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SUBSTITUTED PYRIDINES

Amides and Hydrazides of Pyridine Carboxylic Acids

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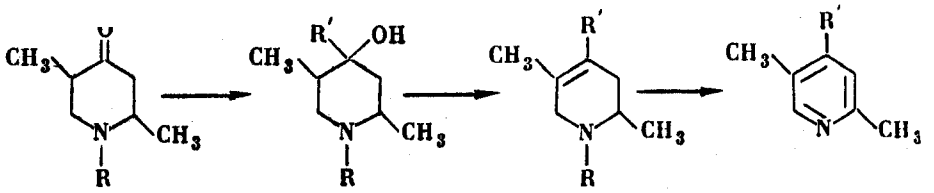
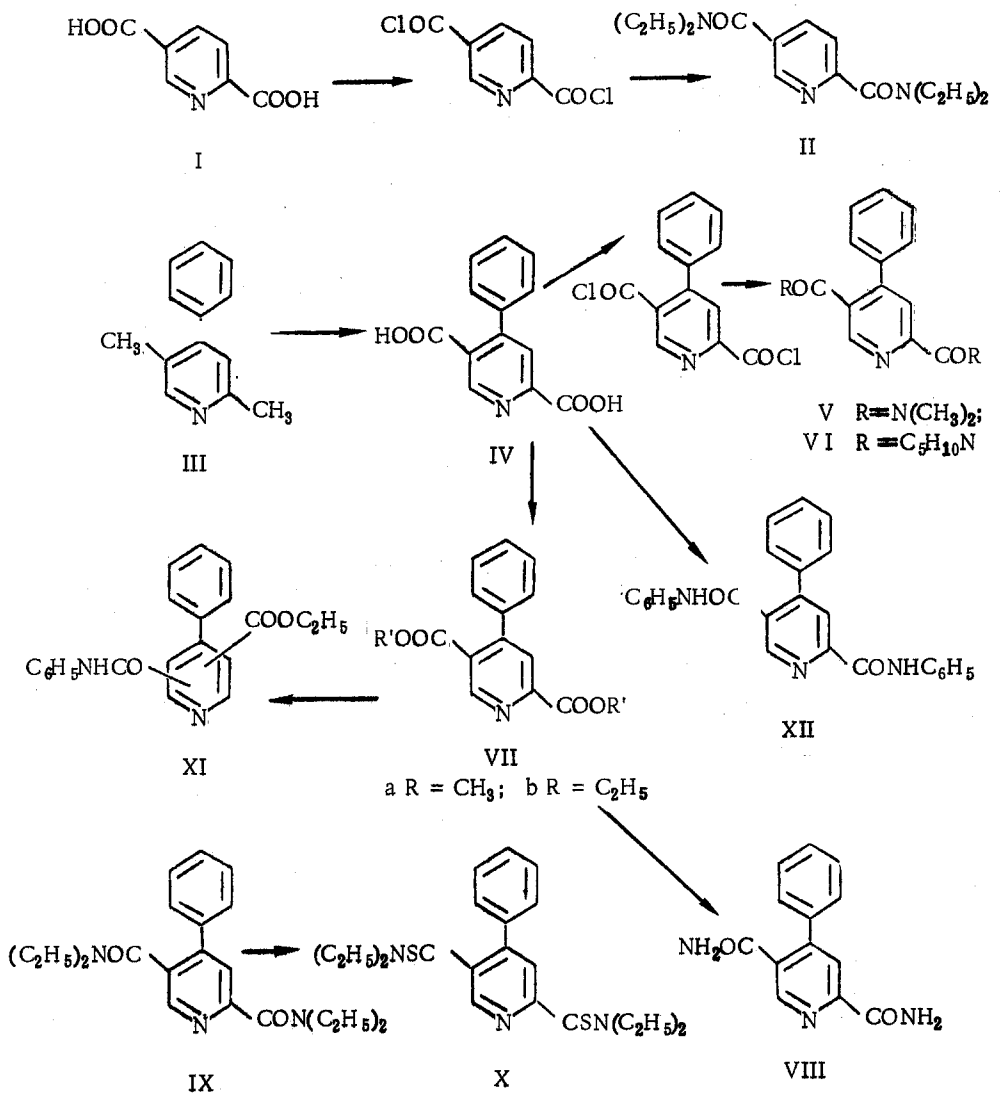
A number of amides and hydrazides of 4-phenyl-2, 5-pyridine dicarboxylic acids are synthesized.

A method worked out in this laboratory makes it possible to prepare individual pyridine bases in satisfactory yield from γ-piperidones by converting to γ-piperidols, dehydrating to the corresponding Δ^4-didehydropiperidines, and finally by catalytic dehydrogenation and N desalkylation, converging the latter to substituted pyridines of desired structure [1].

