HETEROCYCLIC SYSTEMS CONTAINING BRIDGEHEAD NITROGEN ATOM. PART XXXVII. REACTION OF MERCAPTO-AS-BENZOTRIAZINES WITH HALOGENO-ACETIC ACID, α-HALOGENOKETONES AND ALKYL HALIDES.

(Miss) Saroj Bala, Madan Lal Sachdeva, Ram Nath Handa and Hrushi Kesh Pujari*
Department of Chemistry, Kurukshetra University, Kurukshetra 132119, India

Abstract —— Mercapto-as-benzotriazines (IIa,b) obtained by the reaction of corresponding o-phenylenediamines (Ia,b) with thiosemicarbazide, on condensation with halogenoacetic acid, yields benzotriazine-3-thiolacetic acids (IIIa,b) which on treatment with acetic anhydride underwent cyclodehydration to furnish 9H-thiazolo [2,3-c] -as-benzotriazin-3(2H)-ones (IVa,b) and not 5H-thiazolo [3,2-b] -as-benzotriazin-3(2H)-ones (VIIIa,b) as revealed by NMR spectral data. Similar condensation of IIa,b with α-halogenoketones followed by the PPA cyclization of the intermediate ketones (Va,b) yields 9H-thiazolo [2,3-c] -as-benzotriazines (VIa,b). The reaction of IIa with 1,2-dibromoethane yields 9H-2,3-dihydro-6,7-dimethylthiazolo [2,3-c] -as-benzotriazine (VII). Thiazolo-benzotriazine (IV, VI and VII) is a novel and hitherto unknown heterocyclic system and is reported here for the first time.

In continuation of our earlier studies on the orientation of cyclization in a reaction of unsymmetrical mercaptoazoles with bifunctional compounds[1-4], we now wish to report in the present communication our work on the reaction of unsymmetrical azine (mercaptobenzotriazine) with halogenoacid, α-halogenoketone and alkyl halide (vide chart I).

Mercaptobenzotriazines (IIa,b), obtained by the fusion of thiosemicarbazide with appropriate diamines (Ia,b), when condensed with halogenoacetic acid gave 6,7-

dimethyl- (IIIa) and 1,2-dihydro-as-benzotriazine-3-thiolacetic acids (IIIb) respectively. The acid (III) being unsymmetrical, on cyclization, was expected to yield 9H-thiazolo [2,3-c]-as-benzotriazin-3(2H)-one (IV) or 5H-thiazolo [3,2-b]-as-benzotriazin-3(2H)-one (VIII) or both depending upon the direction of cyclization. The acids (IIIa,b), however, when heated in a mixture of acetic anhydride and pyridine, underwent cyclodehydration furnishing a single product (tlc) in each case. The appearance of a band at 1730 cm^{-1} ($\geq N-\underset{\underset{O}{\|}}{C}-$) and at 1740 cm^{-1} ($\geq N-\overset{\overset{O}{\|}}{C}-$) in the IR spectra of the tlc-pure products obtained from IIIa and IIIb respectively corroborated the cyclic structure. The structure IV and not VIII has been assigned to the tlc-pure products on the basis of NMR spectral data.

