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HETEROCYCLIC COMPOUNDS FROM SUGARS

PART IV*. DIASTEREOISOMERIC AND ENANTIOMERIC 3-METHYL-2-(POLYHYDROXYALKYL)-BENZOTHIAZOLINES**

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ABSTRACT

A number of 3-methyl-2-(polyhydroxyalkyl)benzothiazolines (**3a–f**) have been prepared from various aldoses. 3-Methyl-2-(polyacetoxyalkyl)benzothiazolines have been prepared from acetylated *aldehydo*-sugars or by acetylation of compounds **3d–f**. The C-2 diastereoisomers of both series have been obtained in pure state by fractional crystallisation. The stereohomogeneity of the compounds has been investigated by t.l.c. and by spectroscopic methods (i.r. and n.m.r.).

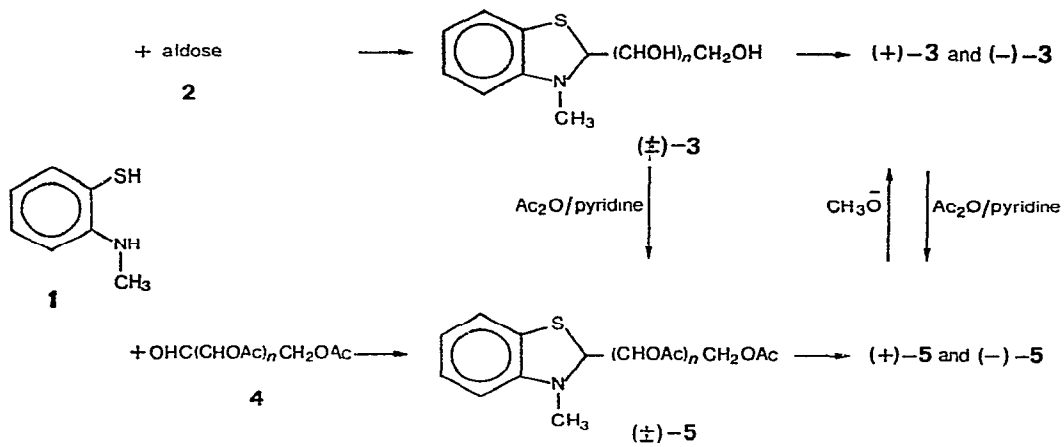
INTRODUCTION

Heterocyclic derivatives having a polyhydroxyalkyl chain attached to the ring and synthesised from simple sugars or sugar derivatives are exemplified by the following compounds. 2-(Polyhydroxyalkyl)benzimidazoles[2], osotriazoles[3], 2-(polyhydroxyalkyl)quinoxalines[4], polyhydroxyalkyl-1*H*-pyrazolo[3,4-*b*]quinoxalines (sugar flavazoles)[5], 2-(polyhydroxyalkyl)-thiazoles[6,7] and -thiazolidines[1,8,9], polyhydroxyalkyl-furans[10] and -pyrroles[11], polyhydroxyalkylimidazoles[12], and 2-(polyhydroxyalkyl)-benzothiazoles[7] and -benzothiazolines[13,14]. The 2-(polyhydroxyalkyl)benzothiazolines were first prepared by Sattler *et al.*[13] from aldoses and *o*-aminobenzenethiol. We have recently studied[14] the synthesis and structure of 2-(polyhydroxyalkyl)- and 2-(polyacetoxyalkyl)-benzothiazolines. Since they contain an "*N,S*-acetal" structure, these compounds are structurally similar to those glycosylamines or 1-thioglycosides which contain a sulphur[15] or a nitrogen atom[16] in the ring. The reaction of *o*-aminobenzenethiol with free monosaccarides[13,14] or with *aldehydo* sugars[14] results in the formation of a new asymmetric centre at C-2 of the benzothiazoline ring. The product obtained is therefore generally a mixture of the two diastereoisomeric forms. There has been no report in the literature of the preparation of such diastereoisomers, and we now describe several examples in which separations of diastereoisomers have been achieved.

