

SYNTHESIS OF THIAZOLO [2,3-c][1,2,4]TRIAZINES AND RELATED DERIVATIVES

R. M. ABDEL-RAHMAN AND M. M. FAWZY

Chemistry Department, Faculty of Education, Ain Shams University, Roxy, Cairo, Egypt

(Received December 9, 1990; revised April 8, 1992)

A number of thiazolo[2,3-c][1,2,4] triazines and related derivatives have been synthesised by reaction of 5,6-diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione with various bifunctional halocompounds. The structure of the new compounds were elucidated by the help of elemental analysis and spectral data.

Key words: Synthesis, Thiazolo-1,2,4-triazine, Derivatives.

Introduction

In continuation of our studies on the chemistry of 3-thioxo-1,2,4-triazine derivatives [1-5], the present work report the synthesis and chemistry of thiazolo-1,2,4-triazines which is part of a programme dealing with the synthesis and comparative chemistry of isolated and fused 1,2,4-triazines.

Results and Discussion

In this paper we found that alkylation of 2,3,4,5-tetrahydro-5,6-diphenyl-1,2,4-triazine-3-thione (I) using *p*-bromophenacyl bromide, 1,2-dibromoethane, chloroacetaldehydiethylacetal, bromopyruvic acid, chloroacetyl chloride, *N*-vinyl-*N*-(chloroacetyl) urea and *N*-phenyl-*N*-(chloroacetyl) urea in sodium ethylate at room temperature give the corresponding *S*-alkyl derivatives IIa-g. That alkylation took place at the sulphur atom [7].

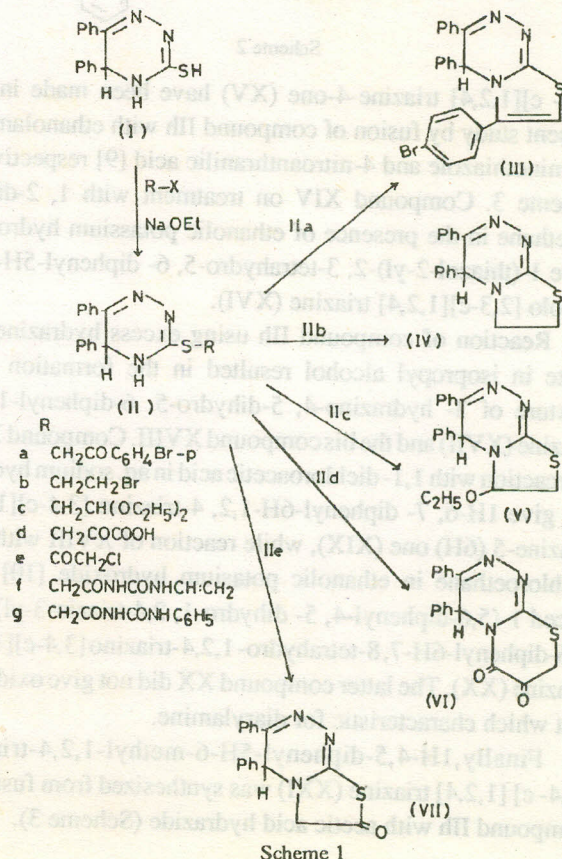
Compounds IIa-e underwent cyclization by heating the reaction mixture in sodium ethylate led to the direct formation of 3-(*p*-bromophenyl)-5,6-diphenyl-3H,5H-thiazolo [2,3-c][1,2,4] triazine (III), 2,3-dihydro-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine (IV), 2-dihydro-3-ethoxy-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine (V), 2-dihydro-6,7-diphenyl-6H-1,3-thiazino [2,3-c][1,2,4] triazine-3,4-dione (VI) and 3-dihydro-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine-2-one (VII) respectively. The route for the synthesis of these compound have been presented in Scheme 1.