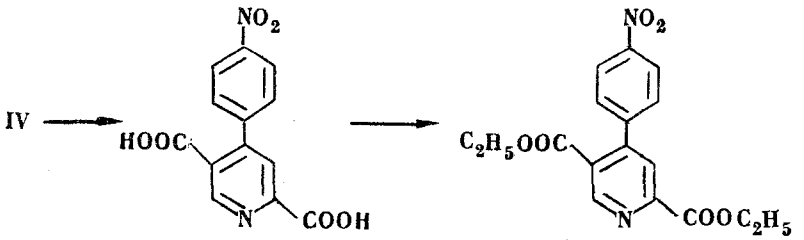


The pyridine dicarboxylic acids obtained by oxidizing the dimethyl-substituted pyridine bases are used for preparing their amides and hydrazides, compounds of potential pharmacological interest.



Isocinchomeronic acid (I) gives, via its dichloroanhydride and diethylamine, its di(diethylamide) (II). A number of diamides of 4-phenyl-2, 4-pyridine dicarboxylic acid (IV) are prepared by oxidizing 2, 5-dimethyl-4-phenylpyridine (III). The di(dimethylamide) (V) and di(pyridylamide) of 4-phenyl-2, 5-pyridine dicarboxylic acid (VI) are prepared via the dichloroanhydride of the latter, and the diamide of VIII is prepared by ammonolysis of dimethyl 4-phenyl-2, 5-pyridine dicarboxylate (VIIa).

Treatment of 4-phenyl-2, 5-pyridine di(diethylcarboxamide) (IX) with phosphorus pentasulfide leads to the isolation of 4-phenyl-2, 5-pyridine di(diethylthiocarboxamide) (X). Heating diethyl 4-phenyl-2, 5-pyridine dicarboxylate (VIIb) with aniline leads to only one of the carboethoxy groups changing to an amide group, the other being unaffected. Up to the present the positions of these groups in the resultant amidoester (XI) are undetermined. 4-Phenyl-2, 5-pyridine di(phenylcarboxamide) is obtained by heating acid IV with aniline and phosphorus pentoxide.

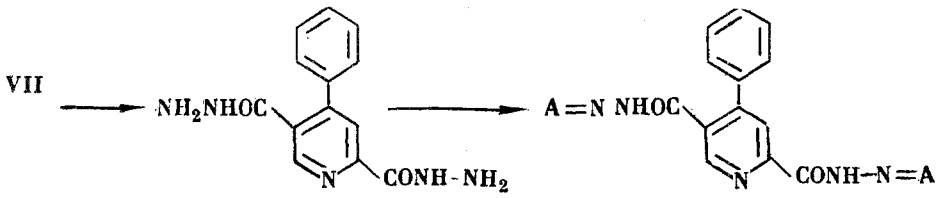


XIII XIV

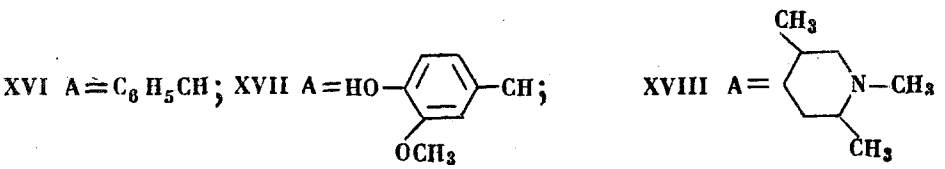
Nitration of 4-phenyl-2, 5-pyridine dicarboxylic acid (IV) gives 4-(p-nitrophenyl)-2, 5-pyridine dicarboxylic acid (XIII), from which a diethyl ester (XIV) is obtained.

Attempts were made to synthesize the tri(diethylamide) of 4-(p-carboxyphenyl)-2, 5-pyridine dicarboxylic acid, starting with the acid, but treatment of the chloroanhydride of the latter with diethylamine gave only the diamide.

Condensation of diethyl 4-phenyl-2, 5-pyridine dicarboxylate (VII) with hydrazine gives the corresponding dihydrazide (XV), which was condensed with benzaldehyde, vanillin, and 1, 2, 5-trimethylpiperidone-4, to give, respectively, the di(benzalhydrazide) (XVI), di(3'-methoxy-4'-hydroxybenzalhydrazide (XVII), and di(1', 2', 5'-trimethyl-4'-piperidylidenehydrazide) (XVIII) of 4-phenyl-2, 5-piperidine dicarboxylic acid.



