stirred for 2 hr at 50–60°, when solution was almost complete. The insignificant quantity of solid I was filtered off, the solvent vacuum-distilled off, the residue treated with 5–10 ml cold water to remove I, the whole filtered, and the solid dried. It was recrystallized from water or EtOH.

b) A solution of Na ethoxide prepared from 0.03 mole Na and 30 ml EtOH was added to a cooled solution of 0.03 mole II hydrochloride in 20–25 ml EtOH. The NaCl was filtered off, and the filtrate added, with stirring, to a suspension of 0.01 mole I in 5–10 ml EtOH, the mixture stirred for 1–2 hr at 50–60°, and further worked up as described in *a* above. The yields obtained by the two methods were identical.

To preclude the possibility of transesterification of esters, in each synthesis the dry alcohol used corresponded to the ester part of the amino acid.

IR spectra were determined with a UR-10 spectrometer, using KBr, NaCl, and LiF prisms, with tablets with KBr.

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ALKYLATION OF 2-AMINOPYRIDINE

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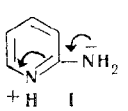
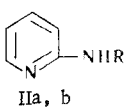
Alkylation of 2-aminopyridine with cyclohexanol or isopropanol in sulfuric acid gives yields of up to 70% of 2-alkylaminopyridines.

As its sodium derivative, 2-aminopyridine is alkylated by alkylating agents, e.g., methyl iodide, to give mixtures of mono and dialkyl substituted derivatives [1]. The literature also describes a method of preparing mixtures of 2-alkylamino and 2-dialkylaminopyridines by passing a mixture of 2-aminopyridine and the appropriate alcohol over a solid catalyst, e.g., Al_2O_3, SiO_2, etc. [2]. Such weak bases as amides of aromatic sulfonic acids [3] and of alkane sulfonic acids [4], and salts of guanidines [5], are readily alkylated by secondary alcohols in 80–85% sulfuric acid. In developing work on alkylation of nitrogen compounds, we undertook the alkylation of 2-aminopyridine. The latter is a monoacid base with pK_a' 6.86 [6], and diacid salts of it have not been described. In formation of salts of 2-aminopyridine, proton addition takes place at the ring nitrogen atom, to give a cation of structure I.



+H I



IIa, b

a R = C_6H_{11}

b R = i-C_3H_7

However, cation I has not lost its capacity to react with strong electrophilic reagents, e.g., with nitro cations, and this follows from the nitration of 2-aminopyridine to 2-nitramidopyridine nitrate [7]. Our experiments showed that salts of 2-aminopyridine are alkylated in 80–85% sulfuric acid by cyclohexanol and isopropanol. However, it proved impossible to alkylate 2-aminopyridine with tert-butanol, all the runs giving unchanged 2-aminopyridine with polyisobutene and tert-butanol.

EXPERIMENTAL

2-Cyclohexylaminopyridine (IIa). 9.4 g 2-aminopyridine was dissolved, with cooling (temperature not over 30°), in 100 ml 80% H_2SO_4, and the mixture stirred till the precipitate of sulfate had dissolved completely. Then the solution was heated to 60°, and at that temperature, 10 g cyclohexanol added over a period of 30 min, then the mixture stirred at 60–70° for 6 hr. After cooling to room temperature, it was poured onto 200 g ice, and neutralized with conc. NH_4OH. The solid amide was filtered off, washed with water, and dried. Yield 12 g (70%), mp 105–110°. Transparent crystals, mp 125° (ex n-heptane) [8]. Picrate, minute yellow needles, mp 184–185° (ex EtOH-AcOH) [9].

2-Isopropylaminopyridine (IIb). This was prepared similarly to IIa, from 9.4 g 2-aminopyridine and 9 g iso-PrOH in 100 85% H_2SO_4 for 6 hr at 80°. After neutralization, the base was extracted with ether

(3 × 30 ml), the extracted dried over anhydrous Na_2SO_4, the ether distilled off, and the residue vacuum-distilled. Yield 9 g (67%). Colorless oil, crystallized on cooling. Bp 84–86° (4–5 mm). Colorless needles, mp 41.5–42.5° (ex n-heptane). Found: N 20.32%. Calculated for $C_8H_{12}N_2$. N 20.58%. Picrate., yellow transparent needles, mp 180–182° (ex dil EtOH). Found: N 19.32%. Calculated for $C_8H_{12}N_2 \cdot C_6H_3N_3O_7$: N 19,16%.