In structure VIII, all the aromatic protons (four protons in VIIIb and two protons in VIIIa) will resonate in close proximity to each other whereas in IVa,b, H_a will be deshielded by the thiazolidinone ring and as a result, H_a will resonate at downfield in comparison to other aromatic protons. The deshielding has its origin in the magnetic anisotropy of the $\geq C=O$ group with minor contribution from the rest of the ring. The downfield shift of one aromatic proton (H_a) in the NMR spectra (vide experimental) of the tlc-pure products obtained from IIIa,b confirmed the structures IVa,b. Moreover, the reaction of IIa with 1,2-dibromoethane gave a single product (tlc) which may be represented by either structure VII or X. In either structure the signal at δ 7.02 and 6.87 are due to H_a and H_b respectively because H_b will be shielded by NH proton. Comparison of the chemical shifts of H_a in VII (or X) with those of IVa support the structural assignment. H_a in VII (or X) has a value at δ 7.02 and the signal at δ 7.52 (a value sufficiently higher than δ 7.02 and is due to the deshielding effect by carbonyl group) exhibited by the cyclized product obtained from the acid IIIa supports the structure IVa. Such a downfield shift would not be expected from the structure VIII. The preferential formation of IV could be resulted from the equilibrium A $\rightleftharpoons$ B (vide chart II). The acid (III) will have the structure A rather than B because in A, the double bond in the triazine ring is in conjugation with the benzene ring whereas B has an isolated double bond (chart II). In A, the pyridine-like Sp^2-nitrogen at N_4, being more nucleophilic than pyrrole-like Sp^3-nitrogen at N_2, will attack the carbonyl carbon of the acid giving XI which underwent prototropic changes followed by the loss of a water molecule giving IV.

Mercaptobenzotriazines (IIa,b) on condensation with α-halogenoketones yielded ketones (Va,b) characterized by their IR spectra (1660-1700 cm^{-1}, C = O) which on treatment with polyphosphoric acid underwent cyclization giving a single compound (tlc) in each case, confirmed by the absence of the carbonyl band, thus corroborating the cyclic structure. Further support for the cyclic structure for this tlc-pure compound forthcame from NMR spectra. The signals at δ 6.52 (1H, s, C_2-H), 6.58 (1H, s, C_2-H), 6.90 (1H, s, C_2-H) and 7.14 (1H, s, C_2-H) in the NMR spectra of the compounds obtained by the cyclization of Va (R_1 = Ph), Va (R_1 = p-BrC_6H_4), Vb (R_1 = p-BrC_6H_4) and Vb (R_1 = p-$O_2NC_6H_4$) respectively confirmed the cyclic structure. The NMR spectral data were not of much help in deciding in favour of either angular product(VI) or the linear product(IX). The formation of VI from the ketone V and also the formation of VII from the reaction of II with 1,2-dibromoethane could be explained similarly as done in case of IV (vide chart II). The ketone(V) (HBr salt or free base) however could not be made to undergo cyclization under milder condition using H_2SO_4 or HCl as cyclizing agents. Compounds VI and VII did not undergo desulphurization indicating thereby that sulphur is a part of the cyclic structure.

Experimental Procedure - Melting points were determined in sulphuric acid bath and are uncorrected. The tlc was done on silica gel plates using acetone-benzene(1:3) as solvent system. IR was run on Beckman IR-20 Spectrophotometer in Nujol mull. The NMR spectra were recorded on a Varian 60 MHz or Perkin-Elmer 90 MHz NMR Spectrometer in TFA or $CDCl_3$ using tetramethylsilane (TMS) as internal reference standard. The chemical shifts are expressed in δ (ppm) downfield from TMS.

6,7-Dimethyl-1,2-dihydro-3-mercapto-as-benzotriazine (IIa) - A mixture of 4,5-dimethyl-o-phenylenediamine (6.8 g, 0.05 mole) and thiosemicarbazide (4.55 g, 0.05 mole) was heated in an oil bath for 5 hr at 180-90°. After an hr, the melt started to get solidified. The reaction mixture was cooled and crystallized from ethanol giving white flakes, m.p. above 290°, yield 5.6 g (58%) (Found: S, 16.55, $C_9H_{11}N_3S$ requires S, 16.58%). $\nu_{max}^{cm^{-1}}$ 1200 (C-S stretching), 3040-3060 (NH broad).

1,2-Dihydro-3-mercapto-as-benzotriazine (IIb) - It was prepared from o-phenylenediamine and thiosemicarbazide following the above procedure, m.p. 290° (light brown flakes from ethanol), yield 48% (Found: S, 19.07, $C_7H_7N_3S$ requires S, 19.39%). $\nu_{max}^{cm^{-1}}$ 1180 (C-S stretching), 3140-3300 (NH Broad).