XV



Experimental

Isocinchomeronic(diethylamide). Isocinchomeronic dichloroanhydride was prepared from 8 g isocinchomeronic acid (mp 223-224°) and 48 ml thionyl chloride by stirring and heating together on a steam bath for 5 hr, after which the excess thionyl chloride was distilled off under reduced pressure, and 60 g freshly-distilled diethylamine added dropwise to the residue held at 0°. The mixture was refluxed and stirred for 8 hr, and the reaction products treated with a saturated sodium carbonate solution and extracted with ether. The ether extract was dried over magnesium sulfate, the ether distilled off along with excess diethylamine, and the residue caused to crystallize by adding dry ether. Yield 4 g yellow crystals II, mp 115° (from n-heptane). Found: N 15.04, 14.88%. Calculated for $C_{15}H_{23}N_3O_2$: N 15.16%.

4-Phenyl-2, 5-pyridine dicarboxamide (VIII). 1.5 g dimethyl 4-phenyl-2, 5-pyridine dicarboxylate was stirred vigorously for 40 hr with 15 ml 25% ammonia, and the products evaporated, to give a crystalline residue mp 175-176° (from alcohol). Found: N 10.78, 10.56%. Calculated for $C_{15}H_{14}N_2O_3$: N 10.39%. The analytical results correspond to a monoamidomonomethyl ester of 4-phenyl-2, 5-pyridine dicarboxylic acid. This product was stirred for a further 48 hr with 15 ml 25% ammonia solution and 20 ml absolute ethanol, and after the alcohol and ammonia were distilled off,

there was obtained 0.9 g VIII, mp 256-257°. Found: N 17.18%. Calculated for $C_{13}H_{11}N_3O_2$: N 17.42%.

4-Phenyl-2,5-pyridine di(dimethylcarboxamide) (V). 4-Phenyl-2,5-pyridine dicarboxylic dichloroanhydride was prepared from 10 g 4-phenyl-2,5-pyridine dicarboxylic acid and 60 g thionyl chloride. It was heated for 8 hr with 80 g saturated aqueous solution of dimethylamine. After distilling off excess dimethylamine and part of the water, the products remaining were treated with sodium carbonate and extracted with ether, the ether extract dried, and after distilling off the ether, the residue crystallized. Yield 6 g colorless crystals V, mp 152-153° (from n-hexane). Found: N 14.15, 14.39%. Calculated for $C_{17}H_{19}N_3O_2$: N 14.09%.

Hydrochloride mp 161-163° (from acetone). Found: N 12.34, 12.30%. Calculated for $C_{17}H_{20}ClN_3O_2$: N 12.61%.

4-Phenyl-2,5-pyridine dipyridylcarboxamide (VI). 4-Phenyl-2,5-pyridine dicarboxylic dichloroanhydride was prepared from 10 g 4-phenyl-2,5-pyridine dicarboxylic acid and 60 ml thionyl chloride. The product was heated with 20 g piperidine for 8 hr on a steam bath, the whole diluted with water, treated with sodium carbonate, and extracted with chloroform. The extract was dried, the chloroform distilled off, and the residue crystallized from absolute alcohol. Yield 6.2 g VI, mp 110-111° (from petroleum ether). Found: N 11.48, 11.48%. Calculated for $C_{23}H_{27}N_3O_2$: N 11.11%.

The diamide VI and hydrogen chloride gave a crystalline compound mp 132-134° (from acetone). Analytical data showed that it contained 3 molecules of hydrogen chloride. Found: N 8.83, 8.65%. Calculated for $C_{23}H_{30}Cl_3N_3O_2$: N 8.64%.

4-Phenyl-2,5-pyridine di(diethylthiocarboxamide) (X). A mixture of 1.2 g IX and 0.8 g phosphorus pentasulfide in benzene was refluxed for 10 hr, the benzene distilled off, and the crystalline residue recrystallized from petroleum ether. Yield 0.5 g X, mp 144-145°. Found: N 10.50, 10.69%. Calculated for $C_{21}H_{27}N_3S_2$: N 10.90%.

Condensation of diethyl 4-phenyl-2,5-pyridine dicarboxylate with aniline.

a) A mixture of 5 g diethyl 4-phenyl-2,5-pyridine dicarboxylate and 4 g aniline was heated at 215-220° for 3 hr, and the resultant ethanol distilled off. The excess aniline was distilled off under reduced pressure, and the residue recrystallized from alcohol. Yield 3.6 g substance mp 118-119°, whose analysis corresponded to the monoethyl ester of XI. Found: N 8.49, 8.34%. Calculated for $C_{21}H_{18}N_2O_3$: N 8.15%.

b) 3 g 4-phenyl-2,5-pyridine dicarboxylic acid, 2 g phosphorus pentoxide, 5 g aniline, and 50 ml dry benzene were refluxed for 8 hr, the reaction products made alkaline with potassium hydroxide solution, and then extracted first with benzene and then with ethyl acetate. The extracts were dried and the solvents distilled off to give 2 g XII, mp 189-190° (from alcohol). Found: N 10.40, 10.44%. Calculated for $C_{25}H_{17}N_3O_2$: N 10.68%.

