Tetrahedron Letters No. 36, pp. 3167-3170, 1970. Pergamon Press. Printed in Great Britain.

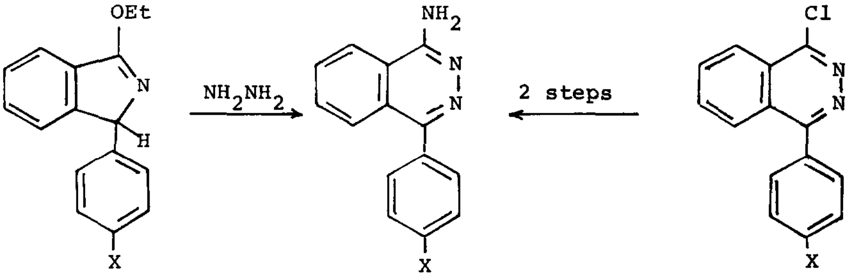
1-AMINO-4-PHENYLPHTHALAZINE FROM 1-PHENYL-3-ETHOXYISOINDOLENINE

Marcel Eberle and William J. Houlihan

Department of Research
Sandoz Pharmaceuticals
Division of Sandoz-Wander Inc.
Route 10, Hanover, New Jersey 07936, USA

(Received in USA 22 June 1970; received in UK for publication 3 July 1970)

We have isolated 1-amino-4-phenylphthalazines 2a,b from reactions of the 1H,1-phenyl-3-ethoxyisoindolenines 1a,b with excess of hydrazine in ethanol. Contrary to our findings is the disclosure (without experimental detail) in a recent paper[1] of this journal that 1H,1-phenyl-3-ethoxyisoindoline behaves like an imidoether and that nucleophilic exchange of the alkoxy group occurs readily with NH acidic groups, e.g., hydrazine to give novel isoindolines and isoindolenines.



1a, X = H
1b, X = Cl

2a, X = H
2b, X = Cl

3a, X = H
3b, X = Cl

Both starting materials 1a,b[2] were prepared in yields of 83% or better from the corresponding 3-phenylphthalimidines[3] via alkylation with triethyloxonium fluoroborate[4] in methylene chloride at room temperature over night and neutralization with a saturated solution of sodium carbonate. Treatment of 1a,b with excess of 97% hydrazine (molar ratio 1:7.4 for 1a; 1:8.5 for 1b) in refluxing ethanol (15 hours under nitrogen) gave the 1-amino-4-phenylphthalazines 2a,b in yields of 64% and 76% resp. The structures were elucidated from spectral data which are summarized in Table I and confirmed by syntheses[5] from the 1-chloro-4-phenylphthalazines 3a,b.

Table I

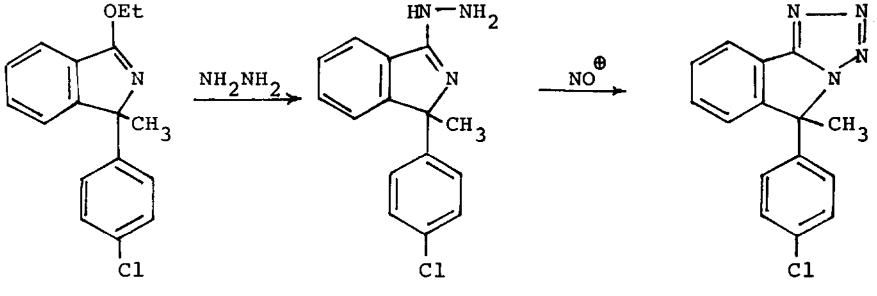
Compd.†	Mp, °C	Yld %	Mass Spec m/e	Infrared cm^{-1} (CH_2Cl_2)	UV (EtOH) mμ, (ε)	NMR δ (ppm) ($CDCl_3$)
1a	93-94	90	237	1640, C=N	275 (943) 283 (906)	5.68, s, 1H, ArCHAr'
1b	100-101	83	271	1640, C=N	275 (1110) 282 (878)	5.65, s, 1H, ArCHAr"
2a*	201-202	64	221		210 (43500) 314 (10020)	6.94, s, 2H, **NH_2 exchangeable in D_2O
2b*	229-232	76	255		210 (45900) 315 (11010)	
4	95-97	83	285	1640*** C=N	225.5 (22100) 275 (1128) 284 (815)	1.80, s, 3H, C_3C-CH_3
5	>340	95		1670, C=N 3400, NH	223 (23400) 283 (6640)	4.0-6.0, 3H, NH, NH_2, exchangeable in D_2O ** 1.87, s, 3H, CH_3
6	113-116	38	282	no abs. in NH, C=O region	223 (21880) 245 (9640) 276 (1308) 284 (1143)	2.22, s, 3H, CH_3