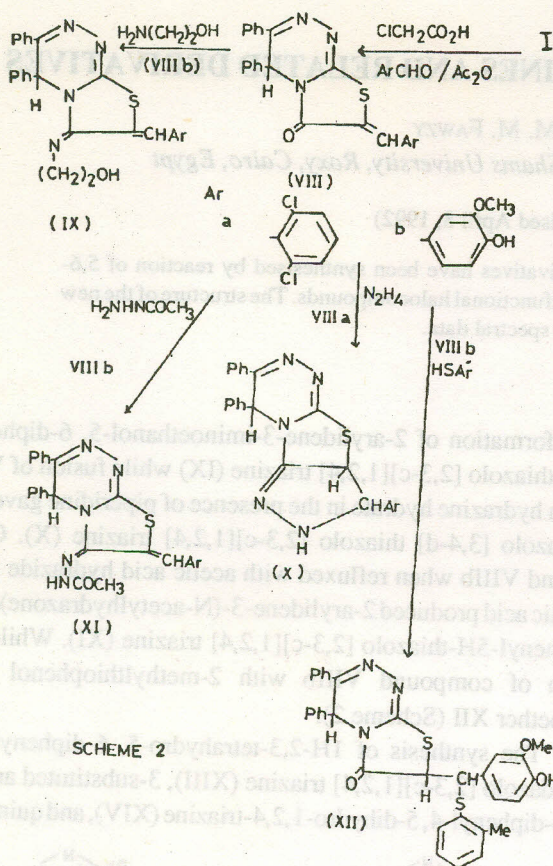
On the other hand, alkylation of compound I using monochloroacetic acid in the presence of aromatic aldehydes such as, 2,6-dichlorobenzaldehyde and/or 3-methoxy-4-hydroxybenzaldehyde with acetic anhydride and fused sodium acetate [8] yielded 2-arylidene-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine-3 (2H) one (VIIIa,b).

The reactivity of exocyclic C=C and/or C=O groups in compounds VIIIa,b prompted us to investigate their behaviour towards amine, hydrazine, acid hydrazide and thiophenol. Thus, fusion of compound VIIIb with ethanolamine resulted in

the formation of 2-arylidene-3-iminoethanol-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine (IX) while fusion of VIIIa with hydrazine hydrate in the presence of piperidine gave 1H-pyrazolo [3,4-d] thiazolo [2,3-c][1,2,4] triazine (X). Compound VIIIb when refluxed with acetic acid hydrazide in gl. acetic acid produced 2-arylidene-3-(*N*-acetylhydrazone)-5,6-diphenyl-5H-thiazolo [2,3-c][1,2,4] triazine (XI). While, fusion of compound VIIIb with 2-methylthiophenol gave thioether XII (Scheme 2).

The synthesis of 1H-2,3-tetrahydro-5,6-diphenyl-5H-imidazolo [2,3-c][1,2,4] triazine (XIII), 3-substituted amino-5,6-diphenyl-4,5-dihydro-1,2,4-triazine (XIV), and quinazolo





SCHEME 2

Scheme 2

[2,3-*c*][1,2,4] triazine-4-one (XV) have been made in our present study by fusion of compound IIIh with ethanolamine, 2-aminothiazole and 4-nitroanthranilic acid [9] respectively, Scheme 3. Compound XIV on treatment with 1, 2-dibromoethane in the presence of ethanolic potassium hydroxide gave 1-(thiazol-2-yl)-2, 3-tetrahydro-5, 6-diphenyl-5H-imidazo [2,3-*c*][1,2,4] triazine (XVI).

