Short Communication

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SYNTHESIS OF NEW 1, 2-DIHYDRO-4-AMINO-2-THIOXO-5H-INDENO 1, 2-d PYRIMIDIN-5-ONE DERIVATIVES

Ezzat M. Kandeel, Saad S. El Morsy, Mohamed T. Zimaity and Mohamed M. Yousif
Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

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INTRODUCTION

For a continuing investigation of the biological activity of indenopyrimidines, as analgesics and/or antipyritic compounds [1] samples of certain substituted 1-amino-4-thioxo-6-, and 7-nitroindenopyrimidine derivatives were needed. The reaction of 2-cyano-6-nitroindan-1, 3-dione and 7-nitro derivatives with thiourea, in a manner similar to that reported for the reaction of 2-cyanoindan-1, 3-dione with thioureas, seemed to be the logical route [2-5]. Literature survey rather unexpectedly revealed that 4- and 5-nitro-2-cyanoindan-1, 3-dione derivatives *Ia* and *Ib* have not yet been reported.

In the present paper we report the synthesis of *Ia* and *Ib* and their utilization for the synthesis of pyrimidine derivatives. The work has resulted in affording an efficient route for the synthesis of the required products. Compounds *Ia* and *Ib* could be successfully prepared via condensation of suitably substituted diethylphthalate with acetonitrile in one molar sodium ethoxide solution. It should be reported here that if higher concentrations of ethoxide are used, yields of the end products would decrease significantly. Under these conditions, acetonitrile seemed to dimerize faster than its condensation with diethylphthalate derivatives.

Compound *Ia*, so obtained, condensed with thiourea to yield a product of molecular formula $C_{11}H_6N_4O_3S$. Four theoretically possible isomeric structures were considered. The thiazine structures were readily eliminated based on the stability of the reaction products under conditions reported to affect cleavage or rearrangement of thiazine ring. Moreover, the IR spectra of the product revealed the absence of exocyclic ring CO absorption. Although structure *IIa* seemed most likely to be based on similarity to the reported behaviour of indan-1, 3-diones toward ureas, an independent structural proof seemed mandatory as in the case under consideration. As the CO at position 3 is the most electrophilic centre in the molecule, it is also the most hindered one and a delicate balance in reactions of polydentate nitrogen reagents between steric factors and relative nucleuophilicities have been previously shown to exist [6, 7]. Structure *IIa* could, however, be established for the reaction product based on IR spectra which revealed ring CO at 1685 cm^{-1} lower than that anticipated for ring CO at 1710 cm^{-1}. Moreover, the compund *IIa* could be converted via diazotization and hydrolysis into the known *IIIa*, the structure of which was recently established by us [1].

Similar to *Ia*, compound *Ib* condensed with thiourea to yield a product for which structure *IIb* could be established based on IR data which revealed CO absorption at 1715 cm^{-1} typical to that anticipated for ring CO at this position. Unequivocal proof was obtained by the conversion of *IIb* by diazotization to known *IIIb* [1].

Compound *IIa, b* prepared could be converted into a variety of inden 1, 2-d pyrimidine derivatives. Thus, *IIa, b* reacted with hydrazine hydrate to yield the hydrazones *IVa, b*. Also compound *IVa, b* afforded the oxo derivatives *Va, b* on treatment with monochloroacetic acid utilizing the standard procedure for conversion of thiocarbonyl heterocycles into their oxo analogues.

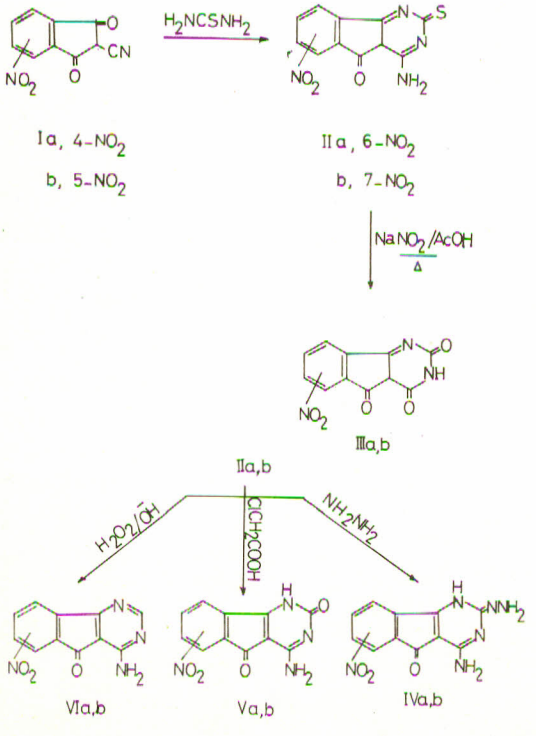
Rather, unexpectedly the attempted oxidations of *IIa, b* into the disulphides or sulphoxides has afforded in our hands the pyrimidine derivatives *VIa, b*. A similar observation has been recently reported by us [1]. The exact mechanism of this transformation is still uncertain.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were obtained on Pye-Unicum SP 1100. Analytical data were obtained from the Analytical Data Unit at Cairo University.

