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SYNTHESIS OF SOME NEW 3-THIOXO-1,2,4-TRIAZINONE DERIVATIVES

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Synthesis of some new 3-thioxo-1,2,4-triazinone derivatives starting from the corresponding N^1 – substituted thiosemicarbazides,1,4-disubstituted thiosemicarbazides and N^1-substituted thiosemicarbazone-4 has been described. The structure of the compounds synthesized have been established by chemical and spectral data. The antibacterial activity of some compounds prepared have been evaluated.

Key words: Synthesis of 3-thioxo-1,2,4-triazinone derivatives, Antibacterial activity.

INTRODUCTION

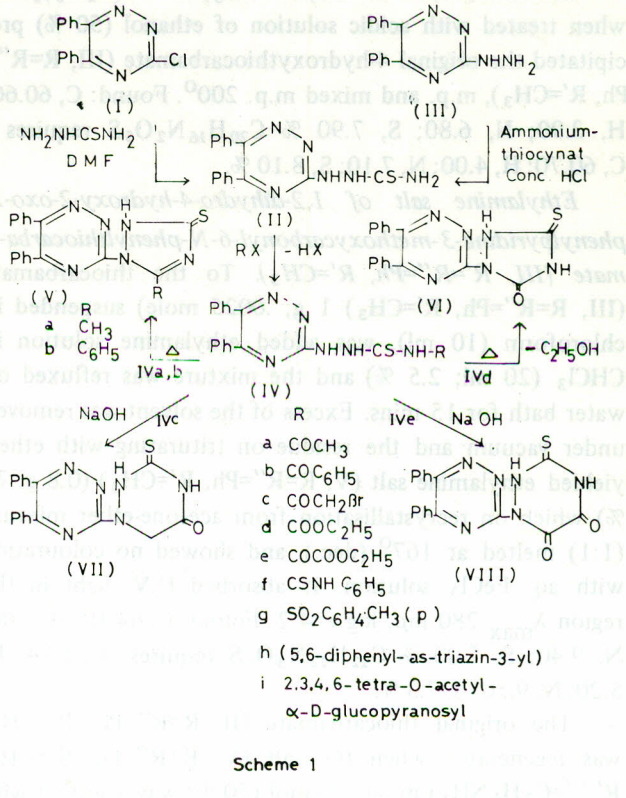
In continuation of our earlier work on 3-thioxo-1,2,4-triazine derivatives [1-3], the present work reports the synthesis of some new 3-thioxo-1,2,4-triazinone derivatives containing a 5,6-diphenyl-1,2, 4-triazine moiety with a view of evaluating their antibacterial activity.

Interaction of 3-chloro-5,6-diphenyl-1,2,4-triazine (I) with thiosemicarbazide in the presence of DMF gave the 1-(5,6-diphenyl-1, 2, 4-triazin-3-yl)-thiosemicarbazide (II) which was also obtained by treatment of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (III) with ammoniumthiocyanate in the presence of HCl (c.f. Scheme 1).

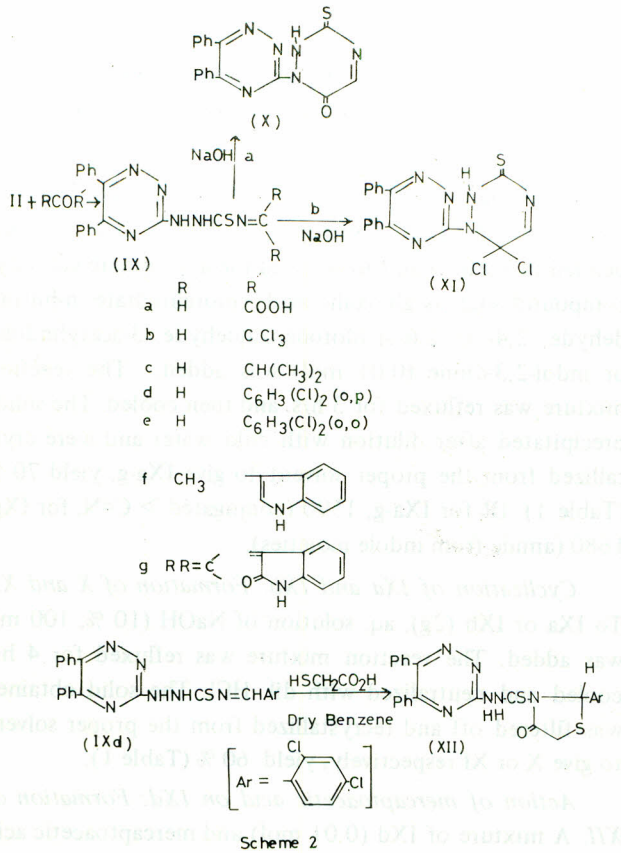
Reaction of II with acid halides, α-halo acid halides, esters, substituted thioisocyanate, or aryl halides, in alkaline medium resulted in the formation of 1,4-disubstituted thiosemicarbazides (IVa-i) as shown in Scheme 1. The structures of IVa-i were established in the following way: [i] presence of an NH band in the IR spectra with disappearance of NH_2 band, as well as strong bands at 1640-1630 (C=O) and 1550 cm^{-1} (CNH of monosubstituted amide). [ii] IVa-i when refluxed with aromatic aldehydes and recovered unchanged. [iii] Solubility of IV in aq. NaOH and [iv] The IR spectra of IVc showed broad bands at 2990-2940 (Str. . .CH_2), 1450-1440 (def. CH_2-Br) and 600-580 cm^{-1} (C-Br), while that of IVg exhibited two bands at 1350-1325 and 1160-1155 cm^{-1} (SO_2NH-). From the above results we can conclude that acylation and alkylation of II takes place as expected at the unsubstituted nitrogen of the thiosemicarbazide moiety [4].

