strong lines at 78 c.p.s. in α and at 76 c.p.s. in β arise from the 5-methyl, and the doublets at 47 and 54 c.p.s. in α and 71.5 and 78.5 c.p.s. in β are due to the 9-methyl. (In the *O*-acetylated derivatives the 9-methyl frequencies are identical with those given above; the 5-methyl frequencies are 80 and 78 c.p.s., respectively.) The 25 c.p.s. difference in the 9-methyl frequency between α and β is the result of a change in environment of the 9-methyl from a position above the aromatic ring in IIa to one near the nitrogen atom in IIIa. In the former case the "ring current" effect will produce a diamagnetic (upfield) shift[22] of the order of 25 c.p.s.[23] The effect of the nitrogen in IIIa is less readily evaluated quantitatively, but it seems likely that repulsion of the electrons in the C—H bond by the negative nitrogen atom might produce a small paramagnetic shift.[24] Since these two effects appear to be the only significant factors in altering the resonance frequency of the 9-methyl protons in the two molecules, IIa should have its 9-methyl absorption at higher field than IIIa. Thus the predominant isomer (α) has the structure IIa, in agreement with the rate studies discussed above.

By means of stereoselective adsorbents[25] it has been shown that (−)-2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan, the analgesically active antipode of IIa is related stereochemically to (−)-3-hydroxy - *N* - methylmorphinan (levorphanol, IV) and morphine. Furthermore, a *cis*-fusion of rings B and C for morphine[26] and the morphinans[9,27] and the epimeric relationship of the isomorphinans[28] at C-14 have been rigorously proved. It follows therefore that the α-benzomorphans[7] are comparable in stereochemistry to IV and V, and that the β-compounds conform to the isomorphinan pattern.

In general, these β-compounds (III) are lower melting, more soluble, and from 7–70 times more potent than the α counterparts (II). Assuming that all the activity resides in the *levo*-enantiomorphs the most active III (R_1=Et, R_2=Me) would have twenty to thirty times the analgesic potency of morphine. Experiments designed to render III more readily available are in progress.

(19) S. E. Fullerton, unpublished.

(20) N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, **22**, 1370 (1957).

(21) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

(22) (a) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); (b) C. E. Johnson, Jr., and F. A. Bovey, *ibid.*, **29**, 1012 (1958).

(23) Using the equations of Johnson and Bovey[22] and distances determined from Dreiding stereo models we calculate a ring current diamagnetic shift of 78 c.p.s. for the proton of the 9-methyl group closest to the aromatic ring in IIa. Averaging due to internal rotation of the methyl group will produce an actual shift of about 1/3 this value, or 26 c.p.s. The almost exact agreement with the observed difference, 25 c.p.s., is undoubtedly fortuitous, but the ring current effect is seen to be of the right magnitude to account for the observed difference.

(24) A somewhat analogous situation occurs, for example, in certain steroids where the angular methyls experience a paramagnetic shift of 6–10 c.p.s. when subjected to the influence of an 11-β-hydroxyl group (*cf.*, J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)).

(25) A. H. Beckett and P. Anderson, *J. Pharm. and Pharmacol.*, **12**, **228T** (1960).

(26) H. Rapoport and J. B. Lavigne, *J. Am. Chem. Soc.*, **75**, 5329 (1953).

(27) H. Corrodi, J. Hellerbach, A. Zust, E. Hardegger, and O. Schnider, *Helv. Chim. Acta*, **42**, 212 (1959).

(28) M. Gates and W. G. Webb, *J. Am. Chem. Soc.*, **80**, 1186 (1958).

Studies in Thiazoles. V. Synthesis of Some 2-Chloro- and 2-Hydroxythiazoles

K. S. DHAMI,[1a] S. S. ARORA, AND K. S. NARANG

Department of Chemistry, Panjab University, Hoshiarpur, India

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A number of new 2-hydroxythiazoles and 2-chlorothiazoles have been prepared from the corresponding ω- and α-thiocyanato ketones reported earlier.[1b] The 2-hydroxythiazoles were screened for their *in vitro* activity against *Str. haemolyticus*, *M. pyogenes varaures*, *B. subtilis*, *S. paratyphi*, *S. schottmuelleri*, *S. typhi*, *B. coli*, *Sh. sonnei*, and *S. paradysenteriae* (Flexener), and some of the compounds have been found to inhibit the growth of a wide variety of bacteria at a dilution of 1 in 1000.

