Synthesis of Some Optically Active Thiazole Derivatives

By **Luciano Lardicci,* Carlo Battistini,** and **Rita Menicagli,** Istituto di Chimica Organica, Facoltà di Scienze M.F.N., Università di Pisa, 56100, Pisa, Italy

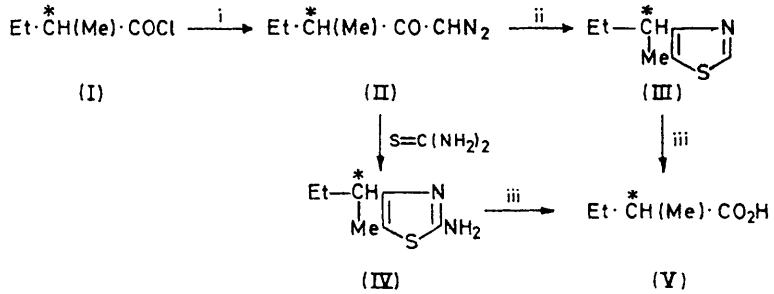
Optically active and racemic 4-s-butylthiazole and 2-amino-4-s-butylthiazole were prepared in 50 and 85% yields, respectively, from s-butyl diazomethyl ketone (prepared from 2-methylbutanoic acid). The optically active heterocyclic compounds were correlated *via* the Chichibabin reaction and the stereoselectivity of the reactions employed was established by ozonolysis of (+)-(*S*)-4-s-butylthiazole and (+)-(*S*)-2-amino-4-s-butylthiazole to (+)-(*S*)-2-methylbutanoic acid.

THE thiazole ring is present in some natural and synthetic products of biological and pharmacological importance,[1] and many synthetic procedures have been suggested for mono- and poly-substituted thiazole rings [2-6] but no simple monosubstituted optically active thiazole derivatives have been prepared to date. In connexion with our investigations on the stereochemistry of cyclization in the synthesis of optically active heterocyclic systems,[7-9] (+)-(*S*)-4-s-butylthiazole (III) and (+)-(*S*)-2-amino-4-s-butylthiazole (IV) were prepared from (+)-(*S*)-2-methylbutanoic acid.[10]

The present paper describes these preparations and the determination of the relationship between the absolute configuration and the sign of the rotation as well as that between the optical purity and optical rotation.

Analogously (III) was prepared by treating (II) with formamide and phosphorus pentasulphide in dioxan solution, under the same conditions as employed for the preparation of methyl thiazoles from the corresponding halogeno-ketones.[4] The results are satisfactory even when crude (II) is employed, so this procedure is to be regarded as a more convenient synthetic approach to the 4-alkyl thiazoles. Compounds (III) and (IV) were obtained in 38—46 and 56—64% yield, respectively [based on the acid chloride (I) used] (see Scheme 1).

The structure of the thiazole derivatives prepared was confirmed by n.m.r.[11,12] and i.r. spectroscopy.[13] The absolute configurations of (III) and (IV) were deduced directly from that of (+)-(*S*)-2-methylbutanoic acid [7-10] employed in their synthesis, as none of the reactions involved the asymmetric centre. Moreover, to obtain



SCHEME 1 *Reagents:* i, CH_2N_2; ii, P_4S_{10}–$HCO{\cdot}NH_2$; iii, a, O_3, b, H_2O_2–OH^-, c, H_3O^+

Although (+)-(*S*)-(III) and (+)-(*S*)-(IV) could be prepared *via* (*S*)-1-chloro-3-methylpentan-2-one [as previously used in the synthesis of (+)-(*S*)-3-s-butylfuran [9]], (IV) was obtained following King and Miller's procedure;[3] (+)-(*S*)-s-butyl diazomethyl ketone (II) [from the reaction between (+)-(*S*)-2-methylbutanoyl chloride (I) (o.p. $\geqslant$ 96%) and diazomethane in ether at 0°] was treated with thiourea in ethanol solution (see Scheme 1).

a quantitative indication of the steric course in the preparation of the two optically active compounds, (III) and (IV) were cleaved by ozonolysis to (+)-(*S*)-2-methylbutanoic acid (V) (Scheme 1).