The reactivity of IV at the N^4 and N^1 positions in IVa-e promoted us to investigate their behaviour towards the action of heat or alkaline medium [5]. Thus, IVa,b when heated above their m.ps, produced 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-monosubstituted-1,2,4-traizole-3 (2H) – thione (Va,b), while pyrolysis of IVd yielded 1-(5,6-diphenyl-1,2,4-traizin-3-yl)1-2,4-triazole-5 (2H, 4H) one-3-thione (IV). On the other hand, basic cyclization of IVc and IVe produced 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-dihydro-1,2,4-triazin-5-(2H, 4H)-one-3-thione (VII) and 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1,2,4-triazin-5,6 (2H, 4H)-dione-3-thione (VIII) respectively (Scheme 1).

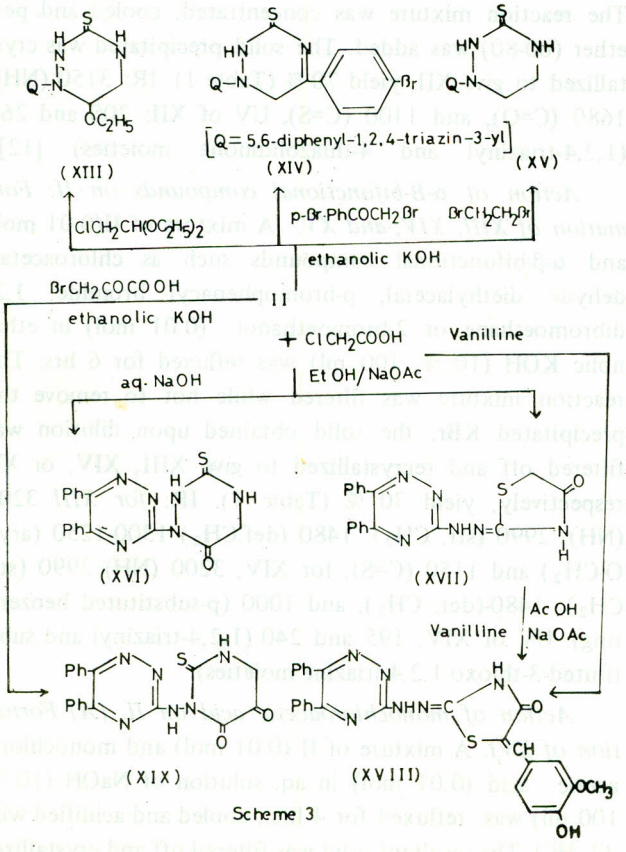
Condensation of II with aldehydes and ketones in the presence of gl. acetic acid-sodium acetate led to direct formation of 4-thiosemicarbazone derivatives (IXa-g). Reflexing IXa,b with aq. 2N NaOH afforded 1-(5,6-di-



Scheme 1



Scheme 2



Scheme 3

phenyl-1,2,4-triazin-3-yl)-1,2,4-triazin-6(2H, 5H) one-3-thione(X) and 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-6-dichloro-1,2,4-triazin-3(2H, 5H)-thione (XI) (c.f. Scheme 2).

