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# CONVERSION OF 2-AMINO-2,3-DIHYDRO-1H-ISOINDOL-1-ONE INTO PYRIDAZINE
## A NOVEL SYNTHESIS OF 3-ARYL-4(1H)-PYRIDAZONES

E. Toja, A. Omodei-Salè* and G. Nathansohn

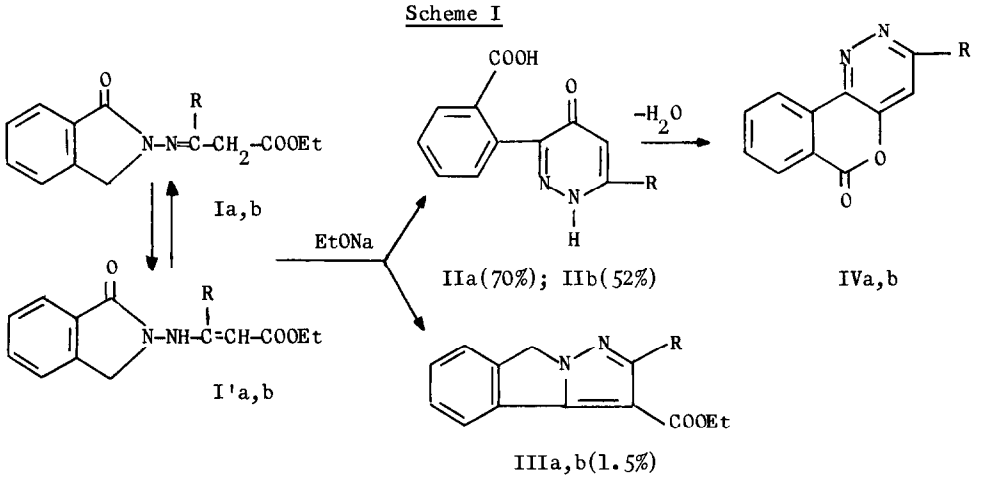
Research Laboratories of Gruppo Lepetit S.p.A., Milan, Italy

*Summary:* *The title conversion was achieved by condensation of 2-Amino-2,3-dihydro-1H-isoindol 1-one with ethyl benzoyl(or aceto)acetate followed by base-promoted rearrangement.*

In a previous paper[1], we reported a novel acid-catalyzed ring expansion of the hydrazone Ia, to give 3-phenyl-1H-pyrazolo[1,2-b]phthalazine-1,5(5H,10H)-dione.

We have now observed that the hydrazones Ia,b[2] undergo a different, base-promoted rearrangement, to afford 3-aryl-4(1H)-pyridazones II as the main products (Scheme I)[3].

Scheme I




a: R = Ph; b: R = Me

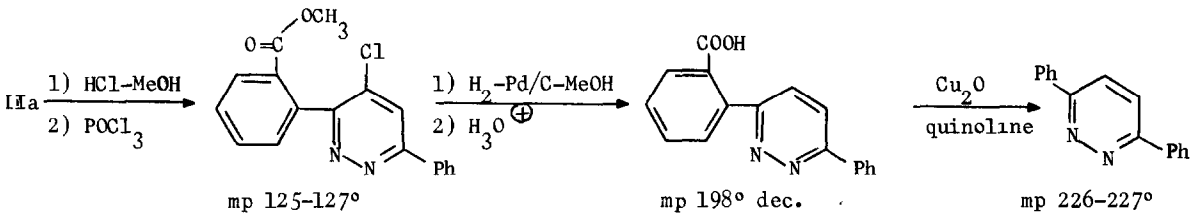
The experimental procedure involved stirring 0.01 moles of I with 0.011 moles of sodium ethoxide in 50 ml of ethanol at 60° for 1 hr (R=Ph) or with 0.015 moles of sodium ethoxide in 25 ml of dimethylformamide at 60° for 4 hrs (R=Me), then distilling off the solvent, pouring into water and stirring until the red solution turned to a pale yellow. Ether extraction removed 3-carbethoxy-8H-pyrazolo[5,1-a]isoindoles III[4]. IIIa, mp 114-115° (i-$Pr_2O$); IIIb, mp 100-101° (i-$Pr_2O$-hexane); IR(Nujol) ν $cm^{-1}$: 1700 (C=O ester); NMR ($CDCl_3$) δ: 5.05 (s, 2H, $CH_2N$). Acidification of the aqueous layer afforded 4(1H)pyridazones.IIa, mp 213-214° dec. (AcOH); IR(Nujol) ν $cm^{-1}$: 3240 (NH), 1660 (C=O acid), 1630 (C=O ketone); NMR (DMSO-$d_6$) δ: 6.60 (s, 1H, $H_5$). IIb, mp 209-210° dec. (EtOH); IR(Nujol) ν $cm^{-1}$: 3200 (NH), 1700 (C=O acid), 1600 (C=O ketone); NMR (DMSO-$d_6$) δ: 2.31 (s, 3H, $CH_3$).