On the basis of the optical rotation of the recovered (V), a minimum optical purity of 61% is estimated for

[1] (*a*) A. Albert, ' Heterocyclic Chemistry,' The Athlone Press, London, 1968, p. 293 and references therein; (*b*) R. M. Acheson, ' An Introduction to the Chemistry of Heterocyclic Compounds,' Wiley, New York, 1967, pp. 46, 323, 326, and related references.

[2] (*a*) R. H. Wiley, D. C. England, and L. C. Behr, *Org. Reactions*, 1951, **5**, 367; (*b*) J. M. Sprague and A. H. Land, in *Heterocyclic Compounds*, vol. 5, ed. R. C. Elderfield, Wiley, New York, 1957, pp. 484—722.

[3] L. C. King and F. M. Miller, *J. Amer. Chem. Soc.*, 1949, **71**, 367.

[4] R. P. Kurkjy and E. W. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 5778.

[5] (*a*) M. Poite and J. Metzger, *Bull. Soc. chim. France*, 1962, 2078, and references therein; (*b*) G. Vernin and J. Metzger, *ibid.*, 1963, 2498.

[6] W. Hampel and I. Müller, *J. prakt. Chem.*, 1968, **38**, 320.

[7] L. Lardicci, C. Botteghi, and P. Salvadori, *Gazzctta*, 1968, **98**, 760.

[8] C. Botteghi, E. Guetti, C. Ceccarelli, and L. Lardicci, *Gazzetta*, 1972, **102**, 945.

[9] C. Botteghi, L. Lardicci, and R. Menicagli, *J. Org. Chem.*, 1973, **38**, 2361.

[10] L. Lardicci, C. Botteghi, and E. Belgodere, *Gazzetta*, 1967, **97**, 610.

[11] (*a*) A. Taurins and W. G. Schneider, *Canad. J. Chem.*, 1960, **38**, 1237; (*b*) R. F. M. White, in ' Physical Methods in Heterocyclic Chemistry,' vol. 2, ed. A. R. Katritzky, Academic Press, New York, 1963, p. 138.

[12] M. Sélim, G. Martin, and M. Sélim, *Bull. Soc. chim. France*, 1968, 3268.

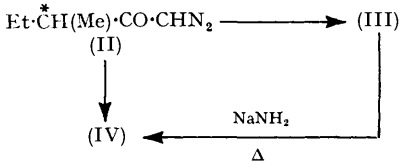
[13] A. Taurins, J. G. E. Fenyes, and R. N. Jones, *Canad. J. Chem.*, 1947, **35**, 423; A. R. Katritzky, *Quart. Rev.*, 1959, **13**, 353; M. P. V. Mijovic and H. Walker, *J. Chem. Soc.*, 1961, 3381; G. Davidovics, G. Garrigou-Lagrange, J. Choteau, and J. Metzger, *Spectrochim. Acta*, 1967, **23A**, 1477.

(III) while only a 50% optical purity is deduced for (IV) (Table).

As previously reported [10] the racemization encountered in the conversion of (+)-(*S*)-2-methylbutanoic acid (V) into (I) was determined hydrolysing a sample of optically active (I) to give (V), the results showing an optical yield ⩾97%.

The minimum optical purity of (II) was evaluated from the data reported for the conversion of the diazoketone into (+)-(*S*)-3-methylpentanoic acid,[14] taking, for the optically pure acid, $[\alpha]_D^{25}$ +8·83°.[15] The results indicate that no racemization occurs in the step (I) ⟶ (II).*

On the other hand, by assuming that in the oxidative degradations of (III) and (IV) no appreciable racemization occurs,[7-9] the racemization evaluated (Table) must therefore take place in the cyclization step.[9] At present we are unable to explain the different extent in the synthesis of (III) (~39%) and (IV) (~50%).† However, to check the results obtained, a direct chemical interrelation between (III) and (IV) was performed; a sample



(II), $[\alpha]_D^{25}$ + 55·12 ± 0·05° (neat)
(IV) from (II), $[\alpha]_D^{25}$ + 10·09° (iso-octane)
(III), $[\alpha]_D^{25}$ + 15·53° (neat)
(IV) from (III), $[\alpha]_D^{25}$ + 12·94° (iso-octane)

SCHEME 2

of (+)-(*S*)-(III) was converted into (+)-(*S*)-(IV) *via* Chichibabin reaction [16] (Scheme 2).