Reaction of compound IIIh using excess hydrazine hydrate in isopropyl alcohol resulted in the formation of a mixture of 3-hydrazino-4, 5-dihydro-5, 6-diphenyl-1,2,4-triazine (XVII) and the bis compound XVIII. Compound XVII on reaction with 1,1-dichloroacetic acid in aq. sodium hydroxide give 1H-6, 7-diphenyl-6H-1,2, 4-triazino [3,4-*c*][1,2,4] triazine-5 (6H) one (XIX), while reaction of XVIII with 1,2-dichloroethane in ethanolic potassium hydroxide [10] produced 1-(5,6-diphenyl-4, 5-dihydro-1, 2,4-triazin-3-yl)-2H-5,6-diphenyl-6H-7,8-tetrahydro-1,2,4-triazino [3,4-*c*][1,2,4] triazine (XX). The latter compound XX did not give oxidation test which characteristic for diarylamine.

Finally, 1H-4,5-diphenyl-5H-6-methyl-1,2,4-triazolo [3,4-*c*] [1,2,4] triazine (XXI) was synthesized from fusion of compound IIIh with acetic acid hydrazide (Scheme 3).

Experimental

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer 521 spectrophotometer (ν_{\max} in cm^{-1}), UV spectra were recorded in pure ethanol on a Perkin Elmer 550 S uv vis spectrophotometer (λ_{\max} in nm) and ¹H-NMR spectra in CDCl₃ solution with TMS as internal standard ($\delta=0$, ppm) are recorded on Varian EM 390 90 MHz NMR spectrometer. 5,6-Diphenyl-2,3,4,5-tetrahydro-1,2,4-triazine-3-thione (I) [6] and 3-ethylthio-4, 5-dihydro-5, 6-diphenyl-1,2,4-triazine (IIIh) [7] were prepared following the procedure described.

Alkylation of I: Formation of S-alkyl derivatives IIa-g. A mixture of I (0.01 mol) was dissolved in abs. ethanol (50 ml) containing sodium ethoxide (0.01 mol, 50 ml) and then treated with the appropriate alkyl halide (0.01 mol). The reaction mixture was left overnight. The crystalline product was filtered and recrystallized from the proper solvent to give IIa-g (Table 1). PMR (IIa); 1.8-2.2 (*m*, 4H, -CH₂-CH₂-), 7.2-7.7 (*m*, 14H, aromatic protons) and 8.2 (*s*, 1H, NH of N⁴-1,2,4-triazine moiety). IR (IIa): 3200 (NH), 2890 (CH₂), 1720-1680 (C=O), 1580 (C=N), 1480 (def. CH₂), 1180 (C-S), 1050 (R-O-Ar), and 700 (C-Br), IIb: 3220-3150 (NH), 2880 (CH₂), 1620 (C=N), 1490 (def. CH₂), 1180 (C-S), and 650 (C-Br), IIc: 3200-3180 (NH), 2860 (CH₂), 1650 (C=N), 1490 (def. CH₂) and 1170 (C-S), IId: 3390 (OH), 3200 (NH), 2910 (CH₂), 1710-1650 (C=O), 1560 (C=N), 1440 (def. CH₂ and 1170 (C-S), IIe: 3280 (NH), 2910 (CH₂), 1740-1650 (C=O), 1570 (C=N), 1480 (def. CH₂) and 1180 (C-S), and IIg: 3280 (NH), 2910 (CH₂), 1740-1650 (C=O), 1570 (C=N), 1475 (def. CH₂) and 1180 (C-S).

Synthesis of compounds III-VII. The S-alkyl derivatives (IIa-e) (0.01 mol) and sodium ethylate (0.01 mol) were heated under reflux for 2 hrs. The reaction mixture was cooled and acidified with dil. HCl. The solid obtained washed with hot water and crystallized from the proper solvent to give III-VII (Table 1). PMR (III); 2.5-3 (*m*, 4H, -CH₂-CH₂-) and 7.1-7.5 (*m*, 14H of aromatic protons of 1,2,4-triazine moiety). IR (III): 2820 (CH₂), 1580 (C=N), 1170 (C-S) and 700-600 (C-Br), (V): 2820 (CH₂), 1560 (C=N), 1480 (def. CH₂), and 1190 (C-S) and 1050 (R-O-Ar). (VI): 3350 (OH), 2820 (CH₂), 1750-1650 (C=O), 1570 (C=N), 1490 (def. CH₂) and 1180 (C-S), and (VII): 3350 (OH), 2910 (CH₂), 1700-1680 (C=O), 1620 (C=N), 1490 (def. CH₂) and 1170 (C-S).