6,7-Dimethyl-1,2-dihydro-as-benzotriazine-3-thiolacetic acid (IIIa) - Mercapto-as-benzotriazine (IIa, 1.93 g, 0.01 mole), bromoacetic acid (1.39 g, 0.01 mole)

and fused sodium acetate (0.82 g, 0.01 mole) in anhydrous ethanol (50 ml) was heated, under reflux, for 8 hr. The reaction mixture was cooled to room temperature and the solid, thus separated, was crystallized from ethanol giving white crystals, m.p. 210°, yield 1.5 g (60%) (Found: S, 12.69; $C_{11}H_{13}N_3O_2S$ requires S, 12.75%). $\nu_{max}^{cm^{-1}}$ 1570 (C=N), 2480-2760 (CO_2H, broad), 3340-3420 (NH broad).

1,2-Dihydro-as-benzotriazine-3-thiolacetic acid (IIIb) — It was prepared from IIb and chloroacetic acid following the above procedure, m.p. 191-93° decomp. (EtOH), yield 45% (Found: S, 14.12, $C_9H_9N_3O_2S$ requires S, 14.35%). $\nu_{max}^{cm^{-1}}$ 2500-2580 (CO_2H, broad), 3300-3440 (NH broad).

6,7-Dimethyl-9H-thiazolo [2,3-c]-as-benzotriazin-3(2H)-one (IVa) The acid (IIIa, 1.0 g) in a mixture of acetic anhydride (1 ml) and pyridine (3 ml) was heated on a steam bath for 30 min. The reaction mixture was cooled to room temperature and poured dropwise into water with constant stirring. The solid, thus separated, was thoroughly washed with water. Crystallization from ethanol furnished light brown needles, m.p. 168-70°, yield 0.3 g (32%) (Found: C, 56.36; H, 5.39; S, 13.71; $C_{11}H_{11}N_3OS$ requires C, 56.65, H, 4.72; S, 13.73%). $\nu_{max}^{cm^{-1}}$ 1510 (C-N stretching), 1585 (C=N), 1730 (C=O), 3420 (NH broad). NMR (TFA): δ 2.5 (6H, s, both CH_3 groups), 4.33 (2H, s, CH_2), 7.05 (1H, s, C_8-H), 7.52 (1H, s, C_5-H) (NH signal was not exhibited in the normal chart).

9H-Thiazolo [2,3-c]-as-benzotriazin-3(2H)-one (IVb) — It was obtained by the cyclization of the acid (IIIb) with acetic anhydride following the procedure adopted in IVa, m.p. 168°, yield (34%), (Found: C, 52.42; H, 3.76; S, 15.28; N, 20.13, $C_9H_7N_3OS$ requires C, 52.67; H, 3.41; S, 15.61; N, 20.48%). $\nu_{max}^{cm^{-1}}$ 1610 (C=C), 1740 (C=O), 3320-3500 (NH broad). NMR ($CDCl_3$): δ 4.31 (2H, s, CH_2), 7.17-7.65 (3H, m, C_6-H, C_7-H and C_8-H), 7.90 (1H, q, C_5-H, $J_{5,6}$ = 8 Hz; $J_{5,7}$ = 2.5 Hz).

1,2-Dihydro-3-p-bromophenacylthio-as-benzotriazine hydrobromide (Vb, R_1 = p-BrC_6H_4) — Mercaptobenzotriazine (IIb, 1.65 g, 0.01 mole) and p-bromophenacyl-bromide (2.78 g, 0.01 mole), in anhydrous ethanol (60 ml) were heated, under reflux, for 8 hr. The reaction mixture was cooled to room temperature and the solid, so obtained, was crystallized from ethanol giving slightly grey crystals, m.p. 235°, yield 2.3 g (52%) (Found: S, 7.03, $C_{15}H_{13}N_3OSBr_2$ requires S, 7.22%). $\nu_{max}^{cm^{-1}}$ 1520 (C-N stretching), 1585, 1620 (C=N and C=C), 1680 (C=O), 3140-3300

(NH broad).