Reaction of 4-(p-carboxyphenyl)-2,5-pyridine dicarboxylic dichloroanhydride with diethylamine. 4-(p-carboxyphenyl)-2,5-pyridine dicarboxylic chloroanhydride was prepared from 10 g of the acid and 60 ml thionyl chloride, and 80 g diethylamine added, with cooling, to the chloroanhydride, after which the reaction mixture was refluxed for 10 hr. Then the excess diethylamine was distilled off, and the residue recrystallized from petroleum ether. Yield 2.3 g compound mp 126-127°, with an analysis corresponding to a di(diethylamide) of 4-(p-carboxyphenyl)-2,5-pyridine dicarboxylic acid. Found: N 10.33, 10.13%. Calculated for $C_{22}H_{27}N_3O_4$: N 10.57%.

Nitration of 4-phenyl-2,5-pyridine dicarboxylic acid. 10 ml of a nitrating mixture (4.5 ml HNO_3 d 1.39 plus 5.5 ml H_2SO_4 d 1.84) was added in portions to 5 g IV (mp 233-234°). Then the reaction mixture was stirred for 1 hr at 70°C, and after this, 5 ml of the nitrating mixture added, and the whole heated for another 1 hr at the same temperature. The yellow crystals which separated after cooling were filtered off and recrystallized from aqueous alcohol. Yield 4.5 g XIII, mp 232-233° (decomp). Mixed mp with the starting acid 214-215°. Found: N 9.38, 9.55%. Calculated for $C_{13}H_8N_2O_6$: N 9.72%.

Diethyl 4-p-nitrophenyl-2,5-pyridine dicarboxylate (XIV). A mixture of 4 g XIII, 30 ml ethanol, and 2.7 sulfuric acid was heated for 5 hr. After removing excess ethanol, the residue was treated with water, and the aqueous solution neutralized with sodium carbonate in the presence of ether. The ethereal extract gave 2 g XIV mp 136-139° (from ous alcohol). Found: N 7.92, 7.88%. Calculated for $C_{17}H_{16}N_2O_6$: N 8.14%.

4-Phenyl-2,5-pyridine dicarboxylic acid dihydrazide (XV). A mixture of diethyl 4-phenyl-2,5-pyridine dicarboxylate (mp 106-108°) and 16.2 ml hydrazine hydrate was heated at 90-100° for 48 hr. The alcohol formed was distilled off under reduced pressure, and the crystalline residue recrystallized from alcohol. Yield 5.8 g XV, forming colorless crystals mp 191-194°. Found: N 25.04, 24.88%. Calculated for $C_{13}H_{13}N_5O_2$: N 25.83%.

Picrate mp 210-211° (from alcohol). Found: N 22.44, 22.66%. Calculated for $C_{13}H_{13}N_5O_2 \cdot C_6H_3N_3O_7$: N 22.40%.

4-Phenyl-2,5-pyridine dicarboxylic acid di(benzalhydrazide) (XVI). A mixture of 5 g XV, 6 g benzaldehyde, and 50 ml ethanol was heated at 80-90° for 10 hr, after which the alcohol was distilled off, and the crystalline residue washed three times with a hot mixture of alcohol and acetone. Yield 3 g hydrazide (XVI), mp 287-288°. Found: N 15.56, 15.48%. Calculated $C_{27}H_{21}N_5O_2$: N 15.66%.

4-Phenyl-2, 5-pyridine dicarboxylic acid di(3'-methoxy-4'-hydroxybenzalhydrazide) (XVII). A mixture of 5 g dihydrazide XV, 7 g vanillin, and 50 ml ethanol was heated at 80-90° for 10 hr. The alcohol was then distilled off, and the crystalline residue washed three times with a mixture of alcohol and acetone. Yield 4 g hydrazide XVII, forming yellow crystals, mp 242-243°. Found: N 12.67, 12.91%. Calculated for $C_{29}H_{25}N_5O_6$: N 12.98%.

4-Phenyl-2, 5-pyridine dicarboxylic acid di(1', 2', 5'-trimethyl-4'-piperidylidehydrazide) (XVIII). A mixture of 5 g dihydrazide XV, 6.25 g 1, 2, 5-trimethylpiperidone-4, and 150 ml absolute alcohol was heated for 10 hr on a steam bath. After distilling off the alcohol the residue was recrystallized from acetone. Yield 3.5 g dihydrazide XVIII mp 182-183°. Found: N 18.70, 18.83%. Calculated for $C_{29}H_{39}N_7O_2$: N 18.95%.

REFERENCE

1. N. S. Prostakov and L. A. Gaivoronskaya, ZhOKh, 32, 76, 1962.

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