2-Arylmethylene-5,6-diphenyl-5H-thiazolo [2,3-*c*] [1,2,4] triazin-3(2H)-one (VIIIa,b). A mixture of I (0.01 mol), monochloroacetic acid (0.01 mol), fused sodium acetate (3 gm), gl. acetic acid (9 ml), acetic anhydride (6ml) and the appropriate aldehydes (0.01 mol) was refluxed for 1 hr. The reaction mixture was cooled and the solid that crystallized out was filtered, washed with hot water and then with ethanol to give

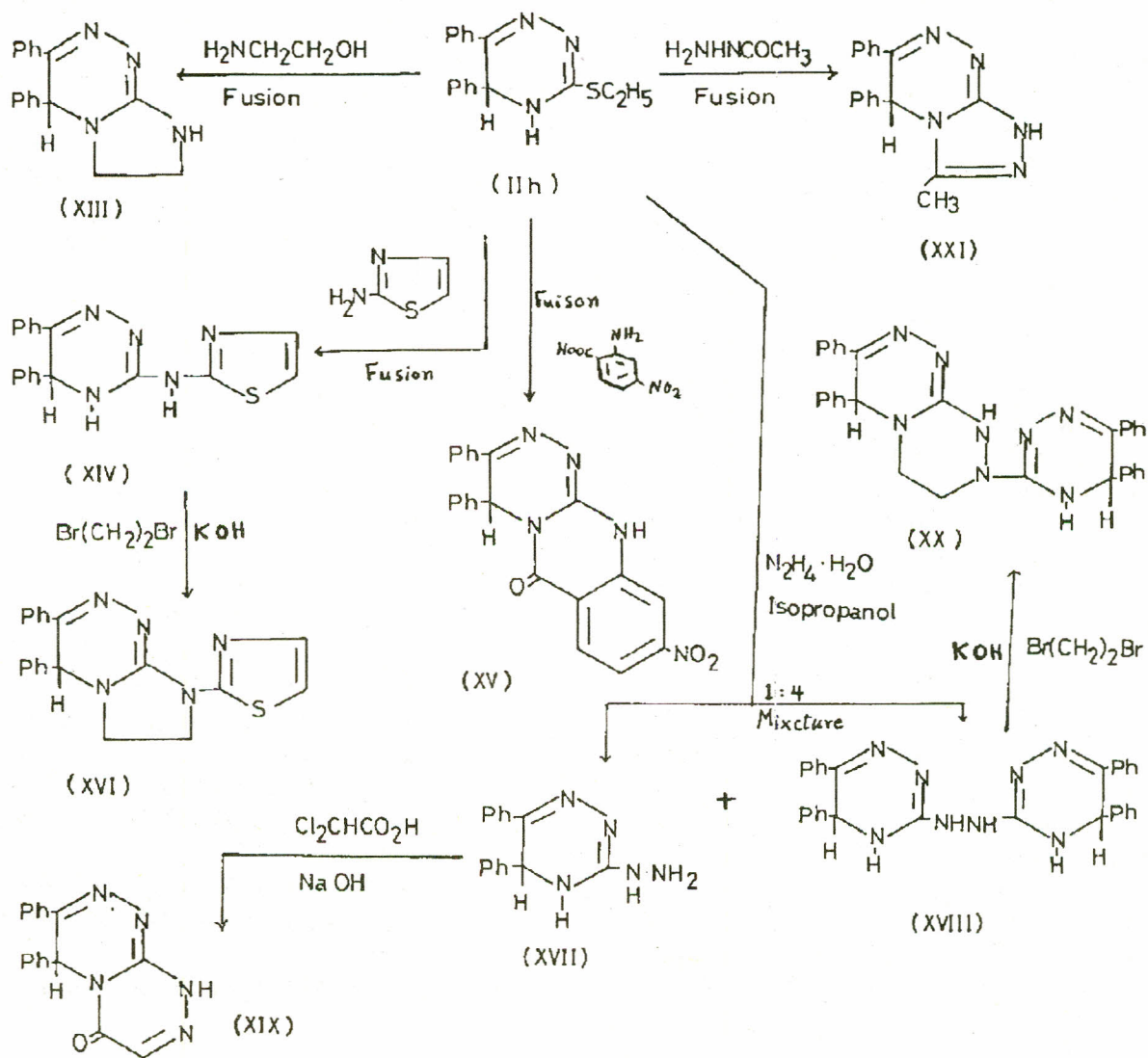
VIIIa, b (Table 1). UV (VIIIb): 350, 240 and 195, IR (VIIIb): 3350 (OH), 2900 (CH_2), 1720 1680 ($\text{C}=\text{O}$), 1570 ($\text{C}=\text{N}$), 1450 (def. CH_2) and 1150 ($\text{C}-\text{S}$) and PMR (VIIIb): 2.4 (s, 3H, CH_3), 3.4 (s, 1H, $\text{C}=\text{CH}$ exocyclic), 4.3 (s, 1H, 5H of 1,2,4-triazino), 7.4-7.6 (m, 3H, aryl moiety), 7.9-7.6 (m, 10H), aromatic protons of 1,2,4-triazino) and 8.2 (s, 1H, OH of phenolic proton).