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SYNTHESIS OF (1-METHYL-3-PIPERIDYLIDENE)DI(2-THIENYL)METHANE CITRATE (BITHIODINE)

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An improved method of synthesizing (1-methyl-3-piperidylidene)di-(2-thienyl)methane citrate, starting from ethyl pyridine-3-carboxylate (ethyl nicotinate).

(1-Methyl-3-piperidylidene)di(2-thienyl)methane (I) is of great interest, as its salts are powerful antitussives and expectorants, without narcotic action [1–4]. Japanese patents [1–4] give information only about preparation of I salts by treatment with citric, salicylic and other acids in ethanol solution, and there are pharmacological data regarding the preparation "Azverin."

A paper [5] describes the preparation of I by reacting a 2-fold excess of Grignard reagent with ethyl 1-methylpiperidine-3-carboxylate (nipecotate), to give a 35% yield of (1-methyl-3-piperidyl)di(2-thienyl)-carbinol (II), dehydrated to I by a large excess of mixed hydrochloric a d sulfuric acids.

By modifying the reaction conditions we were able to effect the synthesis of II in 75% yield. We used 85% formic acid to dehydrate II and obtained a good yield. The starting ethyl 1-methylpiperidine-3-carboxylate (nipecotate) (III) was prepared by hydrogenating the quaternary salt (IV) of ethyl pyridine-3-carboxylate (nicotinate (V) with dimethyl sulfate, over Raney nickel at 50–60°, by analogy with [6].

EXPERIMENTAL

Ethyl 1-methylpiperidine-3-carboxylate (nipercotate) (III). a) 45.3 g (0.3 mole) V in 150 ml benzene was heated to boiling, and to the boiling mixture 40.82 g (0.324 mole) VI added over a period of 40 min, after which the mixture was refluxed for 1 hr. The products were cooled and poured into 100 ml petrol ether. IV was isolated by strongly cooling the mixture, then decanting the solvent. The crude product was used for hydrogenation.

b) A rotating steel autoclave capacity 610 ml was charged with 80 g IV in 200 ml MeOH, 10 g Raney Ni catalyst, and hydrogen introduced at 100 atm. Hydrogenation was effected at 50–60°, in 2–3 hr gas ceased to be absorbed. The autoclave was emptied, the products were poured off, the catalyst in the autoclave was washed with 20 ml MeOH, and the next batch of IV placed with it. The MeOH was vacuum-distilled off from the products, the residue dissolved in 150 ml water, and 60 g K_2CO_3 added. The oil which came out was separated off, and the aqueous solution left extracted with ether. The ether extracts and oil were dried over $MgSO_4$, the ether distilled off, and the residue vacuum-distilled, to give 43.7 g III (85.1%), calculated in V), bp 82—85° (10 mm), n_D^{20} 1.4505; d_4^{20} 0.981; MR_D Found: 46.97. Calculated 46.59.

(1-Methyl-3-piperidyl)di(2-thienyl)carbinol (II). 86.4 g (0.53 mole) bromothiophene was added to 12.72 g (0.53 mole) Mg turnings in 80 ml dry ether, at such a rate that the ether constantly refluxed gently. Then the flask was heated for 2 hr 30 min on a waterbath, until the Mg completely dissolved. The flask was cooled, and 43.7 g (0.255 mole) III in 80 ml dry ether dropped in. Cooling was stopped, the contents of the flask brought to room temperature, heated on a waterbath for 2–3 hr, and left overnight. The products were decomposed with 300 g ice, 250 ml water, and 130 g NH_4C. The crystals which separated out were filtered off with suction, washed with water, then with ethanol, and dried. Yield 56.2 g (75.1%) II, bp 137–139°. Found: C 61.29; 61.00; H 6.69, 6,38; N 5.08%. Calculated for $C_{15}H_{19}NOS_2$. C 61.39; H 6.52; N 4.77%.

(1-Methyl-3-piperidylidene)di(2-thienyl)methane citrate (bithiodine). 30.72 g citric acid was added to a boiling solution of 44.15 g I in 75 ml MeOH, the whole heated for 7–10 min, then left at room temperature for 2–3 hr. The crystals which separated were filtered off, washed with EtOH, then with ether, and dried. Yield 67.3 g I (90%), mp 135–137° (decomp.). Found: C 53.78; 54.19; H 5.47; 5.81; N 2.97, 3.22%. Calculated for $C_{21}H_{25}NO_7S_2$. C 53,83; H 5,39; N 2,99%. After recrystallizing from EtOH it had mp 139° (decomp.).