, mp 101-103°C (from a heptane–ethyl acetate mixture, 10:1). Found: N 4.9%; M^+ 281. $C_{13}H_7Cl_2NO_2$. Calculated: N 5.1%.

α-Phenylisocinchomeronic acid dimorpholide (VI) was obtained from diacid chloride (V) and morpholine in dioxan in 55% yield as yellow crystals of mp 162-163°C (from a heptane–acetone mixture, 12:1). Found: N 10.9%; M^+ 381. $C_{21}H_{23}N_3O_4$. Calculated: N 11.0%.

α-Phenylisocinchomeronic acid dimethyl ester (VII) was obtained by the esterification of acid (IV) in the presence of sulfuric acid in 99% yield and had mp 91-92°C (from heptane). IR spectrum: 1725 cm^{-1} (CO). Found: C 66.6; H 4.9; N 5.3%; M^+ 271. $C_{15}H_{13}NO_4$. Calculated: C 66.6; H 4.8; N 5.2%

3-Methyl-4-azafluorene (VIII) was obtained by the dehydrocyclization of pyridine (I) (11 g: 0.09 mole) in benzene (100 ml) according to [4]. The temperature in the catalyst zone was 540-560°C. The gas (7.8 liters at 21°C, 765 mm) was collected. On redistillation of the condensate a fraction (9.8 g) of bp 120-150°C (4 mm) was collected. The picrate (1.3 g) of azafluorene (VIII) was obtained from this fraction (5 g) and had mp 220-220.5°C (from acetone). Found: N 13.7%. $C_{13}H_{11}N \cdot C_6H_3N_3O_7$. Calculated: N 13.7%.

4-Azafluorenone 3-Carboxylic Acid (IX). A. A mixture of acid (IV) (1.3 g: 0.005 mole) and polyphosphoric acid (5 ml) was heated for 7 h at 190°C, cooled, and poured into water (120 ml). The solid was filtered off, washed with water, and dried in vacuum. Compound (IX) (0.96 g: 80%) was obtained as bright yellow crystals of mp 238-239°C, M^+ 225. The value for analysis of nitrogen content was underestimated by 1.5% in comparison with the theoretical value. IR spectrum: 3275 (OH), 1720 cm^{-1} (CO).

B. Potassium permanganate (10.4 g: 0.07 mole) was added in portions with stirring to a suspension of the mixture (4.5 g) of azafluorene (VIII) and pyridine (I) in water (300 ml) at 100°C. The mixture was maintained at 100°C for 2.5 h. Manganese dioxide was filtered off and washed with water. The combined filtrate was extracted with hexane. Pyridine (I) (3.5 g) was isolated from the hexane extract. The aqueous solution was evaporated to 20 ml and treated with 18% hydrochloric acid to pH 5. The precipitated solid was filtered off, washed with water, and dried in vacuum. Ketoacid (IX) (0.75 g: 6.2% on the azafluorene VIII contained in the initial mixture) was obtained having mp 238-240°C. A mixture of both samples of acid (IX) melted with no depression of melting point.

4-Azafluorenone 3-carboxylic acid methyl ester (X) was obtained by esterification of (IX) in the presence of sulfuric acid in 71% yield as pale yellow crystals of mp 191-192°C (from heptane). IR spectrum: 1755, 1725 cm^{-1} (CO). Found: C 70.1; H 3.8; N 5.5%; M^+ 239. $C_{14}H_9NO_3$. Calculated: C 70.2; H 3.7; N 5.8%.

4-Azafluorenone 3-carboxylic acid chloride (XI) was obtained from acid (IX) and thionyl chloride in 90% yield as yellow crystals of mp 247-248°C (from a heptane–acetone mixture, 5:1). IR spectrum: 1775, 1730 cm^{-1} (CO). Found: N 5.5%; M^+ 243. $C_{13}H_6ClNO_2$. Calculated: N 5.7%.

4-Azafluorenone 3-carboxymorpholide (XII) was obtained from acid chloride (XI) and morpholine in dioxan in 79% yield as yellow crystals of mp 138-140°C (from a heptane–acetone mixture, 10:1). Found: N 9.1%; M^+ 294. $C_{17}H_{14}N_2O_3$. Calculated: N 9.5%.

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REACTION OF 1-METHYLURACIL WITH PHENYLBENZHYDRAZONOYL CHLORIDE

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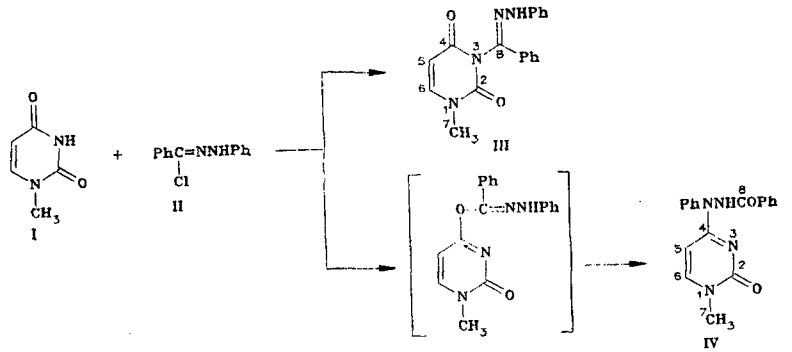
The ambident anion of 1-methyluracil gives with phenylbenzyhydrazonoyl chloride, depending on the conditions, the N-acylation product (polar solvent, room temperature), or the O-acylation product (nonpolar solvent, heating), which rearranges to a cytosine derivative. Convenient methods have been developed for the preparation of 6-methyl-1,3-diphenyl-5,6-dihydro-5-oxopyrimido[4,3-c]triazolium chloride, a fluorescent derivative of 1-methyluracil, from the N-acylation product, and for the rapid base cleavage of the uracil ring under very mild conditions.

The search for new reactions of uracils suitable for the chemical modification of the uracil ring under mild conditions is of great importance and potential for the modification of nucleotides and RNA. In contrast to the well-known alkylation of uracils, acylation has been investigated only in isolated instances [1, 2]. The most suitable model compound for such studies is 1-methyluracil.

The aim of this investigation was to examine the reactions of 1-methyluracil (I) with phenylbenzyhydrazonoyl chloride (II) in the presence of bases. We have found that (II) functions as an acylating agent, and depending on the reaction conditions, gives with (I) the N-acylation products 1-methyl-3-($N_{(1)}$-phenylbenzhydrazonoyl)uracil (III) and 1-methyl-4-($N_{(1)}$-benzoyl-N-phenylhydrazino)-1H-pyrimidin-2-one (IV), which is apparently formed by rearrangement of an O-acylated product of the uracil (I), which we have been unable to isolate.



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