*For Part III, see Ref. 1.
**Dedicated to Professor F. Micheel in celebration of his 70th birthday.

DISCUSSION

Our attention was directed towards *N*-methylated benzothiazoline derivatives since they were expected to undergo racemisation less readily than those unsubstituted on nitrogen. Several 2-(polyhydroxyalkyl) and 2-(polyacetoxyalkyl) derivatives of 3-methylbenzothiazolines have been prepared (Scheme 1).



Scheme I

The pure, diastereoisomeric 3-methyl-2-(polyhydroxyalkyl)benzothiazolines and their acetates were obtained by one of the following methods.

Method A: **1+2→(±)-3→(+)-3** *and* **(−)-3.** — The aldose **2** and *o*-methylaminobezenethiol (**1**) were heated in pyridine at 100°. Unreacted sugar could always be detected in the reaction mixture by paper chromatography, even after a prolonged reaction time. After removing the unreacted sugar, the pure diastereoisomers were obtained by fractional crystallisation.

Method B: **1+4 → (±)-5 → (+)-5** *and* **(−)-5.** — The reaction of the acetylated *aldehydo*-sugar[4] with *o*-methylaminobenzenethiol was carried out in hot ethanol. The components of the diastereoisomeric mixture **[(±)-5]** of 3-methyl-2-(polyacetoxyalkyl)benzothiazolines were separated by fractional crystallization. They were deacetylated (Zemplén) to give the corresponding 3-methyl-2-(polyhydroxyalkyl)benzothiazolines **(+)-3** and **(−)-3.**

Method C: **1+2 → (±)3 → (+)-3** and **(−)-3 → (+)-5** and **(−)-5.** — The pure diastereoisomers of 3-methyl-2-(polyhydroxyalkyl)benzothiazolines (**3**) obtained by Method *A* were acetylated under the usual conditions with acetic anhydride–pyridine.

Method D: **1+2→(±)-3→(±)-5→(+)-5** *and* **(−)-5.** — The diastereoisomeric 3-methyl-2-(polyhydroxyalkyl)benzothiazolines **[(±)-3]** obtained by Method *A* were acetylated in pyridine–acetic anhydride. The diastereoisomeric acetates **[(±)-5]** were separated by fractional crystallisation. This procedure was used in those

cases where the nonacetylated derivatives [(±)-3] could not be separated by crystallisation.

For the 3-methyl-2-(tetrahydroxybutyl)benzothiazolines (3; $n = 3$), acetylation even under mild conditions (acetic anhydride–pyridine at −14°), failed to give crystalline derivatives.

The physical constants for the various benzothiazoline derivatives are given in Tables I and II.

TABLE I

3-METHYL-2-(POLYHYDROXYALKYL)BENZOTHIAZOLINES

Compound	*Configuration of the side chain*	*Method of preparation*	*M.p. (degrees)*	$[\alpha]_D^{23}$ (c *0.5, pyridine*) *(degrees)*
(+)-3a	D-*arabino*	A	178–179	+305
(−)-3a	"	A	171–172	−264
(+)-3b	L-*arabino*	A	170–171	+266
(−)-3b	"	A	178–179	−304
(+)-3c	D-*ribo*	A	135–136	+59[a]
(−)-3c	"	A	156–157	−187
(+)-3d	D-*gluco*	A	140–141	+205
(−)-3d	"	A	135–137	−162[a]
(+)-3e	D-*galacto*	B	174–175	+261
(−)-3e	"	B	169–170	−295
(+)-3f	D-*manno*	A	166–167	+124
(−)-3f	"	D	144–145.5	−82

[a]Mixture of diastereoisomers.

TABLE II

3-METHYL-2-(POLYACETOXYALKYL)BENZOTHIAZOLINES

Compound	*Configuration of the side chain*	*Method of preparation*	*M.p. (degrees)*	$[\alpha]_D^{23}$ (c *0.5, chloroform*) *(degrees)*
(+)-5a	D-*gluco*	C	127–128	+198
(−)-5a	"	C	109–110	−31[a]
(+)-5b	D-*galacto*	B	121–122	+250
(−)-5b	"	B	132	−125
(+)-5c	D-*manno*	C, D	117.5–118	+219
(−)-5c	"	D	145–146.5	−88

[a]Mixture of diastereoisomers.