The synthesis of some 2-chloro- and 2-hydroxythiazoles required as intermediates in the preparation of therapeutically important 10:11 thiopegans was reported earlier.[2–6] The present paper constitutes an extension of the previous work and describes the synthesis of some 2-hydroxy- and 2-chlorothiazoles, with phenolic, alkoxy, alkyl, and acetamino, phenyl moieties in position 4 of the thiazole system. A number of 5-methyl-substituted thiazole derivatives were also prepared with a view to studying the effect of the alkyl group on

(1)(a) To whom inquiries should be made. Present address: Dept. of Chemistry, University of Western Ontario, London, Ontario, Canada. (b) K. S. Dhami, S. S. Arora, and K. S. Narang, *J. Sci. industr. Res.*, **18B**, 392 (1958).

(2) D. S. Bariana, H. S. Sachdev, and K. S. Narang, *J. Indian Chem. Soc.*, **32**, 427 (1955).

(3) R. Adams, *Org. Reactions*, 377 (1955).

(4) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 374 (1945).

(5) G. M. Sharma, H. S. Sachdev, and K. S. Narang, *J. Sci. industr. Res.*, **16B**, 411 (1957).

(6) H. S. Sachdev, K. S. Dhami, and K. S. Narang, *ibid.*, **19C**, 9 (1960).

TABLE I
2-HYDROXYTHIAZOLES

SL. No.	ω-Thiocyanato Ketone	Product	Yield, %	Solvent for Crystallization	M.P.	Molecular Formula	Calcd.	Found
1.	ω-Thiocyanato-*p*-ethoxyacetophenone	2-Hydroxy-4-(4-ethoxyphenyl)-thiazole	87.5 (crude product)	80% Ethanol	180	$C_{11}H_{11}O_2NS$	N, 6.33	N, 6.10
2.	ω-Thiocyanatoaceto-vanillone	2-Hydroxy-4-(3-methoxy-4-hydroxy-phenyl)thiazole	50	Ethanol	170	$C_{10}H_9O_3NS$	N, 6.28 S, 14.35	N, 6.2 S, 14.8
3.	ω-Thiocyanato-3,4-dimethoxyaceto-phenone	2-Hydroxy-4-(3,4-di-methoxyphenyl)-thiazole	26.4	Dilute ethanol	188	$C_{11}H_{11}O_3NS$	N, 5.9 S, 13.5	N, 6.14 S, 13.30
4.	ω-Thiocyanato-2,4-dimethoxyaceto-phenone	2-Hydroxy-4-(2,4-dimethoxyphenyl)-thiazole	96	Dilute ethanol	138–139	$C_{11}H_{11}O_3NS$	N, 5.97	N, 5.63
5.	ω-Thiocyanato-2,5-dimethoxyaceto-phenone	2-Hydroxy-4-(2,5-dimethoxyphenyl)-thiazole	60	Ethanol	183	$C_{11}H_{11}O_3NS$	N, 6.33	N, 6.15
6.	ω-Thiocyanato-*p*-ethyl-acetophenone	2-Hydroxy-4-(4-ethyl-phenyl)thiazole	52.5	80% ethanol	204	$C_{11}H_{11}ONS$	N, 6.82	N, 6.87
7.	ω-Thiocyanato-2-hydroxy-5-methoxy-acetophenone	2-Hydroxy-4-(2-hydroxy-5-meth-oxyphenyl)thiazole	46.6	Ethanol	191	$C_{10}H_9O_3NS$	N, 6.27	N, 6.26
8.	ω-Thiocyanato-2-hydroxy-4-meth-oxyacetophenone	2-Hydroxy-4-(2-hydroxy-4-meth-oxyphenyl)thiazole	60	Ethanol	184	$C_{10}H_{10}O_3NS$	N, 6.25 S, 14.22	N, 6.15 S, 14.05
9.	ω-Thiocyanato-*p*-acetaminoaceto-phenone	2-Hydroxy-4-(4-acetaminophenyl)-thiazole	24	Acetic acid	299	$C_{11}H_{10}O_2N_2S$	N, 11.96 S, 13.67	N, 11.9 S, 13.43
10.	ω-Thiocyanato-2-hydroxy-5-acetami-noacetophenone	2-Hydroxy-4-(2-hydroxy-5-acetami-nophenyl)thiazole	53.6	80% ethanol	260	$C_{11}H_{10}O_3N_2S$	N, 11.2	N, 10.90
11.	ω-Thiocyanato-3-methyl-4-methoxy-acetophenone	2-Hydroxy-4-(3-methyl-4-methoxy-phenyl)thiazole	36.6	80% ethanol	187	$C_{11}H_{11}O_2NS$	N, 6.33	N, 6.08
12.	ω-Thiocyanato-2-methyl-5-methoxy-acetophenone	2-Hydroxy-4-(2-methyl-5-methoxy-phenyl)thiazole	50	Ethanol	230	$C_{11}H_{11}O_2NS$	S, 14.40	S, 14.47
13.	α-Thiocyanatopropio-phenone	2-Hydroxy-4-phenyl-5-methylthiazole	67	Ethanol	168	$C_{10}H_9ONS$	N, 7.3	N, 7.3
14.	α-Thiocyanato-*p*-chloropropio-phenone	2-Hydroxy-4-(4-chlorophenyl)-5-methylthiazole	83	80% ethanol	205	$C_{10}H_8ONSCl$	N, 6.68 S, 15.27	N, 6.36 S, 14.7
15.	α-Thiocyanato-*p*-methylpropiophe-none	2-Hydroxy-4-(*p*-tolyl)-5-methyl-thiazole	60	80% ethanol	184	$C_{11}H_{11}ONS$	N, 6.82	N, 6.64
16.	α-Thiocyanato-*p*-bromopropiophe-none	2-Hydroxy-4-(4-bromophenyl)-5-methylthiazole	61	80% ethanol	231	$C_{10}H_8ONSBr$	N, 11.85	S, 12.40
17.	α-Thiocyanato-*p*-ethylpropiophenone	2-Hydroxy-4-(4-ethyl-phenyl)-5-methyl-thiazole	60	80% ethanol	139	$C_{12}H_{13}ONS$	N, 6.39	N, 6.13