Addition of mercaptoacetic acid [6] to aldehyde-4-thio-semicarbazone (IXd) and further condensation furnished the 2,3-disubstituted 4-thiazolidinone (XII) (Scheme 2). The structure of XII was detected from IR and UV spectrometric data.

Cyclization of II with β-bifunctional compounds [7] such as chloroacetaldehyde diethylacetal, *p*-bromophenacyl bromide, 1,2-dibromoethane or 2-bromoethanol with ethanolic KOH yielded the 1-(5,6-diphenyl-1,4-triazin-3-yl)-3-thioxo-[5-dihydro-6(2H, 4H, 6H)-ethoxy-1,2,4-triazine (XIII) 5(2H, 5H)-aryl-6-dihydro-1,2,4-triazine(XIV) and 2, 4,5,6-hexahydro-1,2,4-triazine (XV)] respectively (Scheme 3).

Investigation of the reaction of II with monochloroacetic acid indicates that the course of this reaction is governed by the medium and the reaction conditions. Thus, 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-dihydro-1,2,4-triazin-6 (2H, 4H)-one-3-thione (XVI) was obtained from reaction of II with monochloroacetic acid in the presence of aq. NaOH, while the 4-thiazolidinone derivative (XVII) derived from reaction of II and monochloroacetic acid in EtOH-sodium acetate [8]. (Scheme 3). The structure of XVII followed from the fact of condensation with vanilline in gl. acetic acid in the presence of sodium acetate gave the product XVIII, which was obtained directly by refluxing II with monochloroacetic acid and vanilline, under similar condition [9].

On the other hand, treatment of II with bromopyruvic acid in ethanolic KOH gave 3-substituted amino -5,6-diphenyl-1,2,4-triazine (XIX).

Furthermore, the compound XIX did not give a positive test for acidity which confirmed the suggested cyclic structure of XIX.

Antibacterial activity. The *in vitro* antibacterial activity of II and IVf-i in 1 % methanol was tested by the diffusion method [3], against the gram+ve bacteria *Bacillus subtilis* ATCC 6633, and against *Escherichia coli* as gram –ve bacterium. The presence of methanol caused no visible change in the bacterial growth. The previous results confirmed the suitability of IVi as antibacterial agent against *Escherichia coli,* and IVg as antibacterial agent against *Bacillus subtilis.* In addition, II had a good antibacterial activity against *Bacillus subtilis* and *Escherichia coli* (Table 2).

EXPERIMENTAL

Procedure

Melting points reported are uncorrected. UV spectra were recorded in pure ethanol on a Perkin-Elmer 550 S uv-Vis spectrophotometer (λ_{max} in nm). IR spectra in KBr on a Perkin-Elmer 521 spectrophotometer (νmax in cm^{-1}), and PMR spectra in $CDCl_3$ solution with $(CH_3)_4Si$ as internal standard (δ = 0 ppm) are recorded on Various HA-60 spectrometer. 3-Chloro-3-hydrazino-5,6-diphenyl-1,2,4-triazine were prepared by reported method [10].

Formation of 1-(5,6-diphenyl-1,2,4-triazin-3-yl) thiosemicarbazide (II) from. (a) *Reaction of thiosemicarbazide with I.* A mixture of equimolar amounts of I and thiosemicarbazide in dimethylformamide (100 ml) was refluxed for 1 hr., cooled neutralized with very dil, hydrochloric acid, and the resultant solid was filtered off and recrystallized from propan-2-ol to give II as orange crystals, m.p. 205°C. Yield 90 % (Found: C, 60.00; H, 4.30; N, 26.00 ; S, 9.85 % $C_{16}H_{14}N_6S$ requires C, 59.62; H, 4.34 N, 26.08; S, 9.93 %). IR: 3350, 3200 (NH_2 and bonded NH), 1600 (def. NH_2) and 1150-1140 (C=S).

(b) *Reaction of ammoniumthiocyanate-conc. HCl with III.* A mixture of III (0.01 mol.), ammoniumthiocyanate (0.03 mol.), concentrated HCl (5 ml) and 250 ml of ethanol was heated under reflux for 12 hrs., the solvent was distilled and water added. The solid obtained was filtered off and crystallized to give II, identified by m.p. and its IR spectrum.

