Synthesis and Spectra of 3-Benzyl(or *p*-tolyl)-5-methyl-2-(substituted benzothiazol-2′-ylimino)-4-thiazolidones

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Some 3-benzyl(or *p*-tolyl)-5-methyl-2-(substituted benzothiazol-2′-ylimino)-4-thiazolidones were prepared. Their structures and the purity of the compounds were corroborated by their analytical and spectral data. Screening tests on these compounds showed the 4-chloro and 6-bromo analogues to be the most active as CNS depressants, muscle relaxants and anticonvulsants.

Certain thiocarbamides and their cyclic analogues are known to possess good pharmacological activity.[1] An interesting structural variation is the cyclisation of thiocarbamides to thiazolidones.[2,3] A number of disubstituted 4-thiazolidones have been prepared[4] and it has been observed that many of these compounds inhibit convulsions in cats and rats.[5] Various other Δ^4-thiazolidones have been reported[6] and the greatest effort has been made in the synthesis of heterocyclic analogues of thiazolidones.[7,8]

In extending the work, we synthesized 3-benzyl (or *p*-tolyl)-5-methyl-2-(substituted benzothiazol-2′-ylimino)-4-thiazolidones by the cyclisation of *N*-benzyl (or *p*-tolyl)-*N*′-(substituted)benzothiazol-2-yl thiocarbamides with α-chloropropionic acid under anhydrous conditions. The structures and the purity of the compounds were determined with the help of NMR, IR, and TLC. The compounds were also tested for their pharmacological activity.

Experimental

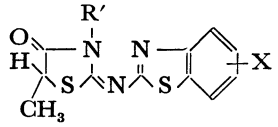
All melting points were measured by the capillary method and are uncorrected. A *Varian-A60D* was used for recording NMR spectra, a *Perkin-Elmer 257* for IR and a *Coleman Analyzer* for analyses.

N-Benzyl-N′-(4-methyl)benzothiazol-2-yl Thiourea (1). A mixture of 4-methyl-2-aminobenzothiazol (4.1 g), benzyl isothiocyanate (3.7 ml) and dry benzene (40 ml) was refluxed on a water-bath for about 5 h at 80—90 °C. The residue was filtered and washed with ether followed by a little 40% HCl solution. The product was crystallised from 80% ethanol, yield 73%, mp 170 °C. TLC: R_f=0.79 (benzene-ether, 3 : 1). Calcd for $C_{16}H_{15}N_3S_2$: N, 13.42; S, 20.45%. Found: N, 13.41; S, 20.54%. IR ν_{max}^{Nujol} cm^{-1}: 3180(〉N-H), 3035m(〉N-H), 1560s(〉C=N- or 〉C=C〈), 1200s(〉C=S), NMR($CDCl_3$) δ(J=Hz): 2.35(3H, s), 5.08 (2H, d, J=5.0), 7.80(1H, broad), 10.95(1H, broad) and 7.50 for aromatic protons (8H, m).

Similarly, other substituted-2-aminobenzothiazoles were converted into their respective thioureas by treating with benzyl isothiocyanate and *p*-tolyl isothiocyanate.

3-Benzyl-5-methyl-2-(4′-methylbenzothiazol-2′-ylimino)-4-thiazolidone (2). *N*-Benzyl-*N*′-(4-methyl) benzothiazol-2-yl thiourea (3.13 g) was dissolved in absolute alcohol (35 ml) and to this was added α-chloropropionic acid (1.5 ml) and anhydrous sodium acetate (2.5 g). The mixture was refluxed on a water-bath for 8—10 h and poured into cold water. On standing overnight, a solid mass precipitated. It was filtered and recrystallised from 80% ethanol into shining needles of (**2**), yield 67%, mp 149 °C. TLC: R_f= 0.79 (benzene-ether, 3 : 1). Calcd for $C_{19}H_{17}N_3OS_2$: N,

TABLE 1. PHYSICAL DATA AND IR PEAKS OF 3-BENZYL(OR *p*-TOLYL)-5-METHYL-2-(SUBSTITUTED BENZOTHIAZOL-2′-YLIMINO)-4-THIAZOLIDONES



