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THE REACTIONS OF 2-PHENYLHYDRAZONOCYANOACETANILIDE WITH ISOTHIOCYANATES, ACTIVE METHYLENE REAGENTS AND ACTIVATED NITRILES

The 1,2,4-triazin-3-thione II was synthesized via reaction of phenylisothiocyanate with I. Also I reacts with benzoyl- or ethoxycarbonyl isothiocyanate in dioxan to give IIIa and IIIb respectively. On the other hand, I reacted with benzoyl isothiocyanate in pyridine to give the 1,2,4-triazin-3-one IV. When I was treated with acetylacetone, ethyl acetoacetate or 3-chloroacetylacetone the acyclic derivatives Va, Vb and VII were obtained. The pyridazine VIII was obtained upon treatment of I with either malononitrile or ethyl cyanoacetate.

1 — INTRODUCTION

Arylhydrazone derivatives of functionalized nitriles have been utilized for the synthesis of several new heterocyclic compounds. For example arylhydrazonomesoxalonitriles were considered as starting material for the synthesis of isoxazole, pyrazole, pyrimidine, triazine, pyridazine and pyrimidine derivatives [1,2]. Also 2-arylhydrazono-3-alkanenitriles were utilized for the synthesis of aminoisoxazoles [3]. this paper reports the use of 2-phenylhydrazonocyanoacetanilide (I) [4] to obtain triazines and pyridazines.

Treatment of I with phenylisothiocyanate gave the 1,2,4-triazin-3-thione derivative. Structure II was suggested for the reaction product based on spectral and elemental data (cf. the experimental). The formation of II might be assumed to proceed via addition of reagent on the hydrazo moiety followed by cyclization to give the isolable product II. The behaviour of I towards phenylisothiocyanate is analogous to the reaction of arylhydrazonomesoxalonitrile with the same reagent [5].

Also compound I reacted with benzoyl isothiocyanate to yield IIIa. On treatment of IIIa with ethanolic sodium ethoxide solution the 1,2,4-triazin-3-one IV was obtained. The formation of IV might be assumed to proceed via hydrolysis of sulphur in compound III under the reaction conditions to give the oxygen analogue which then cyclizes via addition on the cyano function to give IV. Compound IV was obtained directly when the reaction of I with benzoyl isothiocyanate was conducted in pyridine.

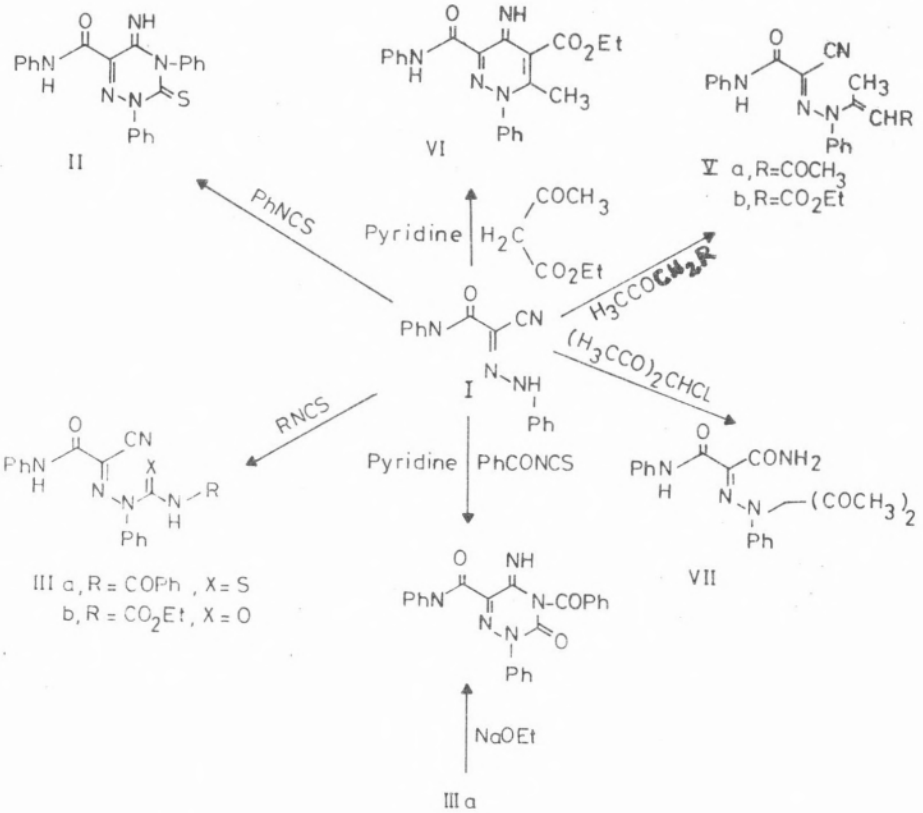
Similarly compound I reacted with ethoxycarbonyl isothiocyanate to afford the acyclic structure IIIb. Trials to effect cyclization of IIIb were unsuccessful.

