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Studies on Heterocyclics. V.[1] Synthesis of Thiazolotriazepines

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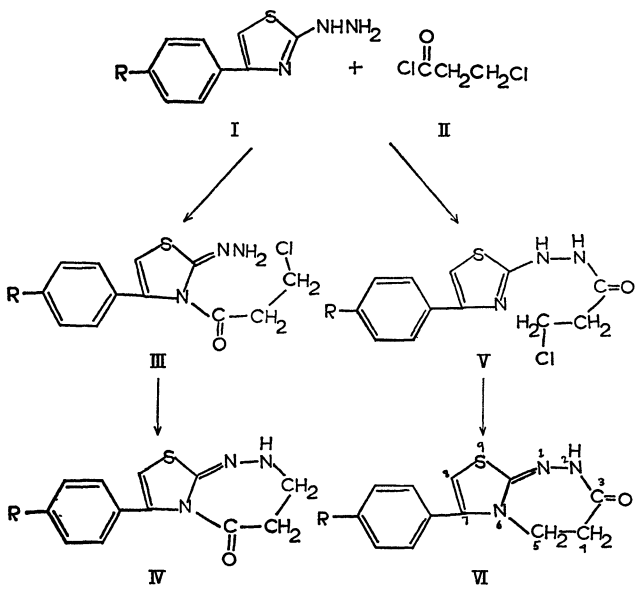
Synopsis. The possible psychosedative, bridgehead thiazolo[2,3-*c*]-1,2,4-triazepines have been synthesized by the condensation of 2-hydrazinothiazoles with β-chloropropionyl chloride.

Recent trends in the synthesis of pharmacologically active compounds, *viz.* thiazolodiazepines[2-4] and oxazolodiazepines,[5] prompted us to carry out the synthesis of thiazolo[2,3-*c*]-1,2,4-triazepines, a new ring system (Scheme 1).

It was anticipated that the most direct route to 2*H*,3*H*,4*H*,5*H*-7-phenylthiazolo[2,3-*c*]-1,2,4-triazepine (VI; R=H) and its derivatives would be from 2-hydrazino-4-arylthiazoles (I)[6] *via* the intermediate V. The method used for the synthesis of thiazolo [2,3-*c*]-1,2,4-triazepines (VI) was analoguos to that used by Fozard and Jones[7] for the synthesis of 2-oxo-2,3,4,5-tetrahydro-1*H*-pyrimido [1,2-*a*] [1,3] diazepinium bromide.

The reaction of I with β-chloro propionyl chloride (II) may give either of the two heterocycles IV[8] and VI. The structure IV can be excluded from the consideration that monoacylation and carbamoylation always occur on the exocyclic amino group[9-14] in α-amino-*N*-heterocyclic compounds. Chloroacyl chloride has been shown to undergo reaction with amines selectively[15,16] with the carbonyl group forming an amide bond leaving V as the only possible intermediate.

Thus $-NH_2$ of hydrazine which is most basic[17] (*i.e.* the strongest nucleophile) will attack at the carbon of the carbonyl which is most electrophilic, resulting in the formation of the intermediate V (Table 1). The IR spectrum of V (R=H) shows characteristic –NH– and >C=O vibrations at 3350 and 1690 cm^{-1}. V is then cyclised in the presence of dry pyridine to VI. The IR spectrum of (VI, R=H) shows bands at 3360 (–NH–); and 1665 (>C=O) cm^{-1}. NMR spectrum (VI: R=Br) taken in $CDCl_3$ (100 MHz) shows a singlet at δ 2.02 (2H) due to $N-CH_2-$ and another singlet at δ 1.8 (2H) due to $-CH_2-\overset{O}{\overset{\|}{C}}-$ and aromatic multiplet at δ 6.8—7.7 (5H) due to $Br-C_6H_4-\overset{|}{C}=CH-$.



Scheme 1.

Experimental

The melting points are uncorrected. Microanalysis was carried out by the Mciroanalytical Service., CSIRO, Australia. IR spectra were obtained in KBr wafers on a Perkin-Elmer Infracord-137 spectrophotometer, and NMR spectra were recorded on a Varian HA-100 spectrometer.