6.21 (s, 1H, $H_5$).

Lactonization of II to 3-substituted-6H-[2]benzopyrano[4,3-c]pyridazin-6-ones IV, was carried out by treatment with dicyclohexylcarbodiimide in refluxing pyridine. IVa, mp 205-206° (AcOEt); NMR ($CDCl_3$) δ: 7.63 (s, 1H, $H_4$). IVb, mp 218-219° (AcOEt); NMR ($CDCl_3$) δ: 7.33 (s, 1H, $H_4$); IR (Nujol) ν $cm^{-1}$: 1760 (C=O lactone).

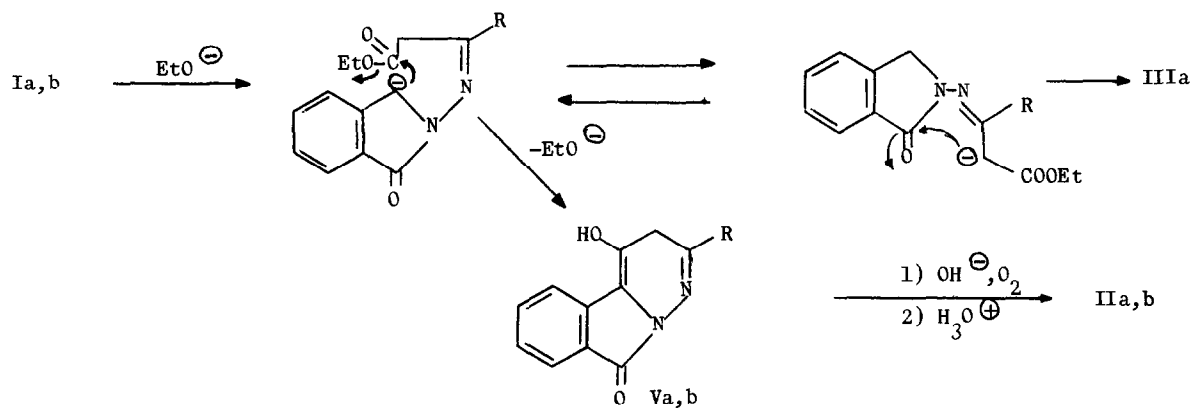
The structure of IIa was confirmed by conversion to the known 3,6-diphenylpyridazine[5], according to Scheme II, and comparison with an authentic sample.

Scheme II




The course of the reaction of I with sodium ethoxide was rationalized by assuming that deprotonation of the benzylic $CH_2$ and subsequent ring closure gives the tricyclic intermediate V (Scheme III). Alkaline hydrolysis and air oxidation of the deep red sodium salt of V affords II.

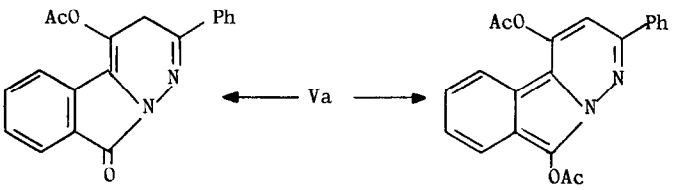
Scheme III




In fact when the reaction was run in an inert atmosphere, under strictly anhydrous conditions and quenched with the stoichiometric amount of hydrochloric acid in ethanol, a yellow precipitate was obtained. This was taken up in deoxygenated water and crystallized from dimethylacetamide, to afford a compound which, on the basis of evidence described below, was shown to be 1-hydroxy--3-phenyl-2H,6H-pyridazino[6,1-a]isoindol-6-one Va, mp 250° dec.; NMR (DMSO-$d_6$) δ: 3.83 (s, 2H, $CH_2$).

Treatment of Va with acetic anhydride (100°, 1 hr) afforded the monoacetate VI, mp 191-195° dec. (AcOEt); IR (Nujol) $\nu$ $cm^{-1}$: 1780 (C=O ester), 1730 (C=O lactam); NMR ($CDCl_3$) $\delta$: 2.43 (s, 3H, $CH_3CO$), 3.85 (s, 2H, $CH_2$).