the therapeutic activity of the thiazole ring as well as of the resulting thiopegan derivatives.

The mechanism of the reaction leading to the formation of 2-hydroxy- and 2-chlorothiazoles has been reported already.[5,6]

2-Hydroxy-4-(4-acetaminophenyl)thiazole has been found to inhibit the growth of *Str. haemolyticus, M. pyrogenes varaures, S. paratyphi, S. schottmuelleri, S. typhi, B. coli, Sh. paradysenteriae* (Flexener), at a concentration of 1 in 1000 and only *Str. haemolyticus* at 1 in 5000 while 2-hydroxy-4-(2,5-dimethylphenyl)thiazole, 2-hydroxy-4-(2-hydroxy-5-methoxyphenyl)thiazole, and 2-hydroxy-4-(4-methylphenyl)-5-methyl thiazole have shown activity against *Str. haemolyticus, M. pyogenes, S. paratyphi, S. schottmeulleri*, and *S. typhi; Str. haemolyticus, M. pyogenes, B. subtilis*, and *S. paratyphi;* and *Str. haemolyticus, B. subtilis*, and *S. paratyphi*, respectively, at a dilution of 1 in 1000.

Experimental

General Procedure for the Preparation of 2-Hydroxythiazoles.—Thiocyanato ketone, 4.0 g., was dissolved in 16 to 20 ml. of glacial acetic acid and to this was added a solution containing 2 ml. of water and 0.5 to 1 ml. of concd. sulfuric acid. The mixture was heated on a water bath for 1–2 hr. After cooling and dilution with 50–60 ml. of water, the product was collected by suction over a Büchner funnel.