The stereochemical purity of the crystalline derivatives listed in Tables I and II was established by t.l.c. and spectroscopic methods. The diastereomeric pairs of 3-methyl-2-(polyacetoxyalkyl)benzothiazolines (5) are well separated on t.l.c. plates in various solvent systems (*e.g.*, benzene–acetone 9:1, and benzene–ether 6:4). On the other hand, the 3-methyl-2-(polyhydroxyalkyl)benzothiazoline pairs (3) did not show any separation in a number of solvent systems.

In the case of derivatives **3a** and **3b**, the stereochemical purity could be verified on the basis of physical constants and infrared spectra. As can be seen from Table I,

the physical constants of the four compounds, (+)-**3a**, (−)-**3a**, (+)-**3b**, (−)-**3b**, are in accordance with their stereochemical inter-relationships, namely, two pairs of diastereoisomers [(+)-**3a**, (−)-**3a** and (+)-**3b**, (−)-**3b**] and two pairs of enantiomers [(+)-**3a**, (−)-**3b** and (+)-**3b**, (−)-**3a**]. The infrared spectra of compounds (+)-**3a** and (−)-**3a** are quite different, whereas those of (+)-**3a** and (−)-**3b** are identical.

The stereohomogeneity of the isomers can also be checked by n.m.r. spectroscopy. The n.m.r. spectra of the diastereoisomers show signals for N–CH_3 groups in the τ 7.05–7.25 region. There is a difference of 0.14–0.18 p.p.m. between the N–CH_3 signals of the diastereoisomeric pairs. There are two peaks at τ 7.07 and 7.22 (of relative intensities 8:7) in the spectrum of (+)-**3c**. On the other hand, there is only one N–CH_3 resonance at τ 7.25 in the spectrum of (−)-**3c**. Thus, compound (+)-**3c** is an 8:7 mixture of the (+)- and (−)-isomers, and this is also indicated by the low optical rotation value of (+)-**3c** (Table I). Similarly, compound (−)-**5a** is a 13:5 mixture of the (−)- and (+)-isomers (N–CH_3 resonances at τ 7.07 and 7.20). All the other compounds listed in Tables I and II were homogeneous when investigated by the above methods.

EXPERIMENTAL

Melting points were determined on a Boetius hot-stage and are uncorrected. Evaporations were performed *in vacuo* at a bath temperature of 35–45°. T.l.c. was performed on Kieselgel G (Merck) plates of 0.25-mm thickness. Compounds were located with iodine vapor. The hydrolysates (M HCl, 100°, 30 min) of the 3-methyl-2-(polyhydroxyalkyl)benzothiazolines were monitored by paper chromatography with *A*, butyl alcohol–pyridine–water (6:4:3); *B*, ethyl acetate–acetic acid–water (44:20:10); and *C*, butyl alcohol–benzene–formic acid–water (100:19:10:25, upper phase). Optical rotations were determined in 1-dm tubes. Infrared spectra were recorded for KBr discs on a Unicam Model SP-200G spectrophotometer. N.m.r. spectra were determined with a Varian HA-100 intrument for solutions in methyl sulphoxide with hexamethyldisiloxane as internal standard. Melting points and $[\alpha]_D$ values for products are recorded in Tables I and II.

