Facile Syntheses of the Three Major Metabolites of Thioridazine

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Efficient, mild syntheses of the three major metabolites **2**–**4** of the important antipsychotic drug thioridazine (**1**) have been developed. The cardiotoxic metabolite **2** with a ring sulfoxide moiety was prepared in 96% yield by oxidation of **1** with $NaIO_4$ under acidic conditions. Four different procedures were elaborated for the selective side-chain sulfide oxidation of **1** to mesoridazine (**3**), giving rise to yields of up to 91%. Finally, sulforidazine (**4**) was synthesised *via* oxidation of the sulfoxide **3** in the presence of either $KMnO_4$ or *t*-BuOOH under basic conditions. Except for the oxidation with *t*-BuOOH, all reactions took place under mild conditions within a few minutes, were nicely reproducible, and afforded medium-to-high yields of the desired products, which could be readily purified by column chromatography.

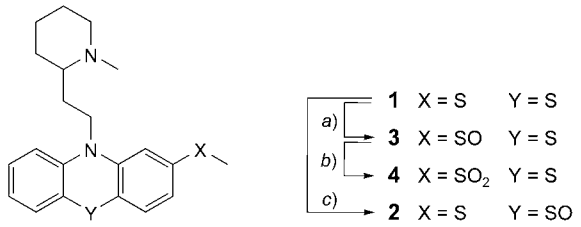
Introduction. – Thioridazine (**1**)[1]) is a chiral, tricyclic drug used in racemic form for the treatment of schizophrenia and other psychiatric disorders, and produces few extrapyrimidal side effects (a regular side effect in antipsychotic therapy) [1–2]. Like all other antipsychotic agents, the ability of **1** to alleviate psychotic symptoms is attributed to antagonistic blocking of central dopamine receptors, which compensates for the overactivity of this neurotransmitter [3]. However, the individual enantiomers of **1** have been shown to produce significantly different pharmacologic effects. Several authors have reported a difference in the distribution of the enantiomers in blood plasma and in various human tissues [4–6]. Furthermore, it has been shown that (+)-(*R*)-thioridazine ((*R*)-**1**; see *Scheme*) has a 2.7-times higher affinity than the (−)-(*S*)-isomer for the important D_2 receptors, which are most strongly related to alleviation of psychotic symptoms in rat brain [3].

It has been recognised that the pharmacologic effects of thioridazine therapy are not only attributed to the parent drug, but also to the major metabolites: the ring sulfoxide **2**, the side-chain sulfoxide *mesoridazine* (**3**), and the side-chain sulfone *sulforidazine* (**4**). All these compound are known to significantly contribute to the overall pharmacological profile of thioridazine-based drug therapy [7–20]. In fact, compounds **3** and **4** have been shown to be *ca.* 50% more potent than the parent drug **1** [7–10], and the ring sulfoxide **2**, although not considered to contribute to the observed antipsychotic activity, is reported to be the major cause of cardiotoxic side effects associated with the administration of **1** [14–20].

Despite the importance of the metabolites **2**–**4**, there is still minimal information regarding the pharmacologic and pharmacokinetic effects of the *isomers* of these compounds, and there are currently only a few useful methods for their synthesis from

[1]) Systematic name: 10-[2-(1-methylpiperidin-2-yl)ethyl]-2-(methylsulfanyl)-10*H*-phenothiazine.

Scheme



a) For example: $TiCl_3/AlCl_3$, aq. 30% H_2O_2, MeOH, r.t., 20 min; 91%. *b*) For example: $KMnO_4$, acetone, 45°, 30 min; 52%. *c*) $NaIO_4$, H_2O/MeOH, HCl (cat.); 96%.

