

NEW SYNTHETIC APPROACH TO BENZO/f/- AND
BENZO/g/- PHTHALAZINES

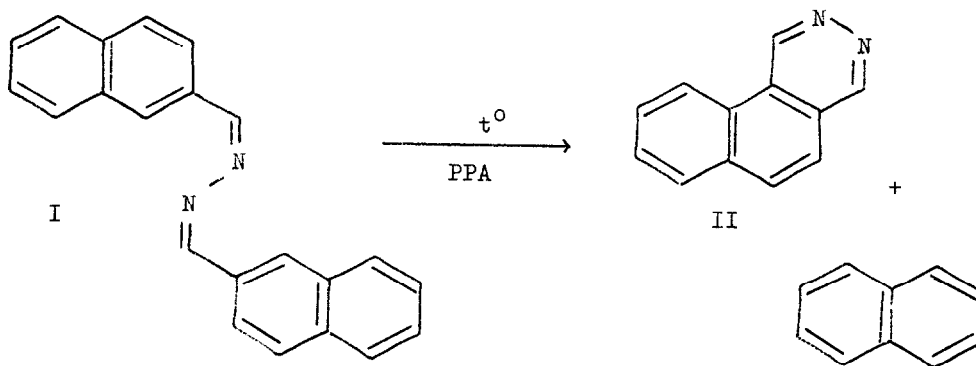
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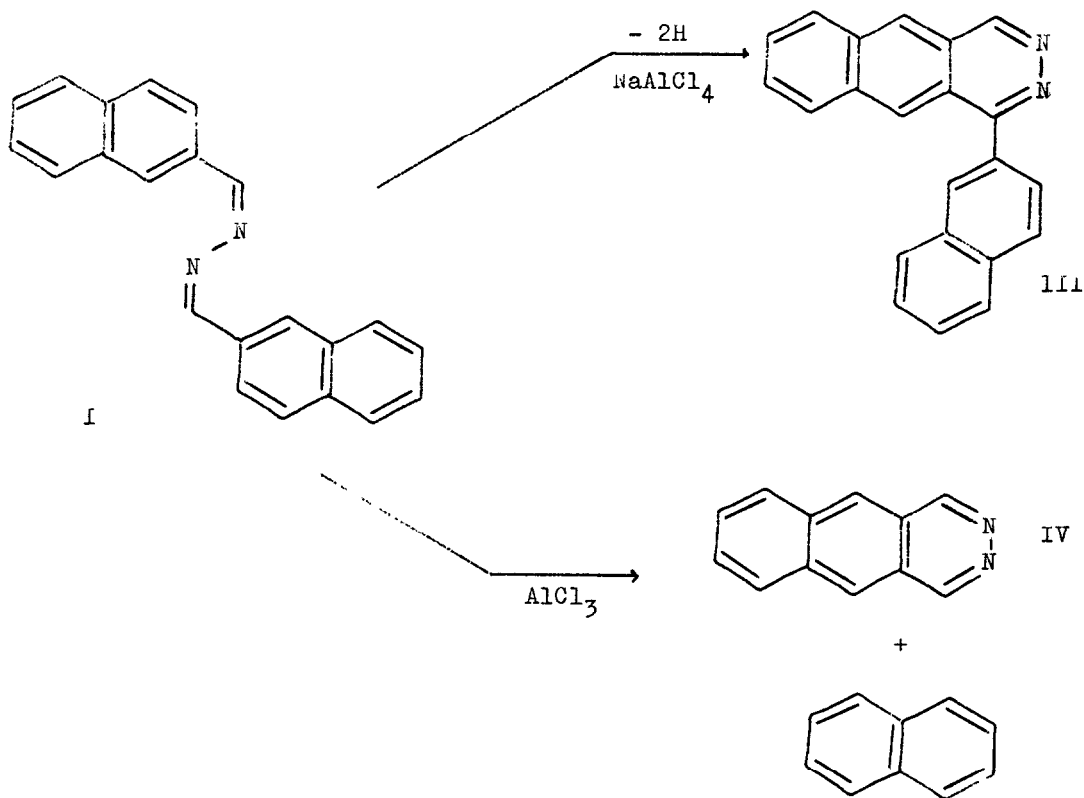
Summary: Benzo/f/- and benzo/g/- phthalazine derivatives were synthesised from 2-naphthaldazine by means of a Lewis acid mediated cyclization with elimination of naphthalene.