The optical purity of the recovered (+)-(*S*)-(IV) (~64%) was in good agreement with that of the starting (+)-(*S*)-(III) (~61%).

According to our previous evidence from the ozonolysis of other optically active heterocyclic compounds,[7-9] this last result confirms in the case of the thiazole ring that cleavage by ozone does not affect the chiral centre of the optically active alkyl substituent and reinforces the reliability of the above assumption.

Maximum racemization in the synthesis of (+)-(*S*)-4-s-butylthiazole (III) and (+)-(*S*)-2-amino-4-s-butylthiazole (IV)

	Starting materials		(III), $[\alpha]_D^{25}$	(IV), $[\alpha]_D^{25}$	(V)	
	$[\alpha]_D^{25}$ (neat) (°)	Opt. purity (%)	(neat) (°)	(iso-octane) (°)	$[\alpha]_D^{25}$ (°)	Opt. purity (%)
(I)	+18·27	97·3 [a]	+15·53		+11·84 (cyclohexane)	61·0 [c]
(II)	+55·07	97·3 [b]				
(I)	+18·03	96·0 [a]	+15·69			
(II)	+54·30	96·0 [b]				
(I)	+18·29	97·4 [a]		+10·09	+9·82	49·6 [d]
(II)	+55·17	97·4 [b]				
(I)	+18·25	97·2 [a]		+6·36		
(II)	+54·80	97·2 [b]				

[a] Opt. pure (+)-(*S*)-2-methylbutanoyl chloride, $[\alpha]_D^{25}$ + 18·78°. [b] Opt. pure (+)-(*S*)-s-butyl diazomethyl ketone, $[\alpha]_D^{25}$ + 56·6°. [c] Opt. pure (+)-(*S*)-2-methylbutanoic acid, $[\alpha]_D^{25}$ + 19·45° (cyclohexane). [d] Opt. pure (+)-(*S*)-2-methylbutanoic acid, $[\alpha]_D^{25}$ + 19·8° (neat).

EXPERIMENTAL

I.r. spectra were determined for liquid films with a Perkin-Elmer 225 spectrophotometer. N.m.r. spectra were determined with JEOL C-60 HL spectrometer operating at 60 MHz with tetramethylsilane as internal standard. G.l.c. was carried out with a C.Erba GT instrument using 2 m columns with nitrogen as carrier gas. Columns were packed with 10% butanediol succinate and 10% Igepol CO880 on 60/80 mesh Chromosorb W. All rotations, unless otherwise indicated, were taken neat on a Schmidt–Haensch polarimeter in 0·5, 1·0, and 2·0 dm tubes.

(+)-(S)-2-*Methylbutanoyl Chloride* (I).—Thionyl chloride (96·6 g, 0·81 mol) was added dropwise to well stirred (+)-(*S*)-2-methylbutanoic acid (41·0 g, 0·40 mol), b.p. 85° at 20 mmHg, n_D^{25} 1·4044, $[\alpha]_D^{25}$ +19·72°, in dry ether (100 ml) at 0°. After 40 h at room temperature the mixture was refluxed 1 h and the ether was distilled off. Formic acid (99%; 18·6 g, 0·40 mol) was added to the stirred mixture which was then heated to 30—40° for 5 h. The crude product was distilled to yield (+)-(S)-(I) (37·3 g, 77·5%), b.p. 60° at 110 mmHg, α_D^{25} (*l* 0·5) +8·89°.

In a similar manner (+)-(*S*)-2-methylbutanoic acid, $[\alpha]_D^{25}$ +19·75°, yielded (+)-(*S*)-(I), α_D^{25} (*l* 0·5) +9·02°.

(+)-(S)-*s-Butyl Diazomethyl Ketone* (II).—To *ca.* 2 l of an ice-cold ethereal solution of diazomethane [prepared from *N*-nitrosomethylurea (200·0 g, 1·94 mol)], was added, under nitrogen, (+)-(*S*)-(I) (31·8 g, 0·26 mol), α_D^{25} (*l* 0·5) +8·89°, in dry ether (100 ml). After standing 15 h the solvent was removed under reduced pressure (60—100 mmHg), and the residue was filtered and distilled to give (+)-(*S*)-(II) (29·3 g, 88·4%) which, after redistillation, showed b.p. 87—89° at 20 mmHg, n_D^{25} 1·4757, $[\alpha]_D^{25}$ +54·30° (lit.,[19] b.p. 75° at 13 mmHg, n_D^{25} 1·4770, d_4^{25} 0·969, $[\alpha]_D^{25}$ −9·00°). One other preparation, starting