THD (**1**). The only previously documented method for the direct oxidation of the side-chain sulfide group of **1** to racemic mesoridazine (*rac*-**3**) is an original patented procedure [21] based on oxidation of **1** · HCl by sodium metaperiodate ($NaIO_4$), which, reportedly, generates **3** in high yield. However, when we repeated this procedure, we found that **3** is produced as a mixture of diastereoisomers in yields below 22%, the other 78% of material being attributed mainly to the ring oxide **2** (69%) and some unmodified starting material **1** (9%). Furthermore, the product detailed in the patent [21] was reported to be a solid, with a melting point of 128–131°. The free base of **3**, however, can be obtained only as an oil. It is, therefore, possible that the authors had actually isolated the solid metabolite **2** rather than the desired **3**. Indeed, the reported melting point for **3** (128–131°) lies in the upper range of the broad melting point of diastereoisomeric **2** (113.5–128.5° [21]). In addition to the lack of useful procedures for the synthesis of **3**, there are currently no procedures for the synthesis of **4** through *direct* oxidation of the parent compound, and there is only one previously reported procedure for the synthesis of **2** from **1** [22].

The present study now introduces straight-forward, reproducible procedures for the syntheses of the three major metabolites of **1** in good yields (*Scheme*).

Results and Discussion. – 1. *Synthesis of Racemic Mesoridazine* (**3**). Due to the low yield of **3** obtained by the patent procedure [21], numerous oxidations were performed to establish a suitable process for the specific side-chain oxidation of *rac*-**1** to *rac*-**3** (*Scheme*). A number of straight-forward, non-stereochemically controlled oxidative procedures based on H_2O_2 and different metal salts were developed (in decreasing order of efficiency): *1*) $TiCl_3/AlCl_3$, H_2O_2 (91%); *2*) V_2O_5, H_2O_2 (85%); *3*) $(CF_3)_2CH-OH$, H_2O_2 (78%); and *4*) SeO_2, H_2O_2 (68%).

The high yields of **3** are most likely due to the electrophilic nature of the reagents employed. In the case of V_2O_5 and $TiCl_3/AlCl_3$ oxidations, the H_2O_2 coordinates to the metal ion to form a peroxo–metal species. The metal ion activates the peroxide O–O bond, which leads to an increase in electrophilicity of the oxidant, promoting nucleophilic attack by the sulfide S-atom [23–27]. In the case of the reaction in the presence of hexafluoroisopropanol, the electron-withdrawing nature of the two CF_3 groups results in strong H-bonding between HFIP and H_2O_2, which activates the OH leaving group, making H_2O_2 more reactive [28]. Finally, SeO_2 reacts with H_2O_2 to form perselenic acid (a peroxy acid) as the resulting oxidising agent [29]. The Se peroxy acid

is a highly electrophilic oxidant that is much more reactive towards sulfides compared to H_2O_2 and alkyl peroxides.

The selectivity of the above oxidants for the side-chain sulfide group of **1** compared to the ring sulfide centre is expected to be determined by the influence of the aromatic rings. The ring sulfide S-atom is less nucleophilic compared to the side chain S-atom, which, thus, is more reactive towards the electrophilic oxidants.

Upon reaction of **3** with benzenesulfonic acid, the corresponding benzenesulfonate ('besylate') was obtained for characterisation. However, there was a discrepancy between the melting points of the besylate isolated in this study (171–173°) and that reported (180–182°) [30]. This is most probably due to the observations that the besylate of **3** undergoes preferential crystallisation of one pair of diastereoisomers, as shown previously by NMR [31]. The diastereoisomeric ratio of the isolated besylate is likely to be dependent on crystallisation method and conditions. Actually, the synthesis of **3** by any of the stereochemically nonselective oxidative procedures mentioned above afforded a 50:50 mixture of diastereoisomeric pairs. However, upon recrystallisation of the still-racemic besylate salt, the diastereoisomeric ratio was dramatically altered to 87:13.

