

SYNTHESIS OF α -NITROMETHYLPYRIDINE AND DERIVATIVES

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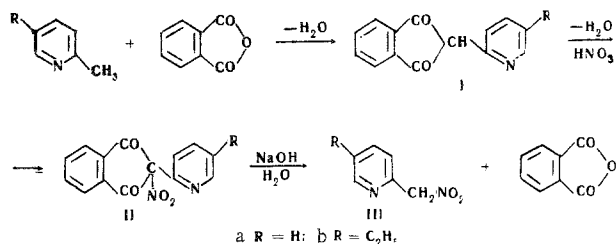
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α -Nitromethylpyridine and α -nitromethyl- β' -ethylpyridine are obtained by treating the corresponding nitrophthalones with 10% aqueous alkali. Treatment of the compounds with bromine gives the hydrobromides of the dibromo derivatives, which on treatment with aqueous sodium bicarbonate solution give the corresponding bases. Addition products of α -nitromethylpyridine at the double bond of chalcone and 2-benzylidenindan-1,3-dione were obtained.

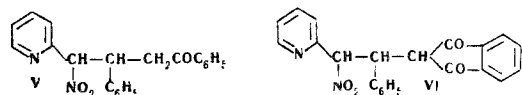
Previously one of us [1] found a method of introducing the nitro group into the methyl group of quinaldine, and this was later extended to alkyl-substituted quinaldines, and α -methylbenzothiazole [2]. It made readily available previously unknown α -nitromethyl derivatives of nitrogen ring compounds.

In the present paper a similar route is used to obtain α -nitromethylpyridine (IIIa) and α -nitromethyl- β' -ethylpyridine (IIIb):



Nitromethyl derivatives of pyridine proved to be difficult to purify (liquids decomposing on distillation). Consequently they were isolated as crystalline halogen acid salts IV, which were also used for subsequent reactions.

A previously developed method [3] was used to prepare addition products between the hydrobromide of α -(nitromethyl pyridine and chalcone, i. e., 2-(α -nitro- β -phenyl- γ -benzoylpropyl)pyridine (V) or 2-benzylidenindan-1,3-dione i. e., 2-(α -nitro- β -phenyl-phenyl- γ -phthaloylpropyl)pyridine (VI):



Compounds V and VI are of interest for synthesizing α -(α' -pyridyl)-pyrrole derivatives, to which they can give rise on reduction, and which are potential analytical reagents, and physiologically active compounds.

As expected, the hydrogen atoms in the methylene group of nitrocompounds III are readily replaced by halogen. Thus treatment of the nitro compounds in chloroform solution with bromine, at room temperature, gives bromo derivatives VII as the halogen acid salts.



EXPERIMENTAL

The starting phthalones I were prepared by condensing 2-methyl-5-ethylpyridine and α -picoline with phthalic anhydride in the presence of ZnCl₂ [4].

2-Nitropyrophthalone (IIa). Pyrophthalone was nitrated as described in [5] using HNO₃ (d 1.36). After shaking for half a minute, the reaction products were poured into water, the solid filtered off, dried, and recrystallized ex benzene, yield 60%, mp 152° C.

5-Ethyl-2-nitropyrophthalone (IIb). This was prepared similarly*. Yellow crystals, yield 55%, mp 107°-108° C (ex CCl₄). Found: N 9.30%. Calculated for C₁₆H₁₂N₂O: N 9.46%.

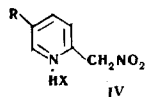
α -Nitromethylpyridines (III). 5 g Nitrophthalone was mixed with 80 ml 10% NaOH solution, the dark-red solution diluted with water, and filtered, the filtrate made acid with dilute AcOH, the precipitate of phthalic anhydride filtered off, and the filtrate treated with CHCl₃. The solvent was distilled off, giving nitro compound III, was a brown liquid. The picrates were yellow crystalline compounds. α -Nitromethylpyridine picrate mp 150° C. Found: C 39.41; H 2.64; N 19.38%. Calculated for C₆H₆N₂O₂ · C₆H₃N₃O₇: C 39.23; H 2.47; N 19.08%. α -Nitromethyl- β' -ethylpyridine picrate, mp 124° C. Found: N 17.48%. Calculated for C₈H₁₀N₂O₂ · C₆H₃N₃O₇: N 17.72%.

Colorless crystalline salts IV (see table) were obtained by passing HCl or HBr gas into CHCl₃ solutions of compounds III.

Addition products of α -(nitromethyl)pyridine hydrobromide and chalcone or 2-benzylidenindan-1,3-dione. Equimolecular amounts (0.01 mole) α -nitromethylpyridine hydrobromide and the α , β unsaturated ketone were refluxed together in 30 ml EtOH, until a white crystalline precipitate formed. Chalcone gave V, yield 45%, mp 139°-140° C. Found: C 72.55; H 5.00; N 8.30%. Calculated for C₂₁H₁₈N₂O₃: C 72.83; H 5.20; N 8.09%. Benzylidenindan-1,3-dione gave VI, yield 39%, mp 147°. Found: C 71.00; H 4.30; N 7.43%. Calculated for C₂₂H₁₆N₂O₄: C 71.35; H 4.33; N 7.56%.

Hydrobromides of α -(dibromonitromethyl)pyridines (VII) were obtained by treating nitro compounds III dissolved in CHCl₃, with bromine.

*With I. Zorina.



R	X	Mp, °C	Formula	Found, %				Calculated, %				Yield, %
				C	H	Br	N	C	H	Br	N	
H	Cl	138	C ₆ H ₆ N ₂ O ₂ · HCl	—	—	—	15.87	—	—	—	16.00	40
H	Br	136*	C ₆ H ₅ N ₂ O ₂ · HBr	32.87	3.45	36.20	12.72	32.89	3.20	36.53	12.79	38
C ₂ H ₅	Br	149—150*	C ₈ H ₁₀ N ₂ O ₂ · HBr	38.60	4.15	32.03	11.08	38.88	4.45	32.40	11.34	35

*ex AcOH.

Hydrobromide VIIa: yield 40%, mp 102°–103° C. Found: C 18.89; H 1.54; Br 63.00; N 7.73%. Calculated for C₅H₄Br₂N₂O₂ · HBr: C 19.09; H 1.32; Br 63.63; N 7.42%.

Hydrobromide VIIb: yield 45%, mp 97°–98° C. Found: C 23.62; H 2.31; Br 59.10; N 6.84%. Calculated for C₈H₃Br₂N₂O₂ · HBr: C 23.70; H 2.22; Br 59.25; N 6.91%.

Base VIIa was obtained by treating the hydrobromide with aqueous NaHCO₃, yield 33%, mp 42°–43° C. Found: C 24.03; H 1.38; Br 53.50; N 9.29%. Calculated for C₆H₄Br₂N₂O₂: C 24.32; H 1.35; Br 54.05; N 9.46.

Denitromethylation of α -nitromethyl- β' -ethylpyridine. 5 g IIIa was mixed with 50 g 80% H₂SO₄, and the mixture heated at 100° for 45 min, with frequent shaking. Then the brown solution was cooled, diluted, and neutralized with CaCO₃. The precipitate of the Ca salt of β' -ethyl- α -pyridylcarboxylic acid was dry-distilled, when it gave β -ethylpyridine. The

picrate formed yellow crystals mp 124°–125° C, undepressed mixed mp with an authentic specimen.

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