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A NOVEL RING EXPANSION OF AN N-AMINOPHTHALIMIDINE TO A CONDENSED DIHYDROPHTHALAZIN-1-ONE. SYNTHESIS OF 1H-PYRAZOLO[1,2-b]PHTHALAZINE DERIVATIVE

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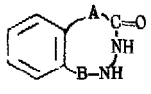
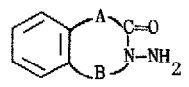
It has been shown that the ring contraction of six membered cyclic hydrazides I into the corresponding N-aminolactams II can be promoted by hydrazine hydrate (1), sodium hydroxide (2) or hydrochloric acid (3). However the inverse transformation of compounds of type II into I has not yet been reported in the literature (4). In this paper we would like to describe the first



I



II

A or B = CH_2

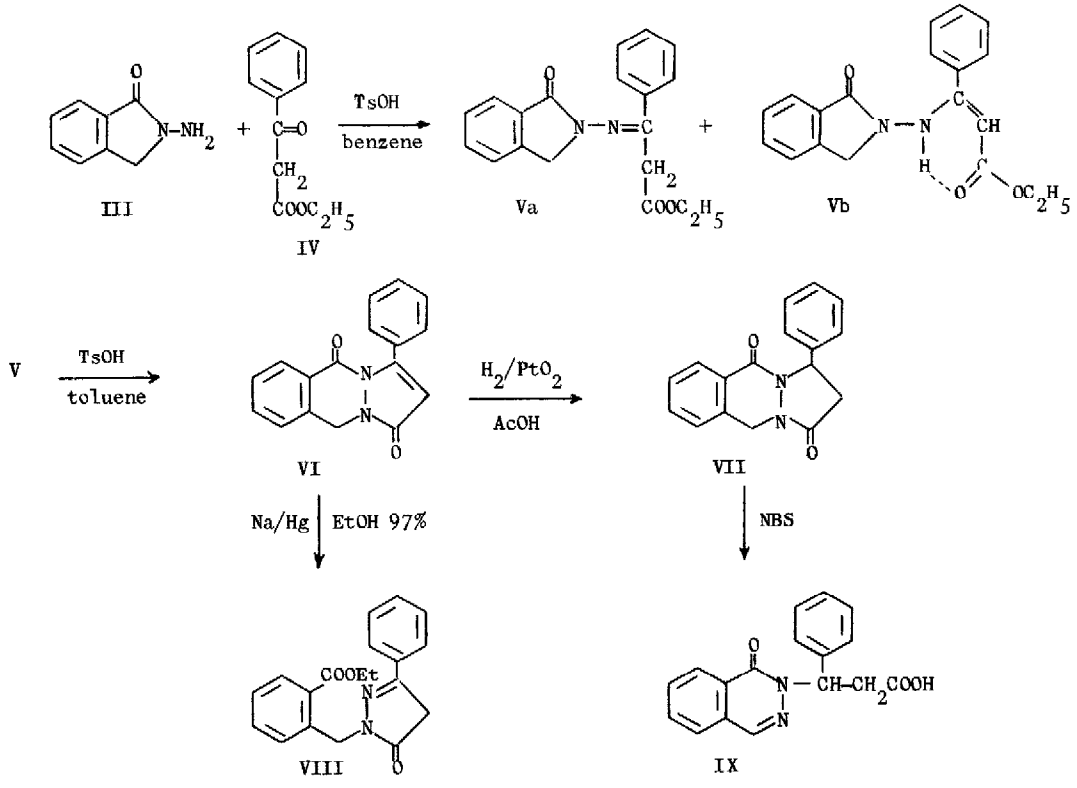
example of this ring expansion. This concerns the N-aminophthalimidine derivative V which is converted into the condensed 2,3-dihydrophthalazine-1(2H)-one VI.

In the course of our work on the synthesis of tricyclic derivatives of isoindole, N-aminophthalimidine III was condensed with ethyl benzoylacetate IV in the presence of p-toluensulfonic acid ($TsOH.H_2O$) for 3 hrs. in refluxing benzene to give compound V in 77% yield, m.p. 110-111°C (i-PrOH).

