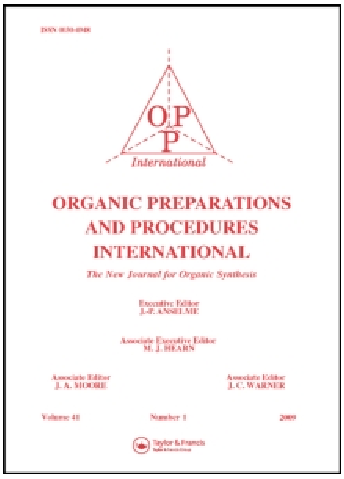

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HETEROCYCLES DERIVED FROM THE CONDENSATION OF HOMOPHTHALIC ANHYDRIDE WITH ETHYLENEDIAMINE

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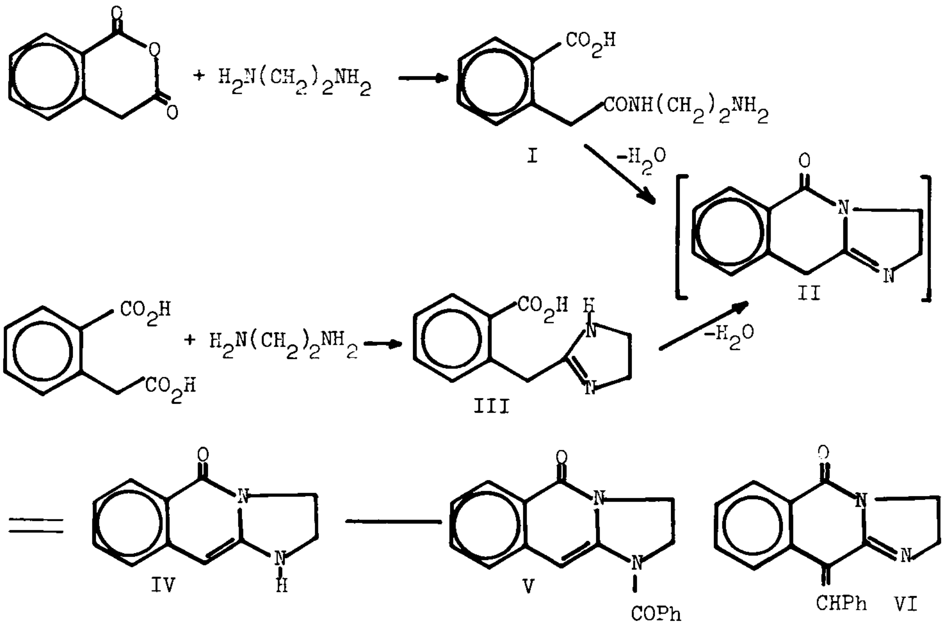
Our study of heterocycles obtained by condensation of dicarboxylic acids derivatives with aliphatic diamines[1,2] led us to investigate the condensation of homophthalic anhydride with ethylenediamine.



The structure of the expected amide I was assigned on the basis of elemental analysis, ir spectroscopy, and the well-known and most probable trend of the homophthalic anhydride to give amides of the β-carboxylic group. This compound upon heating to its melting point, loses two water molecules to give a new compound (A) whose formula was determined to be $C_{11}H_{10}N_2O$ on the basis of elemental analysis and molecular weight determination.

Although IR and NMR spectra were not in agreement with II, showing a NH signal, its structure was confirmed by an unequivocal synthesis. In fact, heating homophthalic acid with ethylenediamine in 4 N hydrochloric acid gave α-(2-imidazolinyl)-o-toluic acid (III) albeit in low yield. This structure was assigned on the basis of the different reactivities of the two carboxylic groups of the homophthalic acid,[3] analysis of the picrate of III, and UV and ir spectra. III was easily transformed into compound A upon heating *in vacuo* at 140°. Schefczic[4] described an analogous compound IV obtained by a different procedure. IV had a melting point similar to that of A. The position of the double bond in the isoquinoline ring of IV was assigned on the basis of method of synthesis (coupling with a diazonium salt; no other chemical nor spectroscopic properties were given.