9H-3-p-Bromophenylthiazolo[2,3-c]-as-benzotriazine (VIb, R_1 = p-BrC_6H_4) —— A mixture of the ketone (Vb, R_1 = p-BrC_6H_4, 1.0 g), phosphorus pentoxide (4 g) and orthophosphoric acid (3 ml) was heated on an oil bath at 150° for 4 hr. The reaction mixture was cooled and basified with potassium carbonate. The solid, thus obtained, was crystallized from ethanol giving pale yellow crystals, m.p. 188-90°, yield 0.6 g (77%) (Found: C, 52.17; H, 2.76; S, 9.17; N, 11.98, $C_{15}H_{10}N_3SBr$ requires C, 52.32; H, 2.91; S, 9.30; N, 12.21%). $\nu_{max}^{cm^{-1}}$ 1550 (C-N stretching), 1570, 1610 (C=N and C=C), 3400 (NH). NMR (TFA): δ 6.90 (1H, s, C_2-H), 6.96-7.28 (4H, m, C_5-H, C_6-H, C_7-H and C_8-H), 7.30 (4H, AB quartet, p-BrC_6H_4, J_{AB} = 9 Hz).

(The properties and analyses of other ketones (V) and thiazolo[2,3-c]benzotriazines (VI) are described in Table 1.).

6,7-Dimethyl-2,3-dihydro-9H-thiazolo[2,3-c]-as-benzotriazine hydrobromide (VII) A mixture of IIa (1.93 g, 0.01 mole) and 1,2-dibromoethane (1.88 g, 0.01 mole) in anhydrous ethanol (50 ml) was heated, under reflux, for 6 hr. The reaction mixture was cooled to room temperature and the solid, thus separated, was crystallized from ethanol giving pale yellow crystals, m.p. above 282°, yield 1.65 g (55%) (Found: S, 10.27, $C_{11}H_{14}N_3SBr$ requires S, 10.67%). $\nu_{max}^{cm^{-1}}$ 1595 (C=N), 3360-3500 (NH broad). NMR (TFA): δ 1.98 (6H, s, both CH_3 groups), 3.92 (2H, t, SCH_2), 4.20 (2H, t, NCH_2), 6.87 (1H, s, C_8-H), 7.02 (1H, s, C_5-H).

Acknowledgements The authors wish to express their sincere thanks to Dr. Nitya Nand, Director, Central Drug Research Institute, Lucknow for NMR spectra, to the Council of Scientific & Industrial Research, New Delhi for an award of JRF to (MLS) and the University Grants Commission, New Delhi for an award of JRF to (SB).

Table 1

Physical data of the ketones (V) and thiazolo [2,3-c] -as-benzotriazines (VI)