3-Methyl-2-(D-arabino-*tetrahydroxybutyl)benzothiazoline* [(+)-**3a**]. — D-Arabinose (5 g, 33.3 mmoles) was dissolved in 40 ml of dry pyridine, and nitrogen was bubbled trough the solution. *o*-Methylaminobenzenethiol (5 g, 4.5 ml; 36 mmoles) was added, and the mixture was heated on a boiling-water bath for 3 h. The solution was evaporated to a yellow syrup which was dissolved in dry ethanol and again evaporated. This process was repeated 2–3 times until the residue solidified. It was then suspended in ether, filtered off, and washed with ether (100–120 ml). The resulting, white, crystalline solid contained a considerable proportion of D-arabinose as revealed by paper chromatography (solvent *A*, detection with silver nitrate). In order to remove the sugar, the mixture was stirred with 50 ml of water for 1 h and then filtered to give (±)-**3a**, which, after two recrystallisations from ethanol, gave (+)-**3a** (1.85 g).

Anal. Calc. for $C_{12}H_{17}NO_4S$: C, 53.05; H, 6.27; N, 5.16; S, 11.80. Found: C, 53.61; H, 6.34; N, 5.16; S, 11.97.

The first mother liquor from the crystallisation of (+)-**3a** was evaporated to dryness, and the residue was recrystallized three times from acetone (100–150 ml/g) to give (−)-**3a** (0.553 g). The i.r. spectrum was identical with that of (+)-**3b**.

3-Methyl-2-(L-arabino-*tetrahydroxybutyl)benzothiazoline* (**3b**). — Compound (±)-**3b** (7.1 g, 79%) was prepared from 5 g of L-arabinose as for the D-isomer.

Two recrystallisations of the crude product from methanol gave (−)-**3b** (0.818 g). The i.r. spectrum was identical with that of (+)-**3a**.

The first mother liquor from the crystallisation of (−)-**3b** was evaporated to dryness, and the residue was recrystallised twice from acetone (100–120 ml/g) to give (+)-**3b** (1.19 g).

Anal. Found: C, 53.16, H, 6.27; N, 5.13; S, 11.78.

3-Methyl-2-(D-ribo-*tetrahydroxybutyl)benzothiazoline* (**3c**). — D-Ribose (2 g) 13.3 mmoles) was dissolved in 20 ml of dry pyridine, and nitrogen was bubbled through the solution. *o*-Methylaminobenzenethiol (2 g, 1.8 ml; 14.3 mmoles) was added, and the solution was heated on a boiling-water bath for 3 h and then evaporated to dryness. The crystalline residue was suspended in absolute ethanol which was then evaporated. This process was repeated until the traces of pyridine were completely removed. The crude product was suspended in ether, filtered off, and washed with ether to give (±)-**3c** (2.32 g, 65%).

The above product was recrystallised twice from absolute ethanol to give (−)-**3c** (1.40 g).

Anal. Found: C, 53.06; H, 6.21; N, 5.19; S, 11.86.

The first mother liquor from the crystallisation of (−)-**3c** deposited crystals of (+)-**3c** (0.55 g). The physical constants remained unchanged on two further recrystallisations from isopropyl alcohol and ethyl acetate.

Anal. Found: C, 52.96; H, 6.19; N, 5.01; S, 11.79.

3-Methyl-2-(D-gluco-*pentahydroxypentyl)benzthiazoline* (**3d**). — Compound (±)-**3d** (4.4 g, 53%) was prepared from 5 g of D-glucose as described for compound (±)-**3a**.

Recrystallisation of (±)-**3a** 5–6 times from ethanol, until the optical rotation remained unchanged, gave (−)-**3d** (0.320 g).

Anal. Calc. for $C_{13}H_{19}NO_5S$: C, 52.03; H, 6.36; N, 4.56; S, 9.99. Found: C, 51.95; H, 6.30; N, 4.65; S, 10.64.

The first mother liquor from the crystallisation of (−)-**3d** was evaporated to dryness, and the residue was recrystallised three times from ethyl acetate to give (+)-**3d** (0.120 g).

Anal. Found: C, 51.80; H, 6.31; N, 4.75; S, 10.57.