2. *Synthesis of Sulforidazine* (**4**). Theoretically, the oxidation required to synthesise the side-chain sulfone **4** could be achieved either by direct oxidation of **1** or, alternatively, by oxidation of the SO group of **3**. The first way was expected to be more difficult, since direct oxidation of a sulfide proceeds *via* the sulfoxide, followed by further oxidation to the sulfone, two reactions based on different mechanisms. The second approach, the conversion of an (electrophilic) SO group to an SO_2 moiety requires a *nucleophilic* oxidant, in contrast to the oxidation of a nucleophilic sulfide S-atom to a sulfoxide, which proceeds best with *electrophilic* reagents. Nevertheless, oxidising agents with high electrophilic O-transfer ability, such as peroxy acids, can be strong enough to oxidise sulfides to sulfoxides, followed by further oxidation to the sulfone [32]. This, however, would be inappropriate in the case of **1**, as a highly reactive oxidant would promote oxidation of both the ring *and* side-chain sulfide centres. Thus, a more-suitable approach is to proceed through the nucleophilic oxidation of the previously synthesised mesoridazine (**3**).

Selective nucleophilic oxidation of the side-chain SO group was achieved by refluxing **3** with *t*-BuOOH under basic conditions [33], giving rise to nucleophilic attack of *t*-$BuOO^-$ at the SO group. The reaction proceeded slowly and required vigorous reflux for several hours, but did afford sulforidazine (**4**), however, in moderate yield (37%) only. We, thus, developed a more-efficient method based on the use of $KMnO_4$. As oxidations with this reagent proceed both under milder conditions and more rapidly with sulfoxides than with sulfides, selective oxidation of **3** was possible, and the yield of **4** could be increased to 52% [34][35].

3. *Synthesis of Metabolite* **2**. Oxidation of the ring sulfide S-atom of **1** could be achieved by a previously reported oxidative method involving $NaNO_2$ and a few drops of concentrated HCl [22], which generated *rac*-**2** in yields of at least 94%. Nevertheless, upon slight modification of the reported reaction conditions, we were able to increase the yield of **2** to $>96\%$. Again, all four stereoisomers were present in equal amounts.

Experimental Part

1. *General.* All commercial reagents were used as received. Reactions were monitored by thin-layer chromatography (TLC; aluminium-backed plates (0.2 mm)) on silica-gel *60 F_{254}* (*Merck*). Flash chromatography (FC) was performed on silica gel *60* (230–400 mesh; *Merck*). HPLC was carried out using a *Milton Roy CM4000* pump, a manual injector, and an *LDC/Milton Roy Spectromonitor III* detector. Melting points (m.p.) were determined on a *Griffin Gallenkamp* melting-point apparatus; uncorrected. IR Spectra: *Nicolet Protégé-460* spectrometer, thin film or KBr discs; in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *General Electric QE-500* instrument at 500 and 125 MHz, resp.; chemical shifts δ in ppm rel. to Me_4Si as internal standard; coupling constants *J* in Hz. EI-MS (70 eV): *AEI-MS 902* instrument; accurate molecular weights were determined by the peak-matching method using perfluorokerosene as a standard reference.

2. *Special Analytical Methods.* 2.1. *TLC Analysis* [24][28]. The TLC method used for the analysis of thioridazine (**1**) and its metabolites **2**–**4** followed that previously reported [22][35], using acetone/12N aq. NH_4OH soln. 100:7 and *Merck* silica gel *60 F_{254}* Al sheets (0.2 mm). For all compounds (except **4**, which had not been investigated in previous reports [22][36]), the elution order was as reported. Retention factors (R_f values; see *Table*) were marginally different from those reported, which is probably due to the different silica gel plates employed. Note that the two diastereoisomeric pairs of **2** were visually separated under these conditions, whereas those of **3** where unresolved (single spot on TLC plate). All components were clearly visible under UV light. Further identification could be achieved by the notable colour changes upon spraying with 10% H_2SO_4 in EtOH, followed by heating at 60° in an oven (to distinguish **2** and **4**) colour changes at this stage, and finally spraying the plate with *Folin–Coiceleaus* reagent (to distinguish **1** and **3**).