* By starting from a sample of (−)-(*R*)-(I), o.p. 16%, through Wolff rearrangement of (−)-(*R*)-(II) by the silver benzoate–triethylamine method, Wiberg and Hutton [14] recovered (−)-(*R*)-3-methylpentanoic acid having o.p. 15·2%. In our opinion the racemization (~5%) occurs in the conversion of (II) into 3-methylpentanoic acid [14] rather than in the conversion of (I) into (II). According to this hypothesis the maximum rotation of (II) is to be deduced from that of the acyl chloride (I).

† The racemization of (II) could take place in principle before the same cyclization step and/or in this last one; in the mechanism proposed by Hampel and Müller [6] for the reaction between a diazoketone and thiourea to give an aminothiazole, the cyclization proceeds through ionic intermediates which in our case, could be responsible for the observed racemization.[9]

[14] K. Wiberg and T. W. Hutton, *J. Amer. Chem. Soc.*, 1956, **78**, 1640.
[15] L. Lardicci and L. Conti, *Ann. Chim.* (*Italy*), 1961, **51**, 823.
[16] (*a*) E. Ochiai and F. Nagasawa, *J. Pharm. Soc. Japan*, 1939, **59**, 43; (*b*) W. Solomon, *J. Chem. Soc.*, 1946, 934· (*c*) J. Lecocq, *Bull. Soc. chim. France*, 1950, 190.

from (+)-(*S*)-(I), α_D^{25} (*l* 0·5) +9·02°, afforded (+)(*S*)-(II) (77%) having b.p. 78—79° at 15 mmHg, n_D^{25} 1·4763, $[\alpha]_D^{25}$ +55·17°.

(*RS*)-(II), b.p. 78—79° at 15 mmHg, n_D^{25} 1·4753—1·4759, was prepared analogously (90%).

(+)-(S)-4-*s-Butylthiazole* (III).—Formamide (16·4 g, 0·36 mol) was added to phosphorus pentasulphide (17·0 g, 0·076 mol) in dioxan (40 ml) (refluxed and distilled over sodium wire), with cooling (ice–water), then (+)-(*S*)-(II) (29·3 g, 0·23 mol), $[\alpha]_D^{25}$ +54·30°, in dioxan (30 ml), was dropped in over 1 h. The solution was refluxed (2·5 h) under nitrogen and set aside overnight.

A solution of conc. hydrochloric acid (50 ml) in water (30 ml) was added and the mixture was steam-distilled to remove volatile organic materials. The mixture was then made basic with 50% sodium hydroxide solution and steam-distilled again. The distillate was saturated with potassium carbonate and organic product was extracted with ether, dried, and distilled to give (+)-(*S*)-(III) (16·7 g, 51·0%) which, after redistillation, showed b.p. 77° at 20 mmHg, n_D^{25} 1·4994, d_4^{25} 1·008, $[\alpha]_D^{25}$ +15·69°, $[\alpha]_D^{25}$ +13·50° (*c* 3·371 in iso-octane), picrate, m.p. 106°. Similar treatment of crude (+)-(*S*)-(II) [obtained from (+)-(*S*)-(I), α_D^{25} (*l* 0·5) +9·01°], afforded (+)-(*S*)-(III) (50%), b.p. 70° at 13 mmHg, n_D^{25} 1·4994, $[\alpha]_D^{25}$ +15·53°.

(*RS*)-(III), prepared in a similar way (44%) showed, after redistillation, b.p. 71—72° at 14 mmHg, n_D^{25} 1·4993 (Found: C, 59·4; H, 8·05; N, 10·15; S, 22·35. $C_7H_{11}NS$ requires C, 59·55; H, 7·85; N, 9·9; S, 22·65%), $\nu_{max.}$ 3110, 3080, 1505, 1405, 920, 875, and 810 cm^{-1}, δ(neat) 8·90 (1H, d, $J \sim 2$ Hz, H-2) and 7·00 (1H, d, H-5).