The actual location of the double bond in A was proven by the formation of N-benzoyl and C-10 benzylidene derivatives (V and VI) by reaction of IV with benzoyl chloride in pyridine and with benzaldehyde in acetic acid-sodium acetate, respectively. These reactions suggest the existence of a tautomeric equilibrium between II and IV. Structure IV is the one observed in the solid phase IR spectrum and in the NMR spectrum in DMSO-d_6 and in $CDCl_3$. It is concluded that structure IV is the predominant and more stable tautomeric form, although II may be formed first during the condensation process, but cannot be isolated.

EXPERIMENTAL[5]

N-(o-Carboxyphenylacetyl)ethylenediamine (I).- To a suspension of 2.2 g (13.5 mmoles) of homophthalic anhydride in ethanol (15 ml) was added dropwise with stirring 1.1 ml of ethylenediamine in ethanol (5 ml). The reaction mixture was stirred for 45 minutes and deposited a white solid which was filtered and washed with chloroform. Recrystallization from acetic acid-methanol gave 1.69 g (53%) of a microcrystalline white product, mp. 242-243°. IR: 3400 (NH of amide group, broad), 3100 (ν CO of amide group, "Band I"), 1500 ("Band II"). NMR (D_2O): 3.2 (t, 2H, CH_2-NH_2, J = 6Hz), 3.6 (t, 2H, NH-CH_2, J = 6Hz), 3.9 (s, 1H, CH-CO), 4.0 (s, 1H, CH-CO), 7.5 (m, 4H, arom., J = 6Hz).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.39; N, 12.78.
Found: C, 59.60; H, 6.48; N, 12.71.

1,2,3,5-Tetrahydroimidazo-[1,2-b]-isoquinoline-5-one (IV).- I (0.8 g, 3.6 mmoles) was heated in an oil bath at 185-190°. Once the dehydration was completed, the temperature was raised at 200-205° and the product sublimed at 2-3 mmHg gave 0.64 g (96%) of yellow needles, mp. 216-217°. Upon recrystallization from ethanol-water (2/1), a white product was obtained, mp. 217-218°. IR: 3.800 (ν NH of amine group), 1680 (ν CO of lactam group), 1650 (ν C=C of CH=C-N group). NMR ($CDCl_3$): 1.7 (s, 1H, NH, confirmed by exchange with D_2O at room temperature), 3.7 (t, 2H, CH_2-NH, J = 6Hz), 4.22 (t, 2H, CH_2-N-CO, J = 6Hz), 5.6 (s, 1H, CH=C), 7.25 (t, 3H, arom., J = 6Hz), 8.2 (d, 1H, arom., J = 9Hz). UV ($CHCl_3$): λ_{max}: 227 mm; log ε = 4.37. Molecular weight: Calcd. for $C_{11}H_{10}N_2O$: 186; found: 185.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.96; H, 5.37; N, 15.05.
Found: C, 71.06; H, 5.41; N, 15.18.

α-(2-imidazolinyl)-o-toluic acid (III).- A mixture of 6.75 g (37.5 mmoles) of homophthalic acid, 1.7 ml (25.4 mmoles) of ethylenediamine and 24 ml of 4 N hydrochloric acid was heated to reflux for 2 hrs and then filtered hot.

The solution was then evaporated to dryness using a rotatory evaporator. The solid residue was dissolved in water and neutralized with sodium hydroxide (0.834 g). This solution was filtered, the filtrate was evaporated under reduced pressure and the residue was extracted with boiling methanol. Evaporation of the methanol left a yellow oil (2.103 g). Subsequently, 10 ml of dry ethanol was added in order to separate the last traces of sodium chloride. The cooled alcoholic solution was filtered and the filtrate was concentrated to dryness to afford 1.67 g of a dark yellow oil. This oil was dissolved in methanol and purified by preparative chromatography (silica gel $HF_{254+366}$) using methanolacetic acid (9/1) as developing solvent. Two fractions were separated. The major one was eluted with methanol. Evaporation of the eluate at low temperature yielded 0.98 g of a clear yellow viscous gum that could not be induced to crystallize and which showed an homogeneous composition by TLC when a mixture of methanol-acetic acid (1/1) was used as developing solvent. IR ($CHCl_3$): 3500 (ν NH of amine group), 1780 (ν CO of acid group), 1620 (ν NH of amine group). UV (C_2H_5OH): λ_{max}: 250 nm.