Acylation and alkylation of II. Formation of 1,4-disubstituted thiosemicarbazides (IVa-I). A mixture of II(0.01 mol) and acetylcholride, benzoylchloride, bromoacetylbromide, ethylchloroformate, diethyloxalate, phenylthioisocyanate, p-toluenesulphonylchloride, 3chloro-5,6-diphenyl-1,2,4-triazine, or 2,3,4,6-tetra O-acetyl-α-D-glucopyranosylbromide (0.01 mol) in ethanolic KOH (5 %, 100 ml) was refluxed for 1hr., cooled and poured over crushed ice-conc. HCl. The solid obtained after evaporation of the organic layer gave the corresponding 1,4-disubtituted thiosemicarbazide (IVa-i), yield 40 % (Table 1).

Pyrolysis of IVa, IVb and IVd: Formation of Va, Vb and VI. Compounds IVa, IVb or IVd (2g) was heated (oil-bath) at 150°C for 15 min., cooled, the resultant solid recrystallized from the proper solvent to give Va, Vb or VI, yield 80 % (Table 1).

Basic cyclization of IVc, IVe: Formation of VII and VIII. To IVc or IVe (2g) aq. solution of NaOH (10 %, 100 ml) was added. The reaction mixture was refluxed for 4 hrs., cooled, neutralized with dil. HCl and the precipitated solid was recrystallized to give VII or VIII, yield 80 %. (Table 1). IR: for VII, 3200 (NH), 2990 (str. CH_2), 1700 (C=O) and 1150 (C=S), for VIII, 1730 and 1710 (α-diketone) [11].

Condensation of II with aldehydes and ketones: Formation of IXa-g. Compound II (0.015 mol) was suspended in acetic acid (30 ml) and the appropriate carbonyl compound such as glyoxalic acid, chloralhydrate, n-butraldehyde, 2,4- or 2,6-dichlorobenzaldehyde, 3-acetylindole, or indol-2,3-dione (0.01 mol) was added. The reaction mixture was refluxed for 3 hrs. and then cooled. The solids precipitated after dilution with cold water and were crystallized from the proper solvent to give IXa-g, yield 70 % (Table 1). IR for IXa-g, 1590 (conjugated > C=N; for IXg, 1680 (amide from indole moieties).

Cyclization of IXa and IXb: Formation of X and XI. To IXa or IXb (2g), aq. solution of NaOH (10 %, 100 ml) was added. The reaction mixture was refluxed for 4 hrs cooled and neutralized with dil. HCl. The solid obtained was filtered off and recrystallized from the proper solvent to give X or XI respectively, yield 60 % (Table 1).

Action of mercaptoacetic acid on IXd: Formation of XII. A mixture of IXd (0.01 mol) and mercaptoacetic acid (0.01 mol) in dry benzene (50 ml) was refluxed for 6 hrs The reaction mixture was concentrated, cooled and pet. ether (60-80) was added. The solid precipitated was crystallized to give XII, yield 70 % (Table 1). IR: 3150 (NH), 1680 (C=O), and 1100 (C=S), UV of XII: 200 and 265 (1,2,4-triazinyl and 4-thiazolidinone moieties) [12].

Action of α-B-bifunctional compounds on II: Formation of XIII, XIV, and XV. A mixture of II(0.01 mol) and α-β-bifunctional compounds such as chloroacetaldehyde diethylacetal, p-bromophenacyl bromide, 1,2-dibromoethane or 2-bromoethanol (0.01 mol) in ethanolic KOH (10 %, 100 ml) was refluxed for 6 hrs. The reaction mixture was filtered while hot to remove the precipitated KBr, the solid obtained upon dilution was filtered off and recrystallized to give XIII, XIV, or XV respectively, yield 70 % (Table 1). IR: *for XIII* 3200 (NH), 2990 (str. CH_2), 1480 (def.CH_2) 1300-1250 (aryl-O-CH_2) and 1150 (C=S); for XIV, 3200 (NH) 2990 (str. CH_2), 1480-(def. CH_2), and 1000 (p-substituted benzene ring). UV of XIV: 195 and 240 (1,2,4-triazinyl and substituted 3-thioxo-1,2,4-triazine moieties).

Action of monochloroacetic acid on II. (A) Formation of XVI. A mixture of II (0.01 mol) and monochloroacetic acid (0.01 mol) in aq. solution of NaOH (10 %, 100 ml) was refluxed for 4 hrs., cooled and acidified with dil. HCl. The resultant solid was filtered off and crystallized to give XVI, yield 60 % (Table 1).

