SYNTHESIS AND OXIDATION OF 1,4-DIHYDROISONICOTINIC ACID DERIVATIVES

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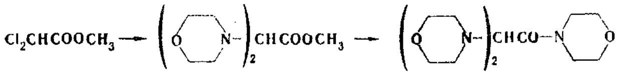
Dimorpholinoacetic acid morpholide was used as an aldehyde in the Hantzsch synthesis, and the morpholides of the corresponding 1,4-dihydroisonicotinic acid derivatives were obtained. The direct esterification of the morpholides of the 1,4-dihydroisonicotinic acid derivatives gave their methyl, ethyl, and isopropyl esters. The oxidation of 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydroisonicotinic acid and its morpholide with sodium nitrite occurs with cleavage, while the oxidation of the methyl esters takes place with retention of the γ substituent. The morpholide of 10,12-dioxo-5,10,11,12-tetrahydrodiindeno[1,2-b;2',1'-e]pyridinecarboxylic acid is oxidized with retention of the γ substituent.

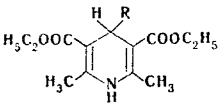
Continuing our research on the synthesis of 1,4-dihydroisonicotinic acid derivatives via the Hantzsch reaction [1], we decided to replace glyoxylic acid with other starting materials. As expected [2-4], an addition product – 2-amino-3-carbethoxy-4-hydroxy-5,5,5-trichloro-2-pentene – is formed in the reaction of ethyl β-aminocrotonate (I) with chloral. The dihydropyridine could not be obtained from the addition product, however.

We subsequently used geminal diamino derivatives, which are reactive aldehyde derivatives but probably have not been used hitherto in the Hantzsch synthesis. Using the method of Kerfanto [5], we carried out the reaction of methyl dichloroacetate (II) with morpholine.

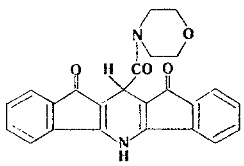


II III IV

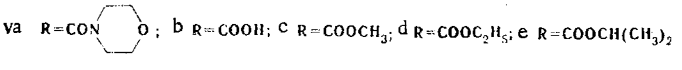
Instead of the expected III, we immediately obtained dimorpholinoacetic acid morpholide (IV). Its structure was proved indirectly using the following arguments. Refluxing methyl ester Vc with morpholine did not lead to the formation of morpholide Va. At the same time, the product of the reaction of II with morpholine on condensation with I gave only Va (rather than Vc), regardless of whether it was freed from morpholine hydrochloride and morpholine (when morpholine was present in large excess, it was removed by vacuum distillation) or obtained according to the description given below, i.e., at no higher than 100°. Compound IV was used without special purification for the synthesis of the dihydropyridines. In acetic acid at 20°, IV reacted with I to give the morpholide (rather than the methyl ester) of 2,6-dimethyl-3,5-dicarbethoxy-1,4-dihydroisonicotinic acid (Va).



Va-e



VI



Va $R=CON$ O ; b $R=COOH$; c $R=COOCH_3$; d $R=COOC_2H_5$; e $R=COOCH(CH_3)_2$

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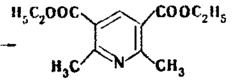
The methyl (Vc), ethyl (Vd), and isopropyl (Ve) esters were obtained by refluxing acid Vb in solutions of the appropriate alcohols in the presence of a small amount of sulfuric acid. Brief heating of IV with indane-1,3-dione and ammonium acetate in acetic acid gave the red-violet morpholide of 10,12-dioxo-5,-10,11,12-tetrahydrodiindeno[1,2-b;2',1'-e]pyridinecarboxylic acid (VI), which dissolves in alcoholic alkali to give a green solution.