Compound I reacts with acetylacetone and ethyl acetoacetate to give Va and Vb respectively. Structure Va and Vb seemed most likely based on both elemental and spectral data (cf. the experimental). On the other hand, the pyridazine derivative VI was obtained upon reaction of I with ethyl acetoacetate in pyridine. Compound VI was formed via condensation of ethyl acetoacetate with I to form the

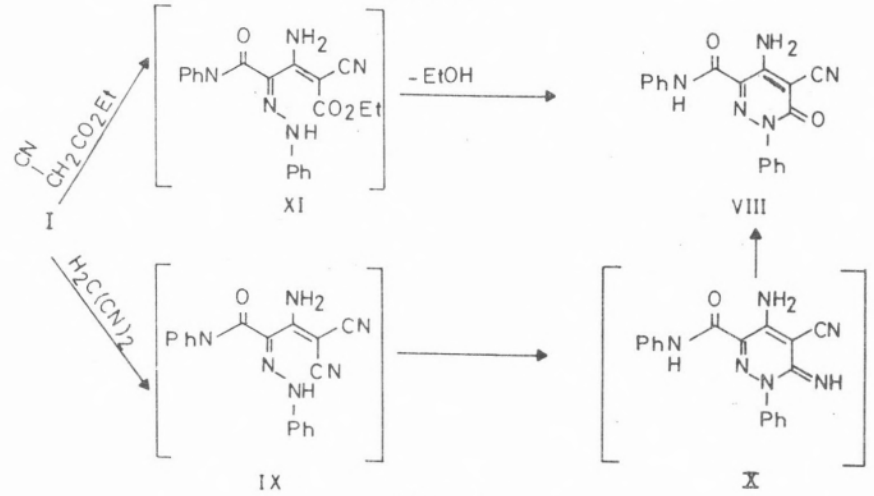
previously isolated Vb which then cyclises in situ to form VI (m.p. and mixed m.p.).

3-Chloroacetylacetone reacts with I to afford compound VII. The isolated product VII was formed on condensation of the reagent with I via loss of HCl. The moisture in the reaction medium effects partial hydrolysis of the cyano group to yield the amide VII.

Compound I reacted with ethyl cyanoacetate to yield the pyridazin-6-one VIII via intermediacy of the 1:1 adduct which then cyclises via loss of ethanol. Also compound I reacts with malononitrile to afford VIII (m.p. and mixed m.p.). Compound VIII was formed according to the sequence illustrated in scheme 2. The structure of VIII was



Scheme 1



Scheme 2

inferred from correct analytical and spectral data (cf. the experimental).

EXPERIMENTAL

All melting points are uncorrected, i.r. spectra were measured (KBr) on a Pye-Unicam SP 1000. ^{1}H-n.m.r. were measured in DMSO on a Varian A 60 MHz using TMS as internal standard and chemical shifts are expressed as δ ppm. The elemental analyses were performed in the Microanalytical Data Unit, Cairo University.

2,4-Diphenyl-6-(N-phenylcarbamoyl-5-imino-2,3-dihydro-1,2,4-triazin-3-thione (II).

A solutionof I [4] (0.01 mol) in pyridine (30 ml) was treated with phenylisothiocyanate (0.01 mol). The reaction mixture was refluxed for 6 hours. The solvent was then evaporated in vacuo. The residue was then triturated with methanol and the resulting solid product was collected by filtration.

Compound II formed yellow crystals from ethanol, m.p. 90°C, yield 85%, $\upsilon_{max.}$: 3290~3060 cm^{-1} (NH), 1600 cm^{-1} (amide CO); ^{1}H-n.m.r. 12.0 (br s, ^{1}H, NH, D_2O exchangeable), 9.0 (br s, ^{1}H, NH, D_2O exchangeable), 7.2~7.55 (m, 15H, 3Ph) (Found: C, 66.1; H, 4.5; S, 8.3 $C_{22}H_{17}N_5OS$ requires C, 66.2; H, 4.3; S, 8.0%).