Table 1. Physical data of the compounds prepared

Compd. No.	Crystallized from	m. p°, Mol. formula °C	Analysis Found % (Calc.) C	H	N	S	Cl
IVa	Ac OH	190, $C_{18}H_{16}N_6$ S O	59.00	4.20	22.90	8.60	–
			(59.34)	(4.39)	(23.07)	(8.79)	–
IVb	Ac OH	115, $C_{23}H_{18}N_6SO$	64.57	4.10	19.50	7.20	
			(64.78)	(4.22)	(19.71)	(7.51)	–
IVc	Ethyl benzene	118, $C_{18}H_{15}N_6SBrO^+$	48.60	3.23	18.75	7.40	
			(48.75)	(3.38)	(18.96)	(7.22)	–
IVd	Benzene	168, $C_{19}H_{18}N_6SO_2$	57.70	4.50	21.20	8.00	–
			(57.85)	(4.56)	(21.31)	(8.12)	–
IVe	Benzene	210, $C_{20}H_{18}N_6SO_3$	56.65	4.00	20.00	7.48	–
			(56.87)	(4.26)	(19.90)	(7.58)	–
IVf	Ethanol	225, $C_{23}H_{19}N_7S_2$	60.20	4.00	20.90	13.61	
			(60.39)	(4.15)	(21.44)	(14.00)	–
IVg	Benzene	135, $C_{23}H_{20}N_6S_2O_2$	57.67	4.10	17.40	13.24	–
			(57.98)	(4.20)	(17.64)	(13.44)	–
IVh	Ethyl acetate	120, $C_{31}H_{23}N_9S$	67.00	4.00	22.50	5.28	
			(67.26)	(4.15)	(22.78)	(5.78)	–
IVi	Ethanol	190, $C_{30}H_{32}N_6SO_9$	55.07	4.75	12.80	4.55	–
			(55.21)	(4.90)	(12.88)	(4.90)	–
Va	Methanol	250, $C_{18}H_{14}N_6S$	62.30	4.00	24.10	8.94	–
			(62.42)	(4:04)	(24.27)	(9.24)	–
Vb	Methanol	265, $C_{23}H_{16}N_6S$	67.45	3.67	20.20	7.54	–
			(67.64)	(3.92)	(20.58)	(7.84)	–
VI	Ethanol	140, $C_{17}H_{12}N_6SO$	5846	3.22	23.90	9.00	–
			(58.62)	(3.44)	(24.13)	(9.19)	–
VII	Dil. Ethanol	122, $C_{18}H_{14}N_6SO$	59.29	3.67	23.10	8.64	–
			(59.66)	(3.86)	(23.20)	(8.84)	–
VIII	Benzene	220, $C_{18}H_{12}N_6SO_2$	56.97	3.00	22.00	8.21	–
			(57.44)	(3.19)	(22.34)	(8.51)	–
IXa	Ethanol	130, $C_{18}H_{14}N_6SO_2$	57.00	3.45	21.90	8.16	–
			(57.14)	(3.70)	(22.22)	(8.46)	–
IXb	Ac OH	132, $C_{18}H_{13}N_6SCl_3$	47.56	2.80	18.20	6.95	22.95
			(47.84)	(2.87)	(18.60)	(7.08)	(23.58)
IXc	Dil. Ethanol	98, $C_{20}H_{20}N_6S$	63.67	5.30	22.40	9.2	–
			(63.82)	(5.31)	(22.34)	(8.51)	–
IXd	Ethanol	100, $C_{23}H_{16}N_6SCl_2$	57.23	3.12	17.30	6.38	14.21
			(57.62)	(3.34)	(17.53)	(6.68)	(14.82)
IXe	Ethanol	110, $C_{23}H_{16}N_6S\,Cl_2$	57.23	3.10	17.35	6.50	14.21
			(57.62)	(3.34)	(17.53)	(6.68)	(14.82)
IXf	Ac OH	120, $C_{26}H_{20}N_7$ S	67.35	4.12	21.00	7.15	–
			(67.53)	(4.32)	(21.21)	(6.91)	–
IXg	Ac OH	125, $C_{25}H_{17}N_7SO$	64.67	3.54	21.53	7.00	–
			(64.79)	(3.67)	(21.16)	(6.91)	–
X	Ethanol	118, $C_{18}H_{12}N_6SO$	59.67	3.31	23.23	8.60	–
			(60.00)	(3.33)	(23.33)	(8.88)	–

(Continued. . . . .)

