PREPARATION OF 3,5-DIETHOXYCARBONYL-2,6-DIMETHYL-1,4-DIHYDROISONICOTINIC ACID AND 3,5-DIACETYL-2,6-DIMETHYL-1,4-DIHYDROISONICOTINIC ACID AND THEIR SALTS

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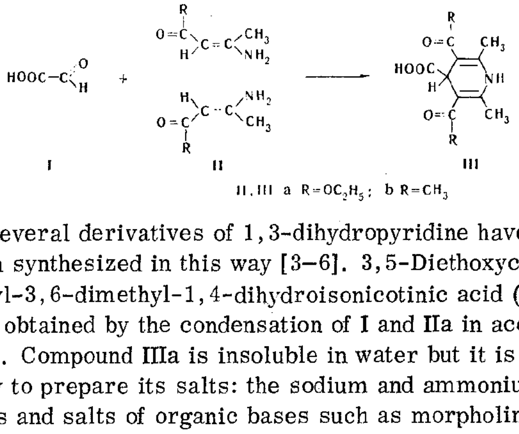
The reaction of glyoxylic acid with ethyl β-aminocrotonate or acetylacetone imine has given the corresponding derivatives of 1,4-dihydroisonicotinic acid and their water-soluble salts.

In order to obtain water-soluble derivatives of 3,5-diacyl-1,4-dihydropyridines we undertook the synthesis of 4-carboxy-1,4-dihydropyridines. Only the preparation of ethyl 3,5-diacetyl-1,4-dihydroisonicotinate [1] and of 2,3(CO)-, 6,5(CO)-dibenzoylenedihydroisonicotinic acid has been described in the literature [2]. This paper describes the condensation of glyoxylic acid (I) with ethyl β-aminocrotonate (IIa) and with acetylacetone imine (IIb):



I II III

II, III a $R=OC_2H_5$; b $R=CH_3$

Several derivatives of 1,3-dihydropyridine have been synthesized in this way [3–6]. 3,5-Diethoxycarbonyl-3,6-dimethyl-1,4-dihydroisonicotinic acid (IIIa) was obtained by the condensation of I and IIa in acetic acid. Compound IIIa is insoluble in water but it is easy to prepare its salts: the sodium and ammonium salts and salts of organic bases such as morpholine. The ammonium salt of 3,5-diacetyl-2,6-dimethyl-1,4-dihydroisonicotinic acid (IIIb) can be obtained directly in the condensation of I and IIb in ethanolic solutions with the liberation of one equivalent of ammonia. The isolation of the acid IIIb itself is complicated by the fact that not only the salts of the acid IIIb but also the acid itself are readily soluble in water. It was impossible to precipitate IIIb with hydrochloric acid. Compound III was obtained by the careful acidification with 30% sulfuric acid of a concentrated solution of its ammonium salt.

The structure of these compounds is confirmed by their IR and UV spectra. Although the IR spectra of the 1,4-dihydropyridines have been little studied [7], the absorption band at 3440–3450 cm^{-1} may apparently be ascribed to the ν_{NH} vibrations. It is known [8] that the UV spectra of the mononuclear derivatives of 1,4-dihydropyridines have a total of three absorption bands, of which the middle one is sometimes absent or appears only as a shoulder to the first band. The compounds that we obtained have absorption bands in the UV spectrum (see table) which agree well with those given for some other 1,4-dihydropyridines [8]. The absorption bands of 1,4-dihydropyridines of similar structure but having a methyl group in the γ-position are also given in the table for comparison.

The acid IIIa and the corresponding anion have only two absorption bands both in ethanolic solution and in aqueous solution, but the acid IIIb and the corresponding anion have three absorption bands in ethanolic solution and two in aqueous solution.

In the IR spectra, the long-wave absorption maximum which characterizes the electronic transition in

Ultraviolet Absorption Spectra

Compound	Medium	λ_{max}, nm (ε)
3,5-Diethoxycarbonyl-2,6-dimethyl-1,4-dihydroisonicotinic acid (IIIa)	C_2H_5OH	230 (17300), 342 (6300)
	$C_2H_5OH+HCl$	230 (20000), 342 (6880)
	$C_2H_5OH+NaOH$	234 (16760), 351 (5880)
	H_2O	232 (16800), 349.5 (6400)
	0.1 N HCl	230.5 (19600), 348 (6160)
	0.1 N NaOH	234 (16400), 351,5 (6200)
3,5-Diethoxycarbonyl-2,4,6-trimethyl-1,4-dihydropyridine*	C_2H_5OH	232 (19000), 252(пл) (8300) 349 (8200)
Ammonium salt of the acid **IIIb**	C_2H_5OH	260 (12100), 295 (15600) 380 (6300)
	$C_2H_5OH+HCl$	254 (13980), 285 (13560) 370 (6140)
	$C_2H_5OH+NaOH$	260 (9840), 295 (12460) 380 (5140)
3,5-Diacetyl-2,6-dimethyl-1,4-dihydroisonicotinic acid (IIIb)	0.1 N HCl	251.5 (16000), 376 (7060)
	Buffer solution, pH 4.2.	253 (13600), 378 (6960)
	0.1 N KOH	260 (12420), 383 (6880)
3,5-Diacetyl-1,4-dihydrocollidine*	C_2H_5OH	255 (13000), 275 (7700), 379 (6200)

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*According to the literature [8]

the conjugated di-(β-ketovinyl)amine system undergoes a bathochromic shift in an alkaline medium.* This is interesting, since the carboxyl group is not conjugated with the di-(β-ketovinyl)amine system. No dissociation of the N—H bond should take place since it is known that mononuclear 1,4-dihydropyridines containing no γ-carboxyl group do not give a bathochromic shift even in a strongly alkaline medium, and these 1,4-dihydropyridines can be obtained in the form of anions only under special conditions [8]. Apparently, although no dissociation of the N—H bond takes place (as is also shown by the small value of the bathochromic shift: 3.5 nm in an aqueous medium and 9 nm in ethanol as compared with 80–100 nm for the dissociation of an NH bond [8]), the γ-substituent (carboxyl group or carboxyanion) affects the conjugation of the di(ketovinyl)amine system. The dissociation constants of the γ-carboxyl groups of compounds IIIa and IIIb were determined in collaboration with I. Turovskii: the pK_a values were 4.65 and 4.24, respectively.