On the basis of spectroscopic and thermal analyses, V was shown to be a 7:3 mixture of ethyl 3-phenyl-3[(1-oxo-2-isoindolinyl)imino]propionate Va; IR ($CHCl_3$). 1730 (ν C=O ester), 1700 (ν C=O lactam), 1625 (ν C=N) cm^{-1}, NMR ($CDCl_3$) δ 1.01 (t, J = 7, 3H, CH_3), 4.00 (q, 2H, $CH_3-\underline{CH}_2$), 4.01 (s, 2H, CH_2-CO) , 4.80 (s, 2H, CH_2N) and ethyl β[(1-oxo-2-isoindolinyl)amino]cinnamate Vb, IR ($CHCl_3$)· 3245 (ν NH), 1700 (ν C=O lactam), 1665 (ν C=O ester H-bonded), 1620 (ν C=C) cm^{-1}, NMR ($CDCl_3$) δ 1.30 (t, J = 7, 3H, CH_3), 4.02 (q, 2H, $CH_3\underline{CH}_2$), 4.26 (s, 2H, CH_2N), 5.06 (s, 1H, CH=C), 9.79 (s, 1H, NH).

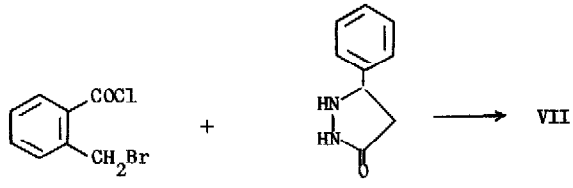
Subsequent treatment of V with a catalytic amount of $TsOH.H_2O$ in toluene for 18 hrs. at reflux in a Dean-Stark apparatus produced a nearly quantitative yield of a compound VI, m.p. 207-208° (AcOEt) $C_{17}H_{12}N_2O_2$, M^+ m/e 276; IR ($CHCl_3$) 1715 and 1670 (ν C=O) cm^{-1}, NMR ($CDCl_3$) δ 5.23 (s, 2H, CH_2N), 5.94 (s, 1H, =CH-CO) and 7.3-7.8 (m, 8H, aromatic H), 8.15 (d, J = 7.5, 1H, H peri to CO).

Scheme I



On the basis of evidence described below, VI was shown to be 3-phenyl-1H-pyrazolo[1,2-b]phthalazine-1,5(5H,10H)-dione. Catalytic reduction of VI over PtO_2 in acetic acid at room temperature afforded the dihydro compound VII, m.p. 128-131° (EtOH 70%); IR ($CHCl_3$) 1710 (ν C=O pyraz.) and 1670 (ν C=O phthalaz.) cm^{-1}; NMR ($CDCl_3$) δ: 2.75 and 3.25 (2 dd, J_{gem} = 17, J_{vic} = 10 and 3, $J_{CH_2-CO-\underset{|}{N}-CH_2}$ = 1, 2H, CH_2CO), 4.65 and 5.37 (2d, J_{gem} = 16, 2H, CH_2N) and 5.90 (dd, 1H, $C\underline{H}-CH_2$) (5).

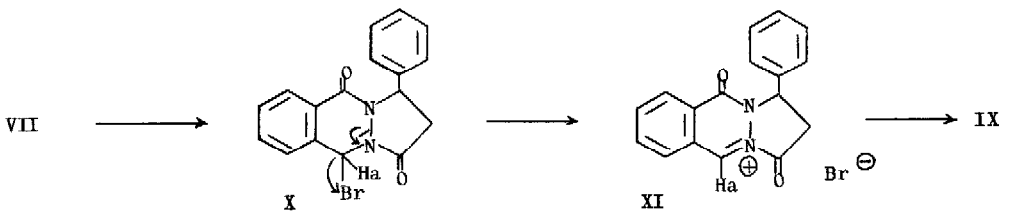
Compound VII was independently synthesized by reacting 2-bromomethylbenzoylchloride with 5-phenyl-pyrazolidin-3-one in dioxane in the presence of triethylamine (6).



An attempt to reduce the C=C double bond of the pyrazole ring of VI by treatment with 3% sodium amalgam in 97% ethanol at 40-50° for 1 hr. gave only ethyl 2-[(2,3-dihydro-3-oxo-5-phenyl-2-pyrazolyl)methyl]benzoate VIII, m.p. 147-148° (AcOEt), IR ($CHCl_3$): 1710 (ν C=O ester) and 1700 (ν C=O pyraz.) cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, J = 7, 3H, CH_3), 3.72 (s, 2H, CH_2-CO), 4.45 (q, 2H, CH_2-CH_3) and 5.47 (s, 2H, CH_2N).