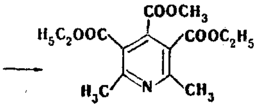
The 1,4-dihydropyridines were oxidized with sodium nitrite in acetic acid. In this case, 2,6-dimethyl-3,5-dicarbethoxypyridine (VII) was obtained both from acid Vb and its morpholide (Va); i.e., the oxidation proceeds with cleavage of the γ substituent. Methyl ester Vc is oxidized with greater difficulty, and methyl 2,6-dimethyl-3,5-dicarbethoxyisonicotinate (VIII) is obtained. It is known [6] that the oxidation of 10,12-dioxo-5,10,11,12-tetrahydrodiindeno[1,2-b;2',1'-e]pyridinecarboxylic acid with the sodium nitrite in acetic acid also proceeds with decarboxylation, and the carboxyl group is retained only when the compound is oxidized with air oxygen in alkaline media. Compound VI is oxidized by sodium nitrite in acetic acid, with retention of the γ substituent, to the morpholide of 10,12-dioxo-10,12-dihydrodiindeno[1,2-b;2',1'-e]pyridinecarboxylic acid (IX).

Va-b —



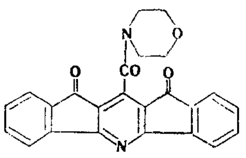
VII

Vc —



VIII

VI —



IX

EXPERIMENTAL

2-Amino-3-carbethoxy-4-hydroxy-5,5,5-trichloro-2-pentene. A 2.94-g (0.02 mole) sample of chloral and 5.16 g (0.04 mole) of I were dissolved in 10 ml of toluene, and the solution was heated for 2 h on a water bath and cooled. The resulting precipitate was removed by filtration, washed with water, and dried to give 2.82 g (51%) of a colorless substance with mp 118-119° (ethanol–water). Found: C 35.15; H 4.15; N 5.20%. $C_8H_{12}Cl_3NO_3$. Calculated: C 34.75; H 4.38; N 5.07%. UV spectrum in ethanol λ_{max}, nm (log ε): 275 (4.38).*

Reaction of Morpholine with Methyl Dichloroacetate (II). A mixture of 7.2 g (0.05 mole) of II and 21.8 g (0.25 mole) of morpholine was heated for 30 min on a water bath, during which the reaction mixture crystallized. The reaction product was a mixture of IV and morpholine hydrochloride (in a molar ratio of ~1 : 2) and was subsequently used without separation.

10,12-Dioxo-5,10,11,12-tetrahydrodiindeno[1,2-b;2',1'-e]pyridinecarboxylic Acid Morpholide (VI). A 2.2-g (15 mmole) sample of indane-1,3-dione and 4.3 g of the product of the reaction of morpholine with II (which corresponds to 7.5 mmole of IV) were dissolved in 10 ml of glacial acetic acid, 1.5 g (20 mmole) of ammonium acetate was added, and the reaction mixture was refluxed for 10 min. The mixture was cooled, and the precipitate was removed by filtration, washed with acetic acid, and purified by dissolving in alcoholic alkali. Acidification of the green filtrate with hydrochloric acid gave 0.71 g (24%) of red-violet VI with mp 352° (dec., acetic acid). Found: C 71.38; H 4.75; N 7.04%. $C_{24}H_{18}N_2O_4$. Calculated: C 72.35; H 4.55; N 7.03%. UV spectrum in ethanol, λ_{max}, nm (log ε): 233 (3.82), 261 (3.88), 321 (3.30), 410 (2.87), 520 (3.11); in ethanol + NaOH: 233 (4.07), 286 (3.94), 347 (3.46), 430 (3.00), and 650 (3.40).

2,6-Dimethyl-3,5-dicarbethoxy-1,4-dihydroisonicotinic Acid Morpholide (Va). A 1.3-g (10 mmole) sample of I and 2.9 g of the product of the reaction of morpholine with II (which corresponds to 5 mmole of IV) were dissolved in 10 ml of glacial acetic acid, and the mixture was allowed to stand at room temperature for 20 h. It was then diluted with water, and the precipitate was removed by filtration to give 0.65 g (48%) of Va with mp 221-222° (ethanol). Found: C 58.83; H 7.27; N 7.38%. $C_{18}H_{26}N_2O_6$. Calculated: C 59.00; H 7.12; N 7.65%. UV spectrum in ethanol, λ_{max}, nm (log ε): 233 (4.38) and 367 (3.87).