In the present paper we report a new synthesis of benzo/f/phthalazine II from 2-naphthaldazine I on heating with polyphosphoric acid (PPA). The cyclization of I to II was accompanied with liberation of naphthalene according to the following scheme



Under the conditions tested the yield of II did not exceed 40%. From the reaction mixture we have isolated also some amounts of 1-(2-naphthyl)-benzo/g/-phthalazine III (about 10%), whose formation is explained by a dehydrogenation cyclization of I parallelling the naphthalene elimination. This process

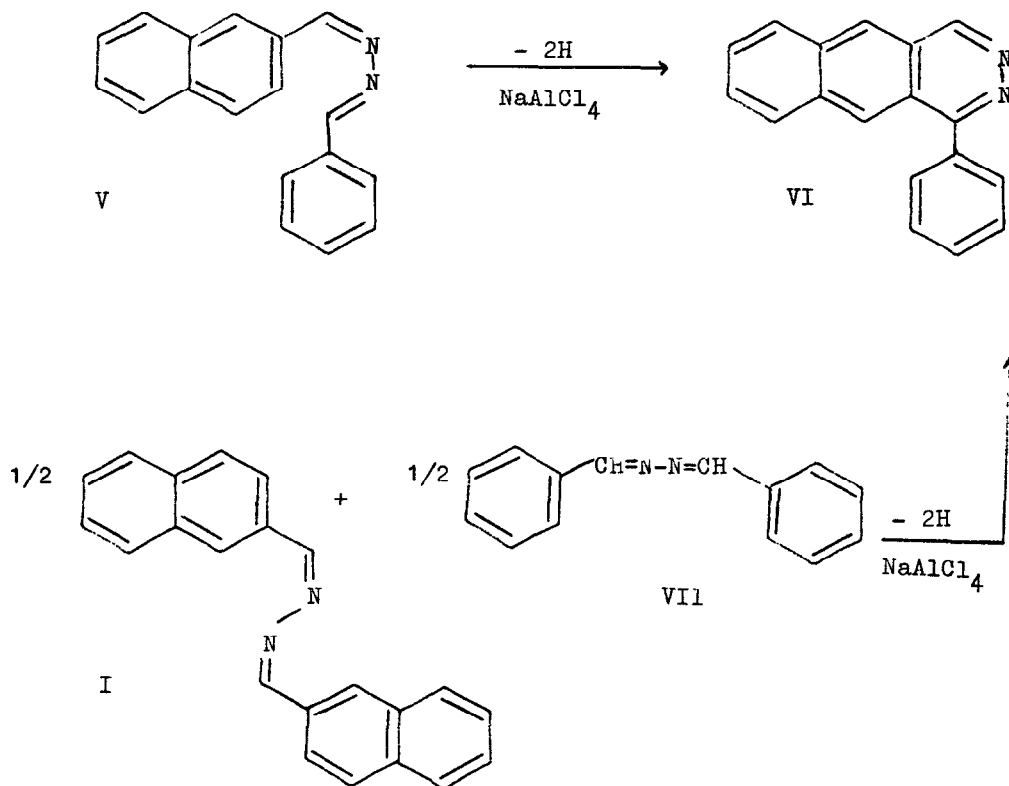
might be related to those described by us earlier^(1,2) as a method for the synthesis of substituted simple phthalazines. When instead of PPA a melt of aluminium chloride and sodium chloride was used the yield of III was increased to 25%. Aluminium chloride used alone or with triethylamine (TEA) in molar ratio 7:1 gave priority of benzo/g/phthalazine IV (yields up to 55%).