Table. *Thin-Layer Chromatographic Properties of Compounds* **1**–**4**

Compound	R_f	H_2SO_4, 60° for 10 min	*Folin–Coiceleaus* reagent
1	0.76	none	blue
2	0.61/0.56[a])	blue	none
3	0.51	none	pink/red
4	0.72	bright pink	none

[a]) Diastereoisomeric pairs clearly separated.

2.2. *HPLC Analysis* [29]. The HPLC analysis of of **1**–**4** was a modification of a previously reported method [37]. A *Hypersil* (5 µm) silica-gel column (4.6 mm × 250 mm) was used, and the mobile phase was 2-chlorobutane/i-PrOH/H_2O/Et_3N (82:17.9:0.08:0.016) at a flow rate of 1.5 ml/min, a temp. of 25°, and detection at 254 nm. These conditions resulted in different elution times for **1**, **2**, **3**, and **4** compared to those reported [29]; however, the elution sequence was identical.

3. *Mesoridazine* (=*10-[2-(1-Methylpiperidin-2-yl)ethyl]-2-(methylsulfinyl)-10*H*-phenothiazine*; **3**). 3.1. *Method A* [38]. A soln. of 30% aq. H_2O_2 (0.52 ml, 5.9 mmol) and $TiCl_3/AlCl_3$ (10 mg) in MeOH (20 ml) was added dropwise over 15 min to a stirred soln. of *rac*-**1**·HCl (2 g, 4.9 mmol) dissolved in MeOH (20 ml), whereupon a colour change to blue-green was observed. The mixture was then stirred for an additional 5 min at r.t., and quenched with H_2O (50 ml). The product was extracted with CH_2Cl_2 (3 × 30 ml), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The resulting yellow oily crude product consisted of **3** (91% by HPLC) and unreacted **1** (9%), and was purified by FC (SiO_2; $CHCl_3$/MeOH 95:5) NMR Analysis indicated a 1:1:1:1 mixture of all four stereoisomers.

For further characterization (m.p.), the benzenesulfonate ('besylate') salt of **3** was prepared by addition of benzene sulfonic acid (0.365 g, 2.31 mmol) to purified **3** (0.882 g, 2.28 mmol) dissolved in EtOH (10 ml). Upon leaving this soln. in the dark, crystals of the besylate were formed in 28% yield (m.p. 171–173°; lit. 180–182° [30]). The diastereoisomeric ratio of the besylate after crystallisation was 87:13, as determined by NMR.

Data of **3** (diastereoisomeric mixture). Yield: 91% (HPLC). IR (KBr): 1179, 1224, 1453, 3442. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.26–2.16 (*m*, 10 H); 2.223, 2.232 (2*s*, MeN); 2.696, 2.699 (2*s*, MeSO); 2.80 (*m*, 1 H); 3.95 (*m*, 2 H); 6.9–7.23 (*m*, 7 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.03, 25.50, 29.80, 30.71 (4 CH_2); 42.9 (MeSO); 44.06, 44.146 (MeN); 44.6, 57.2 (2 CH_2); 62.4 (CH); 109.74, 115.93, 117.16, 123.11, 127.58, 127.60, 127.80 (7 arom.CH); 124.4, 129.10, 144.37, 144.95, 146.68 (5 arom.C). EI-MS: 386 (15, M^+), 126 (7), 98 (100), 70 (10), 41 (5). HR-EI-MS: 386.14709 (M^+, $C_{21}H_{26}N_2OS_2^+$; calc. 386.14866).

3.2. *Method B* [39][40]. A soln. of V_2O_5 (20 mg) in 30% aq. H_2O_2 (0.52 ml, 5.9 mmol) and MeOH (20 ml) was added to a soln. of *rac*-**1**·HCl (2 g, 4.9 mmol) in MeOH (35 ml) over a period of 15 min, whereupon a colour change to blue-green was observed. The mixture was stirred for a further 5 min, and then quenched with H_2O (50 ml). The product was extracted with CH_2Cl_2 (3 × 30 ml), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The resulting yellow oil consisted of **3** (85%), and side products and starting material (15%).

3.3. *Method C* [41]. To a soln. of *rac*-**1**·