Methyl 2,6-Dimethyl-3,5-dicarbethoxy-1,4-dihydroisonicotinate (Vc). Ten drops of concentrated sulfuric acid were added to a solution of 4.5 g (0.015 mole) of Vb [1] in 30 ml of methanol, and the mixture was refluxed for 2 h, cooled, mixed with water, and diluted with NaOH to dissolve the unchanged Vb. The

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* The UV spectra were recorded with an SF-4 spectrophotometer.

precipitate was removed by filtration, washed with water, and dried to give 4.2 g (90%) of a product with mp 144-145° (ethanol–water). Found: C 57.66; H 4.17; N 4.53%. $C_{16}H_{28}NO_6$. Calculated: C 59.06; H 7.12; N 4.30%. UV spectrum in ethanol, λ_{max}, nm (log ε): 231 (4.14) and 341 (3.79).

2,6-Dimethyl-3,4,5-tricarbethoxy-1,4-dihydropyridine (Vd). This compound was similarly obtained in 85% yield from Vb and ethanol and had mp 110-111° (ethanol–water). Found: C 58.83; H 4.17; N 4.53%. $C_{15}H_{23}NO_6$. Calculated: C 59.06; H 7.12; N 4.30%. UV spectrum in ethanol, λ_{max}, nm (log ε): 230 (4.22) and 341 (3.78).

Isopropyl 2,6-Dimethyl-3,5-dicarbethoxy-1,4-dihydroisonicotinate (Ve). This compound was similarly obtained in 65% yield from Vb and isopropyl alcohol and had mp 120-121° (isopropyl alcohol–water). Found: C 60.24; H 7.51; N 4.19%. $C_{17}H_{25}NO_6$. Calculated: C 60.16; H 7.43; N 4.13%. UV spectrum in ethanol, λ_{max}, nm (log ε): 230 (4.32) and 342 (3.87).

Oxidation of VI. A 0.3-g (4.3 mmole) sample of sodium nitrite was added in small portions to a hot solution of 0.3 g (0.75 mmole) of VI in 30 ml of acetic acid. After the red-violet color disappeared, the mixture was diluted with water, and the precipitate was removed by filtration, washed with acetic acid, and dried to give 0.17 g (56%) of IX as a yellow substance with mp 370-372° (dec., acetic acid). Found: C 72.61; H 4.15; N 7.03%. $C_{24}H_{16}N_2O_4$. Calculated: C 72.74; H 4.07; N 7.07%.

Oxidation of Vc. This reaction was carried out similarly except that the excess of sodium nitrite was doubled, and the reaction mixture was heated to the boiling point. The end of the reaction was judged from the disappearance of fluorescence during illumination of a sample with UV light. The reaction mixture was diluted with water, made alkaline, and extracted with benzene. Evaporation of the benzene gave 75% of colorless methyl 2,6-dimethyl-3,5-dicarbethoxyisonicotinate (VIII) with mp 51-53°. Found: C 58.43; H 6.36; N 4.92%. $C_{15}H_{19}NO_6$. Calculated: C 58.26; H 6.19; N 4.53%.

Oxidation of Vb. A 0.7-g (10 mmole) sample of sodium nitrite was added in small portions with stirring to a suspension of 2.0 g (6.7 mmole) of Vb in 10 ml of acetic acid. When the reaction was complete, the mixture was diluted with water, made alkaline, and extracted with ether. Evaporation of the ether gave 1.5 g (89%) of 2,6-dimethyl-3,5-dicarbethoxypyridine (VII) with mp 70-71°. The product did not depress the melting point of a genuine sample.

Oxidation of Va. Compound VII was similarly obtained (except for gentle heating of the reaction mixture) in 80% yield.

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