Reaction of I with benzoyl isothiocyanate and ethoxycarbonyl isothiocyanate in dioxan (IIIa,b).

To a suspension of ammonium thiocyanate (0.01 mol) in dry dioxan (30 ml), either benzoyl chloride or ethyl chloroformate (0.01 mol) was added [6]. The reaction mixture was refluxed for 5 minutes then compound I (0.01 mol) was added. The reaction mixture was refluxed for 5 hours, the solvent was evaporated in vacuo and the resulting oily product was triturated with water. The solid product, so formed, was collected by filtration and identified as IIIa and IIIb respectively.

Compound IIIa formed orange crystals from ethanol, m.p. 202°C, yield 70%, $\upsilon_{max.}$: 3150~3100 cm^{-1} (NH), 2200 cm^{-1} (CN); 1645 cm^{-1} (CO), 1610 cm^{-1} (amide CO); ^{1}H-n.m.r. 11.6 (br s, 1H, NH, D_2O exchangeable), 10.3 (br s, 1H, NH, D_2O exchangeable), 7.2~7.7 (m, 15H, 3Ph) (Found: C, 65.0; H, 4.3; S, 7.4. $C_{23}H_{17}N_5O_2S$ requires C, 64.7; H, 4.0; S, 7.5%).

Compound IIIb formed orange crystals from ethanol, m.p. 198°, yield 65%, $\upsilon_{max.}$: 3200~3100 cm^{-1} (NH), 2210 cm^{-1} (CN); 1610 cm^{-1} (amide CO) (Found: C, 59.8; H, 4.3. $C_{19}H_{17}N_5O_4$ requires C, 60.2; H, 4.5%).

4-Benzoyl-2-phenyl-6-(N-phenylcarbamoyl)-5-imino-2,3-dihydro-1,2,4-triazin-3-one (IV).

The same procedure described above for the synthesis of IIIa was followed but pyridine was used as solvent instead of dioxan. The reaction mixture was refluxed for 6 hours, cooled and poured on ice. The resulting solid product was collected by filtration, washed well with water.

Compound IV forms colourless crystals from dioxan m.p. 240°C, yield 67%. $\upsilon_{max.}$: 3500~3450 cm^{-1} (NH), 1700 cm^{-1} (CO); 1610 cm^{-1} (amide CO); ^{1}H-n.m.r. 12.0 (br s, 1H, NH), 9.9 (br s, 1H, NH), 7.4~8.1 (m, 15H, 3Ph) (Found: C, 67.0; H, 4.3. $C_{23}H_{17}N_5O_3$ requires C, 67.2; H, 4.2%).

A solution of compound IIIa (0.3 g) in absolute ethanol (10 ml) was added to a solution of sodium ethoxide (prepared from 0.2 g of Na and 20 ml of absolute ethanol). The reaction mixture was refluxed for 4 hours, evaporated in vacuo and water was added. To the cold solution acetic acid was added till the solution was acidic to litmus and the solid product, so formed, was filtered off, crystallized from dioxan and identified as IV (m.p. and mixed m.p.).

Reaction of I with acetylacetone and ethyl acetoacetate (Va and Vb).

A solution of I (0.01 mol) in ethanol (50 ml) was treated with either acetylacetone or ethyl acetoacetate (0.01 mol) and few drops of piperidine. The reaction mixture was refluxed for 5 hours, concentrated by evaporation in vacuo and cooled. The resulting solid product was collected by filtration. The products were identified as Va and Vb respectively.

Compound Va formed page crystals from ethanol, m.p. 185°C, yield 70%, $\upsilon_{max.}$: 2210 cm^{-1} (CN); 1660 cm^{-1} (CO), 1610 cm^{-1} (amide CO); ^{1}H–n.m.r. 9.9 (br s, 1H, NH, D_2O exchangeable), 7.1~7.9 (m, 10H, 2Ph and =CH), 3.4 (s, 3H, CH_3); 3.8 (s, 3H, CH_3) (Found: C, 69.3; H, 5.1. $C_{20}H_{18}N_4O_2$ requires C, 69.4; H, 5.2%).