Fusion of VIII with primary amines: Formation of IX, X and XI. An equimolar mixture of VIIIb and ethanolamine, acetic acid hydrazide and/or VIIIa with hydrazine hydrate, were heated at 160-180° for 2 hrs. The residue was triturated with methanol and the solid obtained was crystallized to give IX, X and XI (Table 1). UV: (IX) 368, 275, 240 and 192; PMR (IX): 3.3-3.6 (m, 4H, $-\text{CH}_2-\text{CH}_2-$), 5.5 (s, 1H, $\text{C}=\text{CH}$), 6.6-7.7 (m, 13H, aromatic protons of 1,2,4-triazine and arylidene moieties) and 8.9 (s, 1H, OH of ethanolimino); IR (IX): 3510 (OH), 2920 (CH_2), 1570 ($\text{C}=\text{N}$), 1500 (def. CH_2), and 1190

($\text{C}-\text{S}$), (X); 3320-3220 (NH), 2910 (CH_2), 1600 ($\text{C}=\text{N}$), 1490 (def. CH_2), 1170 ($\text{C}-\text{S}$) and 700 ($\text{C}-\text{Cl}$), (XI): 3350 (OH), 3220-3100 (NH), 828 (CH_2), 1700 1680 ($\text{C}=\text{O}$), 1580 ($\text{C}=\text{N}$), 1480 (def. CH_2), and 1125 ($\text{C}-\text{S}$).

Thioether derivative XII. A mixture of VIIIb (0.01 mol) and 2-methylthiophenol (0.01 mol) was heated at 180-200° for 6 hrs. The reaction mixture was triturated with pet. ether 40-60 and the solid obtained was crystallized to give XII (Table 1). IR: 3450 (OH), 2900 (CH_2), 1750 1700 ($\text{C}=\text{O}$), 1570 ($\text{C}=\text{N}$), 1480 (def. CH_2), 1350 (NCS) and 1180 ($\text{C}-\text{S}$).