S. No.	Substituent X	Molecular formula	Yield (%)	Mp (°C)	Nitrogen (%) Found	Nitrogen (%) Calcd	Sulfur (%) Found	Sulfur (%) Calcd	Characteristic IR peaks (cm^{-1})	R_f values[a]
					R′=-CH_2·C_6H_5					
1	H	$C_{18}H_{15}N_3OS_2$	87	183	11.85	11.89	18.11	18.13	1725 s, 1565 s, 1530 s	0.68
2	4-Cl	$C_{18}H_{14}N_3OS_2Cl$	58	205	10.81	10.84	16.41	16.52	1722 s, 1648 s, 1635m	0.83
3	6-Br	$C_{18}H_{14}N_3OS_2Br$	68	215	9.62	9.72	14.95	14.81	1640 s, 1535 s, 1470m	0.50
4	4-OCH_3	$C_{19}H_{17}N_3O_2S_2$	54	209	10.84	10.96	16.82	16.71	1642 s, 1665 s, 1530m	0.79
					R′=-C_6H_4·CH_3(*p*)					
5	5-CH_3	$C_{19}H_{17}N_3OS_2$	45	189	11.31	11.44	16.91	17.43	1645 s, 1565 s, 1520 s	0.81
6	6-CH_3	$C_{19}H_{17}N_3OS_2$	78	239	11.15	11.44	17.26	17.43	1665 s, 1555 s, 1520 s	0.78
7	6-Cl	$C_{18}H_{14}N_3OS_2Cl$	83	205	10.59	10.83	16.46	16.51	1735 s, 1575 s, 1515m	0.63
8	6-Br	$C_{18}H_{14}N_3OS_2Br$	89	219	9.45	9.72	14.53	14.81	1735 s, 1595m, 1515 s	0.65

a) R_f values were measured on developing the TLC plates (adsorbent, silica gel BDH) in benzene-ether (3 : 1) mixture. s=sharp, m=medium, and w=weak.

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Table 2. Pharmacological activity of 3-benzyl(or *p*-tolyl)-5-methyl-2-(substituted benzothiazol-2′-ylimino)-4-thiazolidones

S. No.[a]	Substituted	Pharmacological activity	MED/MIC	Species
2	4-Chloro	CNS Depress.	160 mg/kg po	Mouse
		Muscle Relax.	160 mg/kg po	
3	6-Bromo	CNS Depress.	160 mg/kg po	Mouse
		Muscle Relax.	160 mg/kg po	
		Electr. Shock	80 mg/kg po	
4	4-Methoxy	None	160 mg/kg po	Mouse
5	5-Methyl	None	160 mg/kg po	Mouse

MED=Minimum effective dose. MIC=Minimum inhibitory concentration. CNS=Central Nervous System.
a) S. Nos. correspond to the serial number of the compounds in Table 1.

11.44; S, 17.44%. Found: N, 11.42; S, 17.52%. IR ν_{max}^{Nujol} cm^{-1}: 1720s(>C=O), 1552s(>C=C< or >C=N-). NMR ($CDCl_3$) δ(J=Hz): 1.75(3H, d, J=7.5), 2.75(3H, s), 4.17 (1H, q, J=7.5), 5.21(2H, s) and 8.25 for aromatic protons (8H, m).

Likewise, other substituted benzothiazolyl thiazolidones were synthesised. Their structures were confirmed by their analytical, spectral and R_f values as recorded in Table 1.