*The products 2a and 2b prepared via either route were compared and found to be identical in the following respects: melting points and mixture melting points, tlc (single compounds and their mixture in 10% MeOH in $CHCl_3$), ir in KBr, uv in EtOH, mass spectra.

**d_6DMSO as co-solvent. ***Nujol.

†Satisfactory C, H, N (Chlorine where applicable) analyses have been obtained for all compounds described in this table.

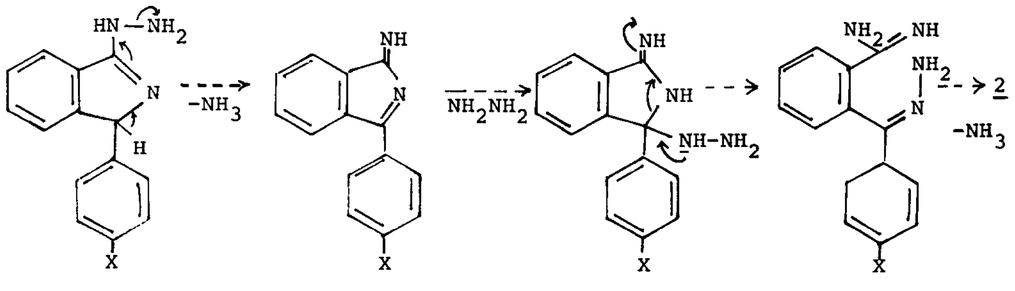
The carbanion of compound 1b is readily generated in absolute DMF with sodium hydride as the base. Reaction of this carbanion with methyl iodide could *a priori* lead to two different products i.e., N-alkylation to give an isoindole or C-alkylation to give an isoindolenine. In fact the latter is obtained in 83% yield.



4 5 6

The uv spectrum of the isolated material is in good agreement with structure 4, i.e., its resemblance to the spectrum of 1b and the absence of any uv band above 300 mμ.[6] To prove this hypothesis chemically the imidoether 4 was reacted with hydrazine and product 5 isolated in good yield. Only the hydrazinoisoindolenine 5 or its tautomer isoindoline are capable to undergo cyclization to the tetrazole 6 when treated with nitrous acid. This reaction was carried out in 38% yield. This further excludes 1-amino-4-methyl-4-p-chlorophenyl-3,4-dihydrophthalazine as a possible product after the reaction of 4 with hydrazine where again a cyclization to the isolated tetrazole 6 would be impossible.

A possible mechanism for this rearrangement is given in the scheme below. Displacement of the ethoxy group in 1a,b can give rise to 7 which then can undergo N-N fragmentation to 8 with subsequent addition of a second molecule of hydrazine to form 9. This in turn can undergo ring expansion with loss of a second molecule of ammonia.



7 8 9 10

Acknowledgement. The authors are indebted to Professor James Hendrickson and Dr. Sandor Barcza for their interest in this work.

References:

1) R. Krehner and H. Hennige, Tetrahedron Letters, 4695 (1969).

2) Additional examples of this class of compounds are reported by Sandoz A.G. Netherlands Patent Appl., 6,909,361 (1969).

3) Imperial Chem. Ltd., Netherlands Patent Appl., 6,402,928 (1964); Chem. Abstr., **62**, 6438 (1965).

4) H. Meerwein,"Organic Synthesis," J. Wiley and Sons, Inc., New York, N.Y., **46**, 113 (1966).

5) E. Hayashi and E. Oishi, Yakugaku Zasshi, **88**, 83 (1968). Chem. Abstr., **69**, 19104 (1968).

6) P. Aeberli and W. J. Houlihan, J. Org. Chem., **34**, 1720 (1969).