Synthesis of heterobicyclic systems XIII, XIV, XV and XXI. An equimolar mixture of IIh and ethanolamine, 2-aminothiazole, 4-nitroanthranilic acid and/or acetic acid hydrazide was heated at 160-180° for 1 hr. The solid obtained was crystallized from the proper solvent to give XIII, XIV, XV and XXI (Table 1). IR: (XIII): 2890 (CH_2), 1570 ($\text{C}=\text{N}$) and 1490



Scheme 3

(def. CH₂). PMR (XIII): 3.6(s, 2H, -CH₂), 4-3.8 (t, 2H, Sc. CH₂) 4.9 (s, 1H, 5H of 1,2,4- triazino), 7.3-7.7 (m, 10H, aromatic protons of 1,2,4-triazino) and 8(s, 1H, NH of imidazolo). IR (XIV): 3400, 3200 (NH), 1630 (C=N) and 1350 (NCS), (XV) 3350 (NH), 1680 (C=O), 1620 (C=N) and 1530, 1340 (asy. & sy. NO₂). UV (XV): 350 340, 250, 240 and 195. IR (XXI) 3300, 3200 (NH), 2910 (CH₂), 1590 (C=N) and 1490 (def. CH₂).

1-(Thiazol-2-yl)-2,3-tetrahydro-5,6-diphenyl-5H-imidazolo [2,3-c][1,2,4] triazine (XVI). A mixture of XIV (0.01 mol) and 1,2-dibromo ethane (0.01 mol) in ethanolic potassium hydroxide (10%, 100 ml) was refluxed for 2hrs,

TABLE 1. PHYSICAL DATA OF THE COMPOUNDS II-XXI.

Compd. No.	Solvent	M. P. (°C)	Yield (%)	Mol. formula*
IIa	EtOH	130-132	80	C ₂₃ H ₁₈ N ₃ SBr ⁺ O
IIb	EtOH	112-114	65	C ₁₇ H ₁₆ N ₃ SBr ⁺⁺
IIc	EtOH	185-186	60	C ₂₁ H ₂₅ N ₃ SO ₂
IId	EtOH	155-157	70	C ₁₈ H ₁₅ N ₃ CO ₃
IIE	EtOH	95 - 96	60	C ₁₇ H ₁₄ N ₃ SCI ⁺⁺⁺ O
IIf	EtOH	210-212	67	C ₂₀ H ₁₉ N ₃ SO ₂
IIg	EtOH	185-187	70	C ₂₄ H ₂₁ N ₃ SO ₂
III	DMF	153-154	65	C ₂₃ H ₁₆ N ₃ SBr ⁺
IV	MeOH	299-300	50	C ₁₇ H ₁₅ N ₃ S
V	DMF	125-127	55	C ₁₉ H ₁₉ N ₃ SO
VI	DMF	180-181	60	C ₁₈ H ₁₃ N ₃ SO ₂
VII	MeOH	249-250	70	C ₁₇ H ₁₃ N ₃ SO
VIIIa	AcOH	148-150	75	C ₂₄ H ₁₅ N ₃ SCI ₂ ⁺⁺ O
VIIIb	AcOH	180-181	70	C ₂₅ H ₁₉ N ₃ SO ₃
IX	MeOH	240-241	50	C ₂₇ H ₂₄ N ₄ SO ₃
X	EtOH	120-122	60	C ₂₄ H ₁₇ N ₃ SCI ₂ ⁺⁺⁺
XI	AcOH	240-241	50	C ₂₇ H ₂₃ N ₃ SO ₃
XII	C ₆ H ₆	112-115	60	C ₃₂ H ₂₇ N ₃ S ₂ O ₃
XIII	Dil.EtOH	165-167	55	C ₁₇ H ₁₆ N ₄
XIV	EtOH	155-156	70	C ₁₈ H ₁₅ N ₃ S
XV	AcOH	80-181	50	C ₂₂ H ₁₅ N ₃ O ₃
XVI	DMF	210- 11	60	C ₂₀ H ₁₇ N ₃ S
XVII	Dil.EtOH	142-144	20	C ₁₅ H ₁₅ N ₃
XVIII	DMF	290-293	70	C ₃₀ H ₂₆ N ₈
XIX	AcOH	171-172	65	C ₁₇ H ₁₃ N ₃ O
XX	MeOH	240-43	60	C ₃₂ H ₂₈ N ₈
XXI	EtOH	260-262	70	C ₁₇ H ₁₅ N ₃

* All the compounds gave satisfactory C,H,N and S analysis.