A similar bathochromic shift is observed in the UV spectra of the acid IIIb. Furthermore, the dark red 2,3(CO),6,5(CO)-dibenzoylene-1,4-dihydroisonicotinic acid prepared previously [2] forms green salts, i.e., a bathochromic shift takes place here, as well. A green salt was isolated in the pure state, and it contained only one equivalent of the cation. It is natural to assume that the salt is formed through the dissociation of the carboxyl group.

EXPERIMENTAL

The UV spectra were taken on an SF-4 spectrophotometer and the IR spectra on a UR-10 spectrophotometer.

3,5-Diethoxycarbonyl-2,6-dimethyl-1,4-dihydroisonicotinic acid (IIIa). With stirring and cooling, a solution of 50 g (0.54 mole) of glyoxylic acid in 200 ml of glacial acetic acid was added dropwise to a solution of 160 g (1.24 mole) of ethyl β-aminocrotonate in 50 ml of glacial acetic acid at such a rate that the temperature of the reaction mixture remained at about +10° C. The reaction mixture rapidly became yellow and a precipitate deposited. After the evolution of heat had ceased, the reaction mixture was left overnight at room temperature. The precipitate was filtered off and was washed with acetic acid and water. Yield 78 g (48%). Crystallization from acetic acid yielded colorless crystals with mp 219–220° C (decomp.). Found, %: C 56.47; H 6.42; N 4.72. Calculated for $C_{14}H_{19}NO_6$, %: C 56.55; H 6.44; N 4.70.

Sodium salt of the acid IIIa. A suspension of 6 g (20 mM) of IIIa in 250 ml of water was treated with 18 ml (22.5 mM) of 5% caustic soda solution. The resulting yellow solution was filtered and evaporated to dryness on the water bath and the residue was crystallized from ethanol. Yield 3.64 g (56.6%). Found, %: C 50.77; H 5.53; N 4.31; Na 7.02. Calculated for $C_{14}H_{18}NNaO_6$, %: C 50.66; H 5.67; N 4.41; Na 7.20.

Ammonium salt of the acid IIIa. A solution of IIIa in hot absolute ethanol was treated with ammonia. Yellow substance, mp (decomp.) 219–220° C (from ethanol). Found, %: C 53.79; H 7.18; N 9.18. Calculated for $C_{14}H_{22}N_2O_6$, %: C 53.49; H 7.05; N 8.91.

Morpholine salt of the acid IIIa. This was obtained by heating the acid IIIa with an excess of morpholine. After cooling, the yellow precipitate that had deposited was filtered off and washed with ether. Mp 217–218° C (from ethanol). Found, %: C 56.43; H 7.37; N 7.86. Calculated for $C_{18}H_{28}N_2O_7$, %: C 56.23; H 7.36; N 7.29.

Ammonium 3,5-diacetyl-2,6-dimethyl-1,4-dihydroisonicotinate. With stirring, a solution of 15 g (0.16 mole) of glyoxylic acid in 40 ml of ethanol was added dropwise to a solution of 58 g (0.58 mole) of acetylacetone imine in 35 ml of ethanol at +10° C. Stirring was continued for another 30 min, and the reaction mixture was left overnight at room temperature. The precipitate that had deposited was filtered off with suction and washed with a small amount of ethanol. Yield 22 g (53%). Yellow substance, mp (decomp.) 159–160° C (from ethanol). For analysis, a sample of the substance was dissolved in hot ethanol and treated with ammonia. The substance liberated was washed with ethanol and dried in vacuum over P_2O_5 at 80° C. Found, %: C 56.55; H 7.48; N 11.17. Calculated for $C_{12}H_{18}N_2O_4$, %: C 56.70; H 7.12; N 11.02.

3,5-Diacetyl-2,6-dimethyl-1,4-dihydroisonicotinic acid (IIIb). With cooling, a solution of 5.0 g of the ammonium salt of the acid IIIb in 20 ml of 15% aqueous ammonia was acidified with 30% H_2SO_4. The precipitate that deposited was filtered off, washed with 5 ml of water, and dried. This gave 2.0 g (43%) of a yellow substance with mp 170° C (from ethanol). Found, %: C 60.73; H 6.32; N 6.38. Calculated for $C_{12}H_{15}NO_4$, %: C 60.73; H 6.37; N 5.90.

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*When this paper was in preparation, a publication appeared [9] in which the acid IIIa was mentioned without a description of its method of preparation. The statement of the authors that "the UV absorption spectrum of IIIa is not sensitive to the dissociation of the carboxyl group" is not completely accurate. Careful measurements show that with an increase in the pH of the solution the long-wave maximum undergoes a bathochromic shift: 348 nm in 0.1 N HCl; 349 nm at pH 3.80; 351 nm at pH 5.82; and 351.5 nm in 0.1 NaOH. In ethanolic solution this difference is still greater (9 nm).