The reaction products III, IV and V were actually present in all cases studied so far but their ratio differed widely with respect to the experimental conditions. Since benzo/f/phthalazine II and benzo/g/phthalazine IV in form of free bases showed considerable solubility in water, whereas 1-(2-naphthyl)benzo/g/phthalazine III is insoluble, the separation of the latter during the work up of the reaction mixture is quite easy.

The dehydrogenation cyclization of I to III prompted us to try the reaction not only with I but also with the benzylidene derivative V of 2-naphthaldehyde hydrazone. Using either PPA or NaAlCl_4 as cyclization reagent we have

isolated the corresponding 1-phenylbenzo/g/phthalazine VI (3), though in low yields (less than 15%). It should be pointed out however that an equimolar mixture of the corresponding symmetrical aldazines I and VII led to the same product VI



All reported compounds except II (4,5) are newly synthesised. Their structure was ascribed on the basis of elemental microanalysis and spectral data. 1,4-Diphenylated IV (6) was obtained from IV or VI and PhHgBr.

Benzo/f/phthalazine II 0,31g(1 mmole) 2-Naphthalaldazine I and 3,0ml PPA were heated for one hour at 230-240°C and after cooling the reaction mixture was treated with 250 ml water, made alkaline with 15% KOH, filtered, the filtrate extracted with benzene and the solvent evaporated. From the obtained semisolid residue containing I and IV (molar ratio 4:1 - 1H nmr) II was purified by crystallisation from benzene/light petroleum. Mp of the pure substance was 116-117°C (4). Yield 72mg(40%). Hydrochloride - mp 226-227°C (5).

1-(2-Naphthyl)-benzo/g/phthalazine III 2,0g(15 mmole) Aluminium chloride and 0,88g(15 mmole) sodium chloride were melted together, 0,31g(1 mmole) 2-naphthaldazine I were added and the mixture was heated for 3 hours at 210-220°C. After cooling III was extracted with hot 2% HCl and obtained as white precipitate after treatment with 15% KOH. Crystallised from benzene/n-hexane it showed mp 206-207°C; yield 77mg(25%).

$C_{22}H_{14}N_2$, M^+ 306; 1H nmr, 80 MHz, $\delta_{CDCl_3}^{TMS}$ 7,25-8,25(13H, m, arom.), 9,51 (1H, H_4) ppm.

Benzo/g/phthalazine IV 0,31g(1 mmole) 2-Naphthaldazine I, 2,0g(15 mmole) aluminium chloride and 0,3 ml(2,2 mmole) TEA were heated for 3 hours at 200-210°C. The reaction mixture was treated with 100 ml ice water, filtered and the dark material on the filter washed three times with hot 2% HCl (50 ml each). The united filtrates were made alkaline with 15% NaOH, the negligible precipitate (containing III) filtered off and the filtrate extracted with benzene. After evaporation of the benzene yellowish needles were collected containing IV and II in ratio 5:1 (1H nmr). Benzo/g/phthalazine IV was isolated by crystallisation from ethanol. mp 203-204°C. Yield 0,10g(5%).

$C_{12}H_8N$, M^+ 180; 1H nmr, 80 MHz, $\delta_{CDCl_3}^{TMS}$ 7,50-8,10(4H, m, H_{6-9}), 8,38(2H, H_5 & H_{10}), 9,47(2H, H_1 & H_4) ppm.

NOTES & REFERENCES

1. S.A.Robev, Tetrahedron Letters, 22(1981)345.
2. S.K.Robev, Bulg.Pat., Reg.No 48921/80 and Bulg.Pat., Reg.No 48922/80.
3. VI - mp 156-157°C(benzene/n-hexane); $C_{18}H_{12}N_2$, M^+ 256; 1H nmr, 80 MHz, $\delta_{CDCl_3}^{TMS}$ 7,50-8,60(11H, m, arom.), 9,51(1H, H_4) ppm.
4. H.H. Perkampus, Th. Bluhm, Tetrahedron, 28(1972)2099.
5. J. Kobe, A. Krbavčič, B. Stanovnik, K. Tišler, Croatica Chemica Acta, 41(1969)245.
6. J.D. Loudon, A.D. Sloan, J.Chem.Soc.(1962)3262.

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