(+)-(S)-2-*Amino*-4-*s-butylthiazole* (IV).—(+)-(*S*)-(II) (8·2 g, 0·065 mol), $[\alpha]_D^{25}$ +55·17°, was treated with thiourea (6·6 g, 0·08 mol) in absolute ethanol (35 ml), under reflux (1 h). After cooling, the mixture was acidified with hydrochloric acid and refluxed again (20 min). The ethanol was evaporated off and the residue was extracted three times with ether and then was made alkaline with ammonium hydroxide, extracted again with ether, and dried (KOH). Removal of the solvent and distillation from KOH afforded (+)-(*S*)-(IV) (85·0%) which, after redistillation, showed b.p. 74° at 0·2 mmHg, n_D^{25} 1·5518, $[\alpha]_D^{25}$ +10·09° (*c* 2·576 in iso-octane). Starting from (+)-(*S*)-(II), $[\alpha]_D^{25}$ +54·80°, adopting the same procedure, crude (+)-(*S*)-(IV) was recovered. This sample was dissolved in hydrochloric acid (50%) and the solution was extracted with ether and then made basic with ammonium hydroxide. Organic product was extracted with ether and dried (KOH). Distillation afforded (+)-(*S*)-(IV) (70%), b.p. 90° at 0·4 mmHg, n_D^{25} 1·5520, $[\alpha]_D^{25}$ +6·36° (*c* 2·162 in iso-octane). (*RS*)-(IV) was also prepared in a similar manner, b.p. 93° at 0·5 mmHg, n_D^{20} 1·5545, n_D^{25} 1·5220, picrate, m.p. 189° (Found: C, 53·8; H, 8·0; N, 17·9; S, 21·25. $C_7H_{12}N_2S$ requires C, 53·85; H, 7·75; N, 17·95; S, 20·5%), $\nu_{max.}$ 3450, 3290, 3120, 1605, 1525, and 1360 cm^{-1}, $\delta(CDCl_3)$ 6·00 (1H, s, H-5) and 6·25, 5·35 (2H, s, NH_2) (50 or 7% solution, respectively).

(+)-(S)-2-*Amino*-4-s-*butylthiazole* (IV) via *Chichibabin Reaction*.—Powdered sodamide (1·66 g, 0·042 mol) was added to purified decalin (60 ml) under nitrogen in a dry flask. (+)-(*S*)-(III) (5·0 g, 0·035 mol), $[\alpha]_D^{25}$ +15·53°, in decalin (10 ml) was added and the mixture was heated at 150° for 22 h then cooled to room temperature and cautiously poured into ice. After acidification with conc. hydrochloric acid the aqueous solution was extracted with ether and then a solution of sodium hydroxide (30%) was added. The organic product was extracted into ether and dried (KOH). Distillation afforded (+)-(*S*)-(IV) (0·570 g, 10%), b.p. 75° at 0·15 mmHg, $[\alpha]_D^{25}$ +12·94° (*c* 3·632 in iso-octane), and unchanged (+)-(*S*)-(III) (1·4 g), $[\alpha]_D^{25}$ +15·65°.

Ozonolysis of (+)-(S)-4-*s-Butylthiazole* (III).—(+)-(*S*)-(III) (5·6 g, 0·04 mol), $[\alpha]_D^{25}$ +15·53°, was dissolved in methylene chloride (90 ml) and a stream of oxygen containing 3—5% of ozone was passed into the solution (6 h) at 0°. The solvent was removed and the ozonide, in ethanol (50 ml) and 10% sodium hydroxide (50 ml), was decomposed with 31% H_2O_2 under reflux (4 h). Ethanol was distilled off and the organic product recovered by the usual procedure. Distillation afforded (+)-(*S*)-2-methylbutanoic acid (0·88 g, 22%), b.p. 75—76° at 13 mmHg, n_D^{25} 1·4042, $[\alpha]_D^{25}$ +11·84° (*c* 3·464 in cyclohexane).

Ozonolysis of (+)-(S)-2-*Amino*-4-s-*butylthiazole* (IV).—(+)-(*S*)-(IV) (4·7 g, 0·03 mol), $[\alpha]_D^{25}$ +10·09° (iso-octane), in methylene chloride (80 ml), was ozonized by the above procedure and (+)-(*S*)-2-methylbutanoic acid (1·48 g, 48%) was obtained, b.p. 76° at 13 mmHg, n_D^{25} 1·4043, $[\alpha]_D^{25}$ +9·82° (neat).

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