TABLE II

2-CHLOROTHIAZOLES

SL. No.	ω-Thiocyanato Ketone	Product	Yield, %	Solvent of Crystallisation	M.P. or B.P./Mm.	Molecular Formula	Calcd.	Found
1.	ω-Thiocyanato-*p*-ethoxyacetophenone	2-Chloro-4-(4-ethoxyphenyl)thiazole	57	Ethanol	100	$C_{11}H_{10}ONSCl$	N, 5.88 S, 13.36	N, 5.66 S, 13.7
2.	ω-Thiocyanatovanillone	2-Chloro-4-(3-methoxy-4-hydroxyphenyl)thiazole Hydrochloride	69	60% ethanol –glacial acetic acid	70 190	$C_{10}H_8O_2NSCl$ $C_{10}H_9O_2NSCl_2$	S, 12.8 N, 5.0	S, 13.2 N, 4.45
3.	ω-Thiocyanato-3,4-dimethoxyacetophenone	2-Chloro-4-(3,4-dimethoxyphenyl)-thiazole	58	40% ethanol	120	$C_{11}H_{10}O_2NSCl$	N, 5.5	N, 5.23
4.	ω-Thiocyanato-2,4-dimethoxyacetophenone	2-Chloro-4-(2,4-dimethoxyphenyl)-thiazole	50	80% ethanol	105	$C_{11}H_{10}O_2NSCl$	N, 5.47	N, 5.30
5.	ω-Thiocyanato-2,5-dimethoxyacetophenone	2-Chloro-4-(2,5-dimethoxyphenyl)-thiazole	69.4	Ethanol	100	$C_{11}H_{10}O_2NSCl$	N, 5.47	N, 5.5
6.	ω-Thiocyanato-*p*-ethylacetophenone	2-Chloro-4-(4-ethylphenyl)thiazole	61	80% ethanol	50	$C_{11}H_{10}NSCl$	N, 6.25	N, 6.1
7.	ω-Thiocyanato-2-hydroxy-5-methoxyacetophenone	2-Chloro-4-(2-hydroxy-5-methoxyphenyl)thiazole	70	80% ethanol	105	$C_{10}H_8O_2NSCl$	N, 5.79	N, 5.78
8.	ω-Thiocyanato-2-hydroxy-4-methoxyacetophenone	2-Chloro-4-(2-hydroxy-4-methoxyphenyl)thiazole	48	80% ethanol	95–96	$C_{10}H_8O_2NSCl$	N, 5.79	N, 5.62
9.	α-Thiocyanatopropiophenone	2-Chloro-4-phenyl-5-methylthiazole	60.7		90–95°/30 mm.	$C_{10}H_8NSCl$	Cl, 16.94	Cl, 17.34
10.	α-Thiocyanato-*p*-chloropropiophenone	2-Chloro-4-(4-chlorophenyl)-5-methylthiazole	88		100°/15 mm.	$C_{10}H_7NSCl_2$	Cl, 29.09	Cl, 28.95
11.	α-Thiocyanato-*p*-methylpropiophenone	2-Chloro-4-methylphenyl-5-methylthiazole	82		100°/15 mm.	$C_{11}H_{10}NSCl$	N, 6.26	N, 6.22
12.	α-Thiocyanato-*p*-bromopropiophenone	2-Chloro-4-(4-bromophenyl)-5-methylthiazole	73.8		100°/8 mm.	$C_{10}H_7NSCl$	N, 4.85 S, 11.09	N, 4.7 S, 11.09
13.	α-Thiocyanato-*p*-ethylpropiophenone	2-Chloro-4-(4-ethylphenyl)-5-methylthiazole	82		100°/12 mm.	$C_{12}H_{12}NSCl$	N, 5.89 Cl, 14.90	N, 5.53 Cl, 14.93

All the hydroxythiazoles were obtained in a fairly pure form. These were, however, crystallized from the appropriate solvents. The yields, physical characteristics and analytical data for 2-hydroxythiazoles is given in Table I.

2-Chlorothiazoles.—Each thiocyanato ketone, 2 g., was dissolved in 100 to 120 ml. of absolute ether which was then saturated with dry hydrochloric acid (*ca.* 2 hr.). After removing the solvent, the residue was triturated with a 2% solution of sodium carbonate in the cold, filtered, washed with water and crystallized from dilute ethanol in light pale needles. The liquid products were distilled *in vacuo*.

In the case of 2-chloro-4-(3-methoxy-4-hydroxyphenyl)-thiazole, the hydrochloride has been isolated. The product after crystallization from glacial acetic acid melts at 190°.

Anal. Calcd. for $C_{10}H_9O_2NSCl_2$: N, 5.0. Found: N, 4.90.

The yields, physical characteristics, and analytical data for 2-chlorothiazoles are listed in Table II.

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