(−)-*3-Methyl-2-*(D-galacto-*pentahydroxypentyl)benzothiazoline* [(−)-**3e**]. — Compound (−)-**5b** was suspended in 150 ml of dry methanol and 2 ml of M methanolic sodium methoxide was added. The substance slowly dissolved, and the solution soon deposited colourless needles. After storage overnight at room temperature, the

mixture was neutralised with acetic acid and filtered, and the filtrate evaporated to a small volume to give another crop of crystals. The two crops were combined (total weight, 1.43 g; 81%) and recrystallised from absolute ethanol to give (−)-**3e**. The physical constants remained unchanged upon two further recrystallisations.

Anal. Found: C, 52.08; H, 6.39; N, 4.66; S, 10.30.

(+)-*3-Methyl-2-*(D-galacto-*pentahydroxypentyl)benzothiazoline* [(+)-**3e**]. — Deacetylation of (+)-**5b** (0.5 g) with sodium methoxide as described above, with recrystallisation of the crude product (0.241 g, 82%) from ethanol, gave (+)-**3e**.

Anal. Found: C, 51.90; H, 6.08; N, 4.75; S, 10.33.

(+)-*3-Methyl-2-*(D-manno-*pentahydroxypentyl)benzothiazoline* [(+)-**3f**]. — This compound was prepared from D-mannose (5 g) in the same way as described for (±)-**3a**. Three recrystallisations (from methanol) of the crude product (4.81 g, 57%) gave (+)-**3f** (1.18 g).

Anal. Found: C, 51.90; H, 6.29; N, 4.63; S, 10.48.

(−)-*3-Methyl-2-*(D-manno-*pentahydroxypentyl)benzothiazoline* [(−)-**3f**]. — Compound (−)-**5c** (1 g) was deacetylated as described above, and the solution was then deionised with Amberlite IR-105 (H^+) cation exchanger and evaporated to dryness. The crude product (0.527 g, 90%) was recrystallised twice from ethyl acetate to give (−)-**3f**.

Anal. Found: C, 52.83; H, 6.26; N, 4.65; S, 10.70.

(+)-*3-Methyl-2-*(D-gluco-*pentaacetoxypentyl)benzothiazoline* [(+)-**5a**]. — Compound (+)-**3d** (0.1 g) was acetylated in a mixture of 5 ml of acetic anhydride and 5 ml of pyridine at 0° for 24 h to give a crude product (0.135 g, 80%) which was recrystallised from ethanol to give (+)-**5a**.

Anal. Calc. for $C_{23}H_{29}NO_{10}S$: C, 53.95; H, 5.81; N, 2.78; S, 6.25. Found: C, 54.20; H, 5.68; N, 2.79; S, 6.17.

(−)-*3-Methyl-2-*(D-gluco-*pentaacetoxypentyl)benzothiazoline* [(−)-**5a**]. — Compound (−)-**3d** (1 g) was acetylated with 10 ml of acetic anhydride and 10 ml of dry pyridine at −14° for 24 h to give a crude product (1.45 g, 86%) which was recrystallised twice from ethanol–water to yield material, m.p. 109–110°, $[\alpha]_D^{23}$ −31° (*c* 0.5, chloroform), which gave two spots on t.l.c. (benzene–acetone, 9:1), one of which had an R_F value identical with that of (+)-**5a**.

Anal. Found: C, 53.96; H, 5.53; N, 2.77; S, 6.28.

3-Methyl-2-(D-galacto-*pentaacetoxypentyl)benzothiazoline* (**5b**). — *aldehydo*-D-Galactose pentaacetate (5 g, 12.8 mmoles) was dissolved in 50 ml of hot, dry ethanol, while nitrogen was bubbled through the solution. *o*-Methylaminobenzenethiol (2 g, 1.8 ml; 14.3 mmoles) was added, and the solution was refluxed for 4 h. After removal of the ethanol, the residue was crystallised from 96% ethanol.

The crude product was treated with light petroleum (b.p. 60–80°) to give (±)-**5b** (4.05 g, 62%) which was recrystallised twice from a small volume of absolute ethanol to yield (−)-**5b**.

Anal. Found: C, 54.10; H, 5.73; N, 2.73; S, 6.19.

The light petroleum extract deposited fine colourless needles on storage at room temperature. Two recrystallisations from dilute ethanol gave (+)-**5b**.