(Table 1, continued)

XI	Ethyl acetate	178, $C_{18}H_{12}N_6S\,Cl_2$	52.10	2.76	20.10	7.51	16.90
			(52.04)	(2.89)	(20.24)	(7.71)	(17.18)
XII	Benzene	150, $C_{25}H_{18}N_6S_2\,Cl_2O$	54.00	3.09	14.98	11.47	11.27
			(54.24)	(3.25)	(15.18)	(11.57)	(12.28)
XIII	Benzene	130, $C_{20}H_{20}N_6SO$	61.00	5.00	21.21	8.00	–
			(61.22)	(5.10)	(21.42)	(8.16)	–
XIV	Dil. Ethanol	140, $C_{24}H_{17}N_6S\,Br^{++}$	57.12	3.12	16.50	6.20	–
			(57.48)	(3.39)	(16.76)	(6.38)	–
XV	Ethanol	125, $C_{18}H_{16}N_6S$	62.00	4.39	24.10	9.10	–
			(62.06)	(4.59)	(24.13)	(9.19)	–
XVI	Methanol	130, $C_{18}H_{14}N_6SO$	59.50	3.67	22.99	8.64	–
			(59.66)	(3.86)	(23.20)	(8.83)	–
XVII	Ethanol	200, $C_{18}H_{14}N_6SO$	59.45	3.57	22.95	8.55	–
			(59.66)	(3.86)	(23.20)	(8.83)	–
XVIII	Ac OH	155, $C_{26}H_{20}N_6SO_3$	62.67	4.00	16.53	6.25	–
			(62.90)	(4.03)	(16.93)	(6.45)	–
XIX	Ethanol	140, $C_{19}H_{14}N_6SO_2$	58.12	3.40	21.33	8.00	–
			(58.46)	(3.58)	(21.53)	(8.20)	–

+ Br 18.55, (18.05).
++ Br . 15.64, (15.96).

Table 2. Antibacterial activity* of the compounds II and IVf-i

Compound No.	*Bacillus subtilis* gram +ve	*Escherichia coli* gram –ve
II	20	20
IVf	14	20
IVg	18	11
IVh	12	12
IVi	17	22
Methanol	–	–

*Results are expressed as diameter of the inhibition zone (mm).

(B) *Formation of XVII.* A mixture of II (0.01 mol), monochloroacetic acid (0.01 mol) and anhyd. NaOAc (0.02 ml) in ethanol (25 ml) was heated under reflux for 5 hrs. on a water-bath. Ethanol was distilled off and the reaction mixture was poured onto crushed ice. The solid obtained was filtered off, washed with water and recrystallized to give XVII, yield 80 %. (Table 1). IR: 3200-3100 (NH), 2980 (str.CH_2), 1750 (C=O), 1580 (> C=N) and 1470 (def. CH_2). H^1nmr: 4.2 (Singlet, 2H, CH_2 of thiazolidinone), 5.5 (Broad, NH-exchangeable with D_2O and 6.9 (Singlet 1H of p-proton of phenyl ring).

Condensation of XVII with vanilline: Formation of XVIII. A mixture of XVII (0.01 mol), vanilline (0.01 mol) and anhyd. NaOAc (0.02 mol) in gl. acetic acid (20 ml) was refluxed for 3 hrs., cooled and poured onto crushed ice. The resultant solid was filtered off and recrystallized to give XVIII, yield 80 % (Table 1).

Cyclocondensation of II with vanilline and monochloroacetic acid: Formation of XVIII. A mixture of II(0.01 mol), vanilline (0.01 mol), monochloro acetic acid (0.01 mol) and anhyd. NaOAc (0.04 mol) in gl. acetic acid (100 ml) was refluxed for 6 hrs., cooled and poured onto crushed ice. The solid obtained was filtered off, washed several times with water and recrystalized to give XVIII, identical (m.m.p.ir. determination) with material as prepared from XVII.

Reaction of II with α-β-γ-trifunctional compound: Formation of XIX. A mixture of II (0.01 mol) and bromopyruvic acid (0.01 mol) was added to ethanolic KOH (10 %, 20 ml) and refluxed for 6 hrs., cooled and acidified with very dil. HCl. The solid obtained was filtered off and recrystallized to give XIX, yield 70 % (Table 1). IR: 3200 (NH), 3010 (aromatic CH), 1670-1650 (C=O in cyclic 1,2-dione), 1450 (def. CH_2) and 1170 (C=S).

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