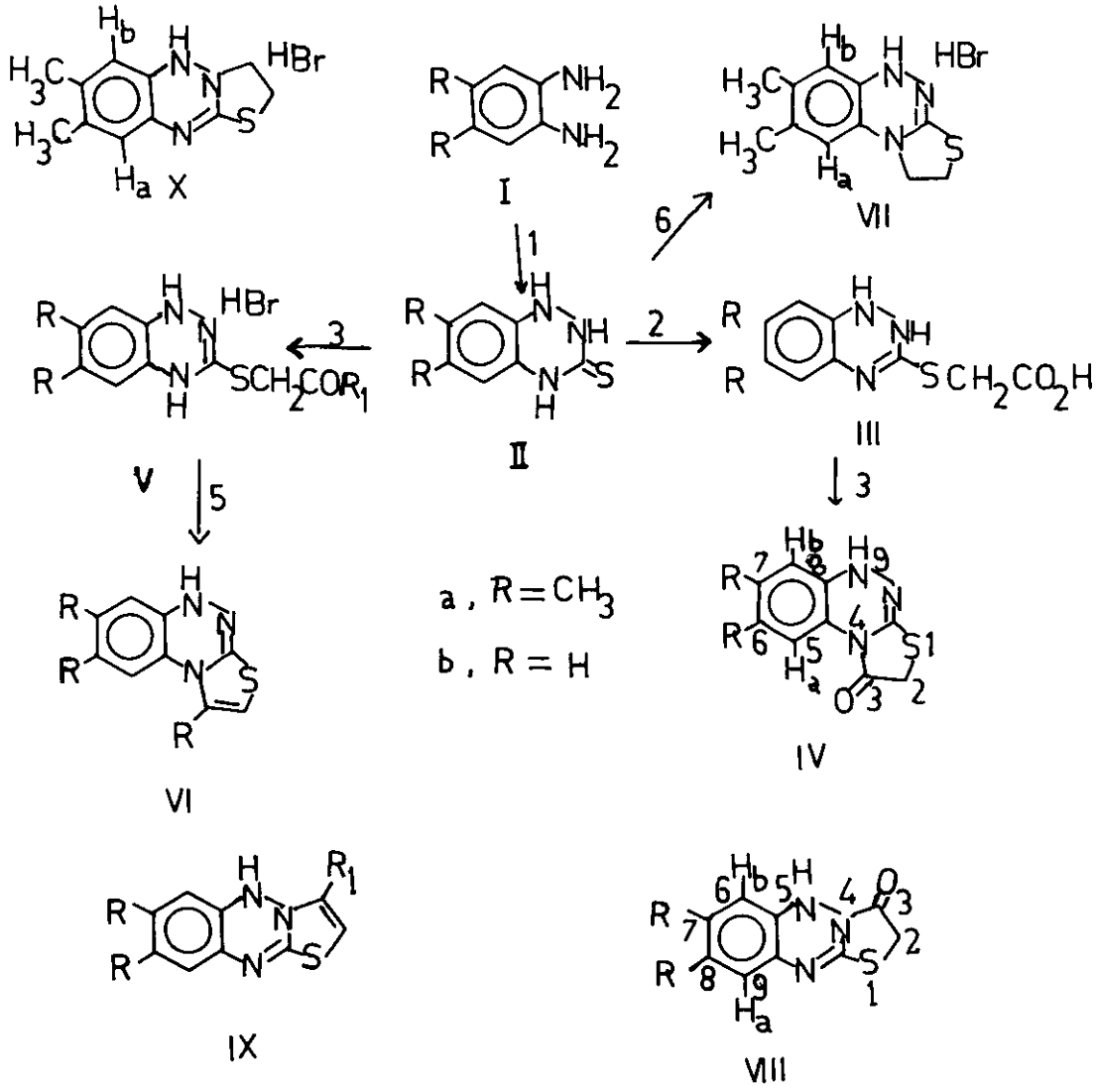
R	R_1	Ketones (V)					Thiazolo-benzotriazines (VI)				
		m.p. °C	Yield %	Mol. formula	S% Found	S% Calc.	m.p. °C	Yield %	Mol. formula	S% Found	S% Calc.
H	p-$O_2NC_6H_4$	248	49	$C_{15}H_{13}N_4O_3SBr$	7.68	7.82	216-17	68	$C_{15}H_{10}N_4O_2S$*	10.13	10.32
H	p-$H_3CC_6H_4$	230	53	$C_{16}H_{16}N_3OSBr$	8.15	8.46	111-14	39	$C_{16}H_{13}N_3S$	11.22	11.47
H	p-ClC_6H_4	243	50	$C_{15}H_{13}N_3OSClBr$	7.81	8.03	198	67	$C_{15}H_{10}N_3SCl$	10.33	10.69
H	C_6H_5	215	55	$C_{15}H_{14}N_3OSBr$	8.42	8.79	142	55	$C_{15}H_{11}N_3S$	11.85	12.08
CH_3	p-BrC_6H_4	240	62	$C_{17}H_{17}N_3OSBr_2$	6.32	6.79	256-57	50	$C_{17}H_{14}N_3SBr$**	8.56	8.60
CH_3	p-$H_3CC_6H_4$	220	61	$C_{18}H_{20}N_3OSBr$	7.52	7.88	186-87	43	$C_{18}H_{17}N_3S$	10.38	10.42
CH_3	m-$O_2NC_6H_4$	236-38	52	$C_{17}H_{17}N_4O_3SBr$	7.03	7.32	228-30	52	$C_{17}H_{14}N_4O_2S$	9.43	9.47
CH_3	C_6H_5	230-32	54	$C_{17}H_{18}N_3OSBr$	7.72	8.16	188-90	45	$C_{17}H_{15}N_3S$***	10.89	10.91