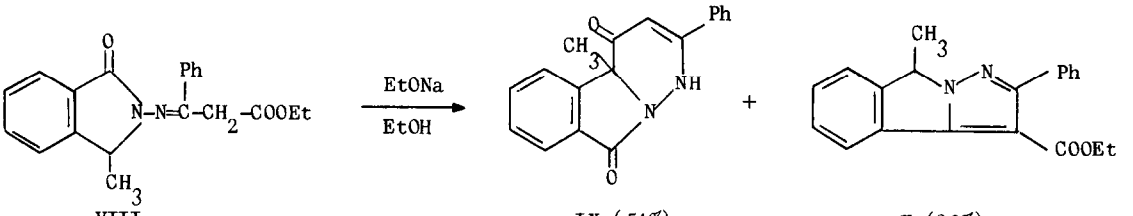
Reaction of Va with acetic anhydride in pyridine (60°, 3 hrs) yielded the diacetate VII as red needles, mp 198° dec. (AcOEt); IR ($CHCl_3$) $\nu$ $cm^{-1}$: 1795 (C=O esters); NMR ($CDCl_3$) $\delta$: 2.53 and 2.55 (2s, 6H, $CH_3CO$), 7.11 (s,1H, $H_2$). Hydrolysis with 1N NaOH, in the presence of air, quantitatively converted Va into IIa.




VI VII

The competitive nucleophilic attack of the carbanion α to the carbethoxy group, which was negligible in the case of Ia,b (Scheme III) became substantial in the case of VIII[6] (Scheme IV). Thus, treatment of VIII with 1.1 equivalents of sodium ethoxide in refluxing ethanol for 2 hrs afforded, after usual work-up X, mp 108-111° (i-$Pr_2O$); NMR ($CDCl_3$) $\delta$: 1.76 (d, J=7Hz, 3H, $\underline{CH_3}CH$), 5.18 (q, 1H, $\underline{H}CCH_3$), and 10b-methyl-3-phenyl-4H,6H-pyridazino[6,1-a]isoindole-1(10b H), 6-dione IX, mp 190-191° dec. (AcOEt); IR (Nujol) $\nu$ $cm^{-1}$: 3120 (NH), 1700 (C=O lactam), 1650 (C=O ketone); NMR ($CDCl_3$) $\delta$: 1.7 (s, 3H, $CH_3$), 5.45 (s, 1H, $H_2$), 9.6-10.3 (broad band, NH).

Scheme IV




VIII IX (54%) X (23%)

Plausible explanations of the increased ratio X/IX compared with III/II, are the decreased acidity of the benzylic proton of VIII and the steric hindrance at the tertiary carbanion. Contrary to what was observed with Va, IX was quantitatively recovered after solution in 1N NaOH and acidification 24hrs later[7]. This different reactivity towards bases, suggests that the hydrolytic cleavage of Va is promoted by the formation of the 10b-carbanion and not by the nucleophilic attack on the amido carbonyl group.

The structure of IX was confirmed by sodium borohydride reduction at 0° in buffered solution (monosodium citrate-methanol, pH5) that afforded 1,2,6,10b-tetrahydro-1-hydroxy-10b-methyl-3--phenylpyridazino [6,1-a]isoindol-6-one, mp 181-182° (AcOEt); IR ($CDCl_3$) ν $cm^{-1}$: 1700 (C=O lactam); NMR ($CDCl_3$) δ: 1.35 (s, 3H, $CH_3$), 2.72-3.13 (2 dd, $J_{vic}$=9 and 6.5 Hz, $J_{gem}$=18 Hz, 2H, $CH_2$), 3.80 (ddd, $J_{CHOH}$=4.5 Hz, 1H, HCOH), 4.32 (d, 1H, OH).

Further synthetic and mechanistic aspects of this reaction are presently under investigation.

Acknowledgment. We wish to thank Dr. P. Ferrari and Miss A. De Paoli for spectral measurements

References and footnotes.

1. E.Toja, A.Omodei-Salè and G.Nathansohn, Tetrahedron Lett. 111 (1976).

2. The procedure for the preparation of Ia is reported on Ref. 1. Similarly was prepared Ib, bp 140°/0.01 mm.

3. Satisfactory analytical data were obtained for all new compounds.

4. We subsequently devised an alternative and specific route to prepare pyrazolo [5,1-a] isoindoles, described in Belgian Patent 835836 (1975).

5. C. Paal and H. Schulze, Chem. Ber., 33, 3795 (1900).

6. Compound VIII was prepared according to Ref. 1; mp 89-90° (i-$Pr_2O$). 2-Amino-3-methyl-2,3-dihydro-1H-isoindol-1-one (mp 72-73°) was synthetized by refluxing methyl-2-(1'-bromoethyl) benzoate and hydrazine hydrate in ethanol for 15 hrs.

7. The sodium salt of IX (1-hydroxy tautomer) was isolated. IR (Nujol) ν $cm^{-1}$: 1670 (C=O lactam). UV : $\lambda_{max}^{0.1N\ NaOH}$ 240 (ε 16,990), 258 (16,300), 288 (19,890), 378 nm (5,510). $pK_a$=6.2.

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