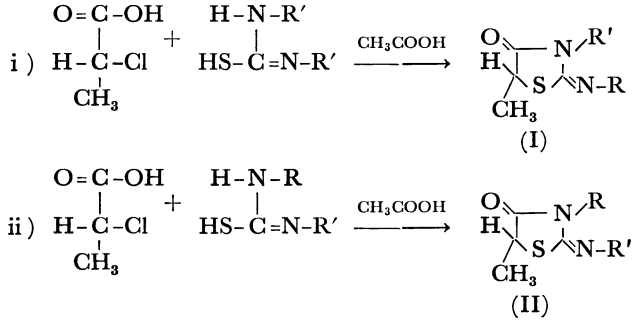
Hydrolysis of 3-Benzyl-5-methyl-2-(4′-methylbenzothiazol-2′-ylimino)-4-thiazolidone (2). 3-Benzyl-5-methyl-2-(4′-methylbenzothiazol-2′-ylimino)-4-thiazolidone (1.83 g), concd HCl (2 ml) and ethanol (20 ml) were refluxed on a water-bath for 8—10 h. After distilling off the ethanol, the reaction mixture was poured into cold water and filtered. The residue was washed with water and crystallised from ethanol to afford 3-benzyl-5-methyl-2,4-thiazolidindione (**3**), yield 76%, mp 186 °C. Calcd for $C_{11}H_{11}NO_2S$: N, 6.33; S, 14.47%. Found: N, 6.53; S, 14.58%. IR ν_{max}^{Nujol} cm^{-1}: 1730s(>C=O), 1720(>C=O), 1552s(>C=C< or >C=N-). On neutralisation with ammonium hydroxide the filtrate gave 4-methyl-2-aminobenzothiazole, melting at 136 °C.

3-Benzyl-5-methyl-2,4-thiazolidindione (3). A mixture of *S*-dibenzyl thiourea (6.0 g), α-chloropropionic acid (2.0 ml) and glacial acetic acid (10 ml) was refluxed on a water-bath for 5 h and then allowed to cool. Addition of excess cold water gave a solid mass which was washed with water and dried. It was crystallised from 80% ethanol, yield 69%, mp 186 °C. Calcd for $C_{11}H_{11}NO_2S$: N, 6.33; S, 14.47%. Found: N, 6.21; S, 14.53%. IR ν_{max}^{Nujol} cm^{-1}: 1732s(>C=O), 1716s(>C=O) and 1565s(>C=C< or >C=N-).

Discussion

The structure of 3-benzyl(or *p*-tolyl)-5-methyl-2-(substituted-benzothiazol-2′-ylimino)-4-thiazolidones was assigned on the basis of the elemental analyses, spectral data and the nature of their degradation products. NMR spectrum of compound (**2**) in $CDCl_3$ shows a singlet at δ 2.75 for the benzene ring methyl protons. A doublet (J=7.5Hz) for the thiazolidone ring methyl protons at δ 1.75 and a quartet (J=7.5Hz) for the thiazolidone ring single proton at δ 4.75 were observed. A singlet at δ 5.21 was assigned to >N–$C\underline{H}_2C_6H_5$ protons. The aromatic protons resonated at δ 8.25 as a multiplet. A strong IR peak at 1720 cm^{-1} for the >C=O group is the characteristic of lactam group.

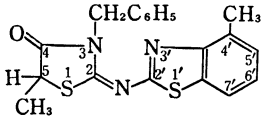
Actually, the possibility of two isomeric products may be assumed here from the two possible tautomeric forms of thiocarbamides undergoing reactions with α-chloropropionic acid. The compound 3-benzyl-5-methyl-2-(4′-methylbenzothiazol-2′-ylimino)-4-thiazolidone after hydrolysis affords a residue which was identified as 3-benzyl-5-methyl-2,4-thiazolidindione by comparing with an authentic sample of the thiazolidindione (**3**) by the mixed melting point method.



R=(substituted)benzothiazol-2-yl-
R′=benzyl or *p*-tolyl-

The structure of 3-benzyl-5-methyl-2,4-thiazolidindione (**3**) is also supported by its IR spectrum which shows an additional peak at 1730 cm^{-1} for the carbonyl group attached to position-2 of the thiazolidindione ring.

Hence the hydrolysis as well as spectral data show the attachment of 2-amino-(substituted)benzothiazoles residue at position-2 and benzyl or *p*-tolyl residue at position-3, thereby confirming the structure as type I but not as type II. Therefore, these findings agree with structure III for compound (**2**).



(III)

Screening Results. The selected compounds have been tested for their pharmacological activities at Bristol Laboratories, Syracuse, New York. The com-

pound 3-benzyl-5-methyl-2-(4′-chlorobenzothiazol-2′-ylimino)-4-thiazolidone was found to be active as a CNS depressant and muscle relaxant and 3-benzyl-5-methyl-2-(6′-bromobenzothiazol-2′-ylimino)-4-thiazolidone as a CNS depressant, muscle relaxant and anticonvulsant.

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