*NMR(TFA): δ 6.98-7.46 (4H, m, C_5-H, C_6-H, C_7-H and C_8-H), 7.14 (1H, s, C_2-H), 7.90 (4H, AB quartet, p-$O_2NC_6H_4$; J_{AB} = 9 Hz).

**NMR($CDCl_3$): δ 2.35 (3H, s, C_6-CH_3 or C_7-CH_3), 2.43 (3H, s, C_7-CH_3 or C_6-CH_3), 6.58 (1H, s, C_2-H), 7.04-7.82 (6H, m, aromatic protons) (Found: C, 54.41, H, 3.81; requires C, 54.84; H, 3.76%).

***NMR($CDCl_3$): δ 2.30 (3H, s, C_6-CH_3 or C_7-CH_3), 2.42 (3H, s, C_7-CH_3 or C_6-CH_3), 6.52 (1H, s, C_2-H), 7.00-7.75 (7H, m, aromatic protons) (Found: C, 69.54, H, 5.32; requires C, 69.61, H, 5.12%).

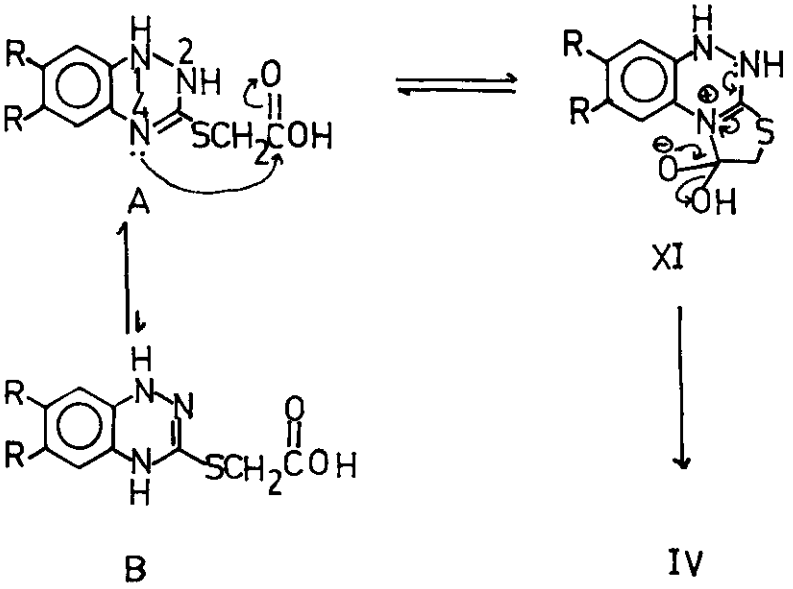
CHART I



1. $H_2NNHCSNH_2$; 2. XCH_2CO_2H , NaOAc ;

3. Ac_2O , pyridine , 4 R_1COCH_2Br ; 5. PPA ; 6. $BrCH_2CH_2Br$.

CHART II



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Received, 9th December, 1978