Compound Vb formed page crystals from ethanol, m.p. 190°C; yield 65%, $\upsilon_{max.}$: 2210 cm^{-1} (CN), 1660 cm^{-1} (CO); 1610 cm^{-1} (amide CO) (Found: C, 67.3; H, 4.9. $C_{21}H_{20}N_4O_3$ requires C, 67.0; H, 5.3%).

5-Ethoxycarbonyl-6-methyl-1-phenyl-3-(N-phenylcarbamoyl)-4-imino-pyridazine (VI).

The same procedure described above for the synthesis of Vb was followed but pyridine was used as solvent instead of ethanol/piperidine.

Compound VI formed colourless crystals from dioxan m.p. 250°C, yield 66%, $\upsilon_{max.}$: 3320~3030 cm^{-1} (NH), 1670 cm^{-1} (ester CO); 1640 cm^{-1} amide CO) (Found: C, 67.1; H, 5.0; $C_{21}H_{20}N_4O_3$ requires C, 67.0; H, 5.0%).

Reaction of I with 3-chloroacethylacetone (VII).

To a solution of I (0.01 mol) in ethanol (30 ml) was added 3-chloroacetylacetone (0.01 mol) and triethylamine (1 ml). The reaction mixture was refluxed for 3 hours, concentrated by evaporation in vacuo and then cooled. The resulting solid product was collected by filtration.

Compound VII forms page crystals from ethanol, m.p. 169°C, yield 75%, $\upsilon_{max.}$: 3420~3300 (NH_2), 1630 cm^{-1} (amide CO); ^{1}H-n.m.r. 10.3 (br s, 1H, NH), 7.1~7.8 (m, 13H, 2Ph, NH_2 and CH), 3,3 (m, 6H, $2CH_3$) (Found: C, 63.5; H, 5.3; $C_{20}H_{20}N_4O_4$ requires C, 63.2; H, 5.3%).

4—Amino-5-cyano-(N-phenylcarbamoyl)-pyridazin-6-one (VIII)

A solution of I (0.01 mol) in ethanol (30 ml) was treated with either malononitrite or ethyl cyanoacetate (0.01 mol) and triethylamine (1 ml) was added. The reaction mixture was refluxed for 3 hours and then evaporated in vacuo. The solid, product, so formed, was collected by filtration and crystallized from ethanol. The products obtained were found to be identical (m.p. and nixed m.p.)

Compound VIII was colourless crystals, m.p. 200°C, yield 83% υ_{max}: 3340 ~ 3310 cm^{-1} (NH_2) 2210 cm–1 (CN), 1670 cm^{-1} (CO), 1640 cm^{-1} (amide CO). ^{1}H-n.m.r. 10.5 (br s, 1H, NH), 6.95 ~ 7.7. (m, 10H, 2 Ph), 4.16 (s, 2H, NH_2) (Found: C, 65.1; H, 4.2 $C_{18}H_{13}N_5O_2$ requires C, 65.3; H, 4.0%).

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REFERENCES

[1] E. M. ZAYED, S. A. S. GHOZLAN, Z. NATURFORSCH. **40b**, 1727 (1985).
[2] F. FREEMAN, SYNTHESIS, 949 (1981).
[3] M. H. ELNAGDI, M. R. H. ELMOGHAYAR, E.A.A. HAFEZ, H. H. ELNIMA, J. Org. Chem. **40**, 2604 (1975).
[4] M. A. E. KHALIFA, A. A. ELBANNANY, G. H. TAMMAM, Curr. Sci. **51**, 1112 (1982).
[5] P. WENTERNITZ, Helv. Chim. Acta **61**, 1175 (1978).
[6] I. B. DOUGLAS and F. B. DAINS, J. Amer. Chem. Soc. **56**, 1408 (1934).

RESUMO

Reacções da 2-fenilhidrazonocianoacetanilina com isotiocianatos, reagentes com metileno activo e nitrilos activados

Sintetizou-se a 1,2,4-triazina-3-tiona II por reacção do fenilisotiocianato com I. O composto I também reage em dioxano com o isotiocianato de benzoilo ou etoxicarbonilo para dar origem a IIIa e IIIb respectivamente. Por outro lado, I reage com o isotiocinato de benzoilo em piridina para originar a 1,2,4-triazina-3-ona IV. Por tratamento de I com acetilacetona ou 3-cloroacetilacetona obtiveram-se os derivados acíclicos Va, Vb, e VII. A piridazina VIII obteve-se através do tratamento de I tanto com malonitrilo como com cianoacetato.