In order to correlate compounds VI and VII, the oxidation of the pyrazolidinone moiety of VII with N-bromosuccinimide (NBS) in CCl_4 was also tried. No VI could be detected, but instead 3-(1,2-dihydro-1-oxo-2-phthalazinyl)-3-phenylpropionic acid IX was isolated in 42% yield, m.p. 159-160° (EtOH 70%), IR ($CHCl_3$) 2800-2200 (ν OH), 1720 (ν C=O acid) and 1665 (ν C=O phthalaz.) cm^{-1}, NMR ($CDCl_3$) δ 3.14 and 3.43 (2 dd, J_{gem} = 16, J_{vic} = 9 and 7, 2H, CH_2-CO), 6.56 (dd, 1H, CH-CH_2) and 8.45 (s, 1H, CH=N).

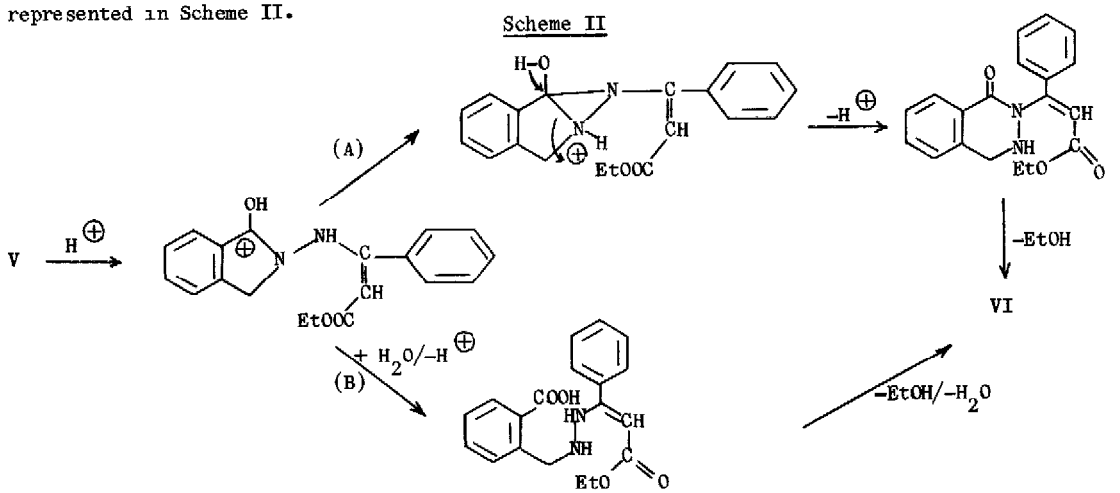
A plausible explanation for this ring opening is the radical attack by NBS on the benzylic carbon of the dihydrophthalazone moiety of VII with subsequent formation of the intermediate acyliminium salt XI which is then opened by water to give the acid IX.



This mechanism is supported by the detection in the NMR spectrum of the crude reaction mixture before water treatment, of a signal at δ 8.34 ($CDCl_3$) assignable to the Ha proton of X or XI.

The acid-catalyzed formation of VI from V could be explained by the two mechanistic pathways represented in Scheme II.

Scheme II



The hydrolytic mechanism (Path B) was excluded when the ring expansion of V was run under strictly anhydrous conditions. In this case, after the usual work-up, compound VI was still isolated in good yield. Furthermore, when the reaction was carried out in the presence of ^{18}O enriched water for 44 hrs. at reflux without a Dean-Stark apparatus, the product VI, obtained in 80% yield, did not contain ^{18}O detectable by mass spectrometry. The mechanism proposed in pathway A seems therefore the most likely one. It involves the formation of an intermediate diaziridine which subsequently evolves into the six membered dihydrophthalazinone derivative. The facile ring closure to form the pyrazolo[1,2-b]phthalazine VI completes the process and can be considered the driving force of the full reaction. *) The same reaction can be performed with $BF_3.Et_2O$ although in lower yield.

Correct microanalytical data have been obtained for all compounds described in this communication.

Acknowledgment. - We are indebted to Miss A.De Paoli for the NMR spectra.

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5. The existence of a J^5 between the two H at C-2 and one of the two H at C-10 has been confirmed by ^1H homodecoupling. Conformational studies on VII and related compounds will be reported elsewhere.
6. a) H.Dorn and D.Arndt, J.Prakt.Chem., 313 (1), 115 (1971).
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*) However a concerted intramolecular mechanism can not, in principle, be excluded.