2-Hydrazino-4-(substituted phenyl)thiazoles (I). 2-Chloro-4-phenylthiazole[6] (3.92 g, 0.02 mol), pyridine (2 ml), hydrazine hydrate (5 ml), and ethanol (20 ml) were taken in a flask. The reaction mixture was heated under reflux for 2 h and the solvent was removed under reduced pressure. The residue was poured into cracked ice and the solid thus obtained was crystallized from ethanol or benzene; yield 3.2 g (84%); mp 162 °C. Found: C, 56.64; H, 4.79; N, 22.25%; while: $C_9H_9N_3S$ requires: C, 56.54; H, 4.71; N, 21.99%. NMR spectrum (100 MHz; $CDCl_3$) shows aromatic protons as multiplet at δ 6.8—7.9 and the $-NHNH_2$ protons at δ 2.5—3.5.

The other 2-hydrazino-4-(substituted phenyl)thiazoles were prepared in an analoguos manner.

2-(3-Chloropropionylhydrazino)-4-(p-substituted phenyl)thiazoles (V). 2-Hydrazino-4-phenylthiazole (1.91 g, 0.01 mol) dissolved in tetrahydrofuran (15 ml) was added with stirring over a period of 15 minutes to an ice cooled β-chloropropionyl chloride (10 ml). The solid separated in the reaction mixture and excess of β-chloropropionyl chloride was decomposed with crushed ice, filtered, washed with cold water, and crystallized from ethanol. Yield, mp, solvent of crystallization, and microanalytical data are given in Table 1.

The other 2-(3-Chloropropionylhydrazino)-4-(*p*-substituted phenyl)thiazoles were prepared in a similar way.

2H,3H,4H,5H-7-(p-substituted phenyl)thiazolo[2,3-c]-1,2,4-triazepine-3-ones (VI). 2-(3-Chloropropionylhydrazino)-4-phenylthiazole (1.0 g) was dissolved in dry pyridine (10 ml) and left to stand at room temperature for 30 minutes. The reaction mixture was diluted with water and the solid obtained was crystallized from ethanol.

The other 2*H*,3*H*,4*H*,5*H*-7-(*p*-substituted phenyl)thiazolo [2,3-*c*]-1,2,4-triazepine-3-ones were prepared in a similar way. Yield, mp, solvent of crystallization and microanalytical data are given in Table 2.

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Table 1. Physical constants of V

Sr. No.	Substituents	Yield %	Mp °C	Molecular formula	Elemental analysis Found % C	H	N	S	Calcd % C	H	N	S
Va	H	71	212	$C_{12}H_{12}N_3OSCl$	51.14	4.48	14.81	11.38	51.24	4.27	14.94	11.38
Vb	CH_3	70	219	$C_{13}H_{14}N_3OSCl$	—	—	14.13	10.67	—	—	14.23	10.84
Vc	OCH_3	68	209	$C_{13}H_{14}N_3O_2SCl$	—	—	13.26	10.20	—	—	13.50	10.28
Vd	Br	75	222	$C_{12}H_{11}N_3OSClBr$	—	—	11.70	8.91	—	—	11.36	8.88
Ve	Cl	72	218	$C_{12}H_{11}N_3OSCl_2$	—	—	13.24	10.05	—	—	13.33	10.15
Vf	C_2H_5	65	226	$C_{14}H_{16}N_3OSCl$	—	—	13.51	10.50	—	—	13.59	10.52

All the compounds (Va—f) were crystallized from ethanol.

Table 2. Physical constants of VI

Sr. No.	Substituents	Yield %	Mp °C	Molecular formula	Elemental analysis Found % C	H	N	S	Calcd % C	H	N	S
VIa	H	75	173	$C_{12}H_{11}N_3OS$	58.43	4.51	17.12	13.06	58.77	4.48	17.14	13.06
VIb	CH_3	70	149	$C_{13}H_{13}N_3OS$	—	—	16.10	12.40	—	—	16.21	12.35
VIc	OCH_3	72	146	$C_{13}H_{13}N_3O_2S$	—	—	14.98	11.41	—	—	15.27	11.63
VId	Br	68	170	$C_{12}H_{10}N_3OSBr$	—	—	13.26	9.71	—	—	12.96	9.87
VIe	Cl	73	155	$C_{12}H_{10}N_3OSCl$	—	—	14.69	11.10	—	—	14.53	11.07
VIf	C_2H_5	62	162	$C_{14}H_{15}N_3OS$	—	—	15.21	11.45	—	—	15.38	11.72

All the compounds (VIa—f) were crystallized from ethanol.

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