+ Found: Br,16.4, Calc: Br,17.2% + Found: Br,17.2, Calc: Br,17.9%
 ++ Br, 20.7, Br, 21.4% ++ Cl, 14.5, Cl, 15.3%
 +++ Cl, 9.6, Cl, 105% +++ Cl, 14.4, Cl, 14.9%

cooled and the solid obtained was filtered and crystallized to give XVI (Table 1). IR: 2950 (CH₂), 1640 (C=N), 1450 (def. CH₂) and 1170 (C-S).

Reaction of IIh with hydrazine hydrate: Formation a mixture of XVII and XVIII. A mixture of IIh (0.01 mol) and hydrazine hydrate (0.01 mol) in isopropyl alcohol (100 ml) was refluxed for 3 hrs, filtered while hot, the solid obtained is XVIII, and the solid which obtained after cooling and dilution was crystallized to give XVII (Table 1). IR (XVII): 3380 (NH₂), 3100 (NH), 1610 (def. NH₂) and 1570 (C=N).

1,2,4-Triazino [3,4-c][1,2,4] triazinone (XIX). A mixture of XVII (0.01 mol) and 1, 1-dichloroacetic acid (0.01 mol) in aq. sodium hydroxide (10 %, 100 ml) was refluxed for 4 hrs, cooled and acidified with dil. HCl. The solid obtained crystallized to give XIX (Table 1). IR: 328 (NH), 2900 (CH₂), 1700-1670 (C=O), 1600 (C=N), and 1480 (def. CH₂).

Reaction of XVIII with 1, 2-dibromoethane: Formation of XX. A mixture of XVIII (0.01 mol) and 1, 2-dibromoethane (0.01 mol) in ethanolic potassium hydroxide (10%, 100 ml) was refluxed for 1 hr, cooled and diluted with aq. HCl. The solid obtained was crystallized to give XX (Table 1), IR: 3300, 3200 (NH), 2910 (CH₂), 1630 (C=N) and 1480 (def. CH₂), PMR: 4-5 (m, 4H, -CH₂-CH₂-), 6.6-7.6 (m, 20H, of aromatic protons of fused and isolated 1,2,4-triazine moieties) and 8.8 (s, 1H, NH of fused 1,2,4- triazine moiety).

References

- H. Zaher, H. Jahine, M. Seada and R. Mohammady, Pak. j. sci. ind. res., **34**, 4 (1982).
- H. Zaher, R. Mohammady and Y. A. Ibrahim, J. Heterocycl Chem., **21**, 905 (1984).
- R. M. Abdel-Rahman, Pak. j. sci. ind. res., **30**, 490 (1987).
- R.M. Abdel-Rahman and M. S. Abdel-Malik, Pak. j. sci. ind. res., **33**, 142 (1990).
- R. M. Abdel-Rahman, II Farmaco, **46**, 379 (1991).
- S. S. Amagin, V. E. Bogacheva, USSR 432, (Cl. CO 7d); Chem. Abstr., **81**, 469 (1974).
- M. I. Ali, A. M. Abdel-Fattah, H. A. Hammouda and S. M. Hussein, Indian J. Chem., **13** (2), 109 (1975).
- M. I. Ali, Abdou A. El-Sayed, and H. A. Hammouda, J. Prakt Chem., **316** (1), 163 (1974); Chem. Abstr., **81** (9), 391 (1974).
- A. K. Mansour, S. B. Awad, and S. Antoun, Z. Naturforsch. Teil-B 1974, **29** (11/12) 792-6; Chem., Abstr., **83**, 625 (1975).
- R. M. Abdel-Rahman, Pak. j. sci. ind. res., **33**, 520 (1991).