Anal. Found: C, 54.50; H, 5.77; N, 2.65; S, 6.01.

(−)-*3-Methyl-2-*(D-manno-*pentaacetoxypentyl)benzothiazoline* [(−)-**5c**]. — Crude (±)-**3f** (2.25 g) was acetylated in a mixture of 20 ml of acetic anhydride and 20 ml of pyridine at −10° for 17 h to give material (3.52 g, 93%) which was recrystallised three times from a 1:2 mixture of ethanol–light petroleum (b.p. 80–100°) to give (−)-**5c**.

Anal. Found: C, 54.50; H, 5.84; N, 2.81; S, 6.10.

(+)-*3-Methyl-2-*(D-manno-*pentaacetoxypentyl)benzothiazoline* [(+)-**5c**]. — Compound (+)-**3f** (0.5 g) was acetylated in a mixture of 5 ml of acetic anhydride and 5 ml of pyridine at −14° for 24 h to give a crude product (0.770 g, 91%) which was recrystallised from aqueous ethanol to give (+)-**5c**. The physical constants did not change upon further recrystallisations.

Anal. Found: C, 53.96; H, 5.41; N, 2.73; S, 6.25.

The combined mother liquors from the crystallisation of (—)-**5c** were evaporated to dryness. The residue {$[\alpha]_D^{23}$ +190° (*c* 0.5, chloroform)} was recrystallised from aqueous ethanol to give (+)-**5c** which was identical (mixed m.p., i.r. spectra) with the product described above.

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REFERENCES

1 R. BOGNÁR, L. SOMOGYI, AND Z. GYÖRGYDEÁK, *Ann.*, 68 (1970) 738.
2 N. K. RICHTMEYER, *Advan. Carbohyd. Chem.*, 6 (1951) 175.
3 H. EL KHADEM, *Advan. Carbohyd. Chem.*, 18 (1963) 99.
4 H. OHLE AND J. J. KRUYFF, *Ber.*, 77 (1944) 507.
5 H. OHLE AND G, A. MELKONIAN, *Ber.*, 74 (1941) 279.
6 H. BEYER AND U. SCHULTZ, *Ber.*, 87 (1954) 78.
7 R. BOGNÁR, I. FARKAS, L. SZILÁGYI, M. MENYHÁRT, É. N. NEMES, AND I. F. SZABÓ, *Acta Chim. Acad. Sci. Hung.*, 62 (1969) 179.
8 P. M. SCHUBERT, *J. Biol. Chem.*, 130 (1939) 601.
9 T. TAKATORI AND T. TAGUCHI, *Yakugaku Zasshi*, 88 (1969) 527; *Chem. Abstr.*, 69 (1968) 87392a.
10 F. GARCIA GONZÁLEZ, *Advan. Carbohyd. Chem.*, 11 (1965) 97.
11 F. GARCIA GONZÁLES AND A. GÓMEZ SÁNCHEZ, *Advan. Carbohyd. Chem.*, 20 (1965) 303
12 J. FERNÁNDEZ-BOLAÑOS, H. MARTIN LOMAS, D. MARTINEZ RUIZ., AND M. A. PRADERA, *Anales Real Soc. Espan. Fis. Quim.* (Madrid), 64B (1968) 203; *Chem. Abstr.*, 69 (1969) 52453a.
13 S. SATTLER, F. W. ZERBAN, G. L. CLARK, AND CHIA-CHEN CHU, *J. Amer. Chem. Soc.*, 73 (1951) 5908.
14 R. BOGNÁR, Z. KOLODYNSKA, L. SOMOGYI, Z. GYÖRGYDEÁK, L. SZILÁGYI, AND É. N. NEMES, *Acta Chim. Acad. Sci. Hung.*, 62 (1969) 65.
15 T. VAN ES AND R. L. WHISTLER, *J. Org. Chem.*, 29 (1964) 1087.
16 H. PAULSEN, *Angew. Chem.*, 78 (1966) 501.