Table 1. Newly synthesised compounds.

Compd.	Solvent	M.p. (°C)	Yield %	Mol. Form Mol. Wt.	Found Analysis % Calcd.	C	H	N	S
1a	Benzene	154	65	$C_{10}H_4N_2O_4$	55.2	1.8	12.4	
					55.6	1.9	12.9	
Ib	Ethanol/benzene	270	60	$C_{10}H_4N_2O_4$	55.6	2.0	12.3	
					55.6	1.9	12.9	
IIa	Ethanol	115	50	$C_{11}H_6N_4O_3S$	48.0	2.0	20.0	11.5
					48.2	2.2	20.4	11.67
IIb	Ethanol	192	52	$C_{11}H_6N_4O_3S$	48.0	1.9	20.1	11.9
					48.2	2.2	20.4	11.67
IVa	Ethanol	152	45	$C_{11}H_8N_6O_3$	48.8	2.9		
					48.5	2.94		
IVb	Ethanol	132	65	$C_{11}H_8N_6O_3$	48.5	3.0		
					48.5	2.94		
Va	Ethanol	186	45	$C_{11}H_6N_4O_4$	50.8	2.6		
					51.1	2.32		
Vb	Ethanol	168	40	$C_{11}H_6N_4O_4$	51.0	2.3		
					51.1	2.32		
VIa	Ethanol	128	40	$C_{11}H_6N_4O_3$	55.0	2.6		
					54.5	2.5		
VIb	Ethanol	113	40	$C_{11}H_6N_4O_3$	55.0	2.6		
					54.5	2.5		



2-Cyano-4-nitroindan-1, 3-dione Ia and Ib. To a sodium ethoxide solution (prepared from 2.3 g of sodium metal and 35 ml absolute ethanol) were added 5 g of nitro diethyl phthalate with stirring over a 5 min period. To the resulting solution 5.8 ml of acetonitrile was added over a period of one hr. The mixture was then refluxed for 8 hr and the sodium salt was then dissolved in hot water and acidified with dil HCl acid. The precipitated solid was then crystallized from the proper solvent (Table 1).

1, 2-Dihydro-4-amino-2-thioxo-6-nitro-5H-indeno [1, 2-d] –pyrimidine IIa and the corresponding 7-nitro derivative IIb. To a sodium ethoxide solution (prepared from 2.3 g of sodium metal and 200 ml ethanol) was added a mixture of 22.8 g of *Ia* (*Ib*) and 10 g of thiourea. The mixture was refluxed for 10 hr. The solvent was then removed *in vacuo*. The remaining product was dissolved in water and acidified with dil HCl. The solid product was then crystallized from the proper solvent (Table 1).

Diazotization of IIa, b. A solution of *IIa* or *IIb* (0.01 mole) in 20 ml acetic acid and 5 ml HCl acid was treated at 5° with a solution of sodium nitrite (0.7 g) in the least amount of ethanol. The reaction mixture was left overnight at room temperature and then diluted with water. The solid

product, so formed, was then crystallized from the proper solvent (Table 1).

Reactions of IIa, b: (a). *With hydrazine hydrate.* To a solution of each of *IIa* and *IIb* (1.0 g) in 50 ml ethanol was added 1.2 ml 99% hydrazine. The reaction mixture was heated to reflux and left to cool. The solid product was then crystallized from the proper solvent (Table 1).

(b) *With monochloroacetic acid.* A suspension of 1.0 g of each of *IIa* and *IIb* in 100 ml water was treated with 1.5 g of monochloroacetic acid. The reaction was refluxed for 2 hr, reduced to 25 ml by evaporation *in vacuo* and then left to stand at room temperature. The solid product formed on standing was collected and purified by dissolution in 10% sodium hydroxide solution, filtration from insoluble impurities and reprecipitated by hydrochloric acid (Table 1).

(c) *With hydrogen peroxide.* A solution of 1.0 g of each of *IIa* and *IIb* in 20 ml (5%) of sodium hydroxide was added gradually with stirring to 1 ml of hydrogen peroxide (30%). The reaction mixture was left to stand for 2 hr and the solid formed was crystallized from a proper solvent (Table 1).

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