Picrate of α-(2-imidazolinyl)-o-toluic acid.- To a solution of III in ethanol was added an alcoholic solution of picric acid slowly. The resulting solution was refluxed for 15 minutes and upon cooling a microcrystalline yellow solid deposited and it was filtered and washed with a small volume of ethanol, mp. 226-228°.

Anal. Calcd. for $C_{17}H_{15}N_5O_9$: C, 47.1; H, 3.46; N, 16.2.

Found: C, 47.2; H, 3.44; N, 16.3.

1,2,3,5-Tetrahydroimidazo-[1,2-b]-isoquinoline-5-one (IV) from α-(2-imidazolinyl)-o-toluic acid (III).- Compound III (0.7 g, 3.4 mmoles was heated at 140-150° and then sublimed at 190-200° at 2 mmHg. The yellow solid obtained was recrystallized from ethanol-water (2/1) to give white crystals, mp. 216-218°. Mixture melting point with an authentic specimen of IV was not depressed and the ir spectra were identical.

1-Benzoyl-1,2,3,5-tetrahydroimidazo-[1,2-b]-isoquinoline-5-one (V).- To a solution of 0.75 g (4 mmoles) of IV in 12 ml of pyridine, was added 2 ml of benzoyl chloride. This solution was heated to reflux for 4 hrs and concentrated to dryness *in vacuo*, to afford a red syrup. After addition of hot benzene (20 ml) and stirring, the reaction mixture deposited a solid which was filtered and washed repeatedly with benzene. The solid was dissolved in ligroine-benzene, refluxed with activated carbon and then filtered, dried and recrystallized from benzene-cyclohexane to give 0.55 g (50%) of a yellow product, mp. 149-150°. IR: 1680 (ν CO of lactam group), 1620 (ν CO of amide group, "Band I"), 1515 ("Band II"). NMR ($CDCl_3$): 4.10 (t, not resolved), 4H, CH_2-CH_2), 8.9 (s, 1H, CH=C), 7.5 (m, complex), 9H, arom., J = 6Hz).

Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65.
Found: C, 74.54; H, 4.75; N, 9.70.

10-Benzilidene-1,2,3,5-tetrahydroimidazo-[1,2-b]-isoquinoline-5-one (VI).- A mixture of 0.7 g (3.8 mmoles) of IV, 1 g of anhydrous sodium acetate and 40 ml of glacial acetic acid was stirred at room temperature for 45 minutes after which 0.5 ml of benzaldehyde were added. The reaction mixture was heated to reflux for 12 hrs. The dark solution was concentrated to dryness *in vacuo* and the resulting oil was dissolved in ethanol (20 ml). Upon stirring it solidified to a yellow product which was refluxed for 45 minutes. Then the mixture was cooled, the solid separated and recrystallized from water-DMF to give 0.60 g (58%) of a clear yellow product, mp. 284-285° (dec.). IR: 1650 (ν of C=N group), 1700 (ν CO of lactam group), 1290, 1810 (ν of CH-C). NMR ($CDCl_3$): 4.12 (t, not resolved , 4H, CH_2-CH_2), 6.9 (s, 1H, CH=C), 7.6 (m, complex , 9H, arom., J = 6Hz).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.33; H, 5.10; N, 10.21.
Found: C, 78.41; H, 5.07; N, 10.29.

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5. Melting points were determined on a Buchi capillary apparatus and are uncorrected. IR spectra (potassium bromide) were obtained on a Perkin-Elmer 700 A spectrophotometer. The NMR spectra were recorded on a 60 Mc Perkin-Elmer R-12 spectrometer and chemical shifts are reported in parts per million (δ) downfield from TMS. UV spectra were determined in a Perkin-Elmer 350 spectrophotometer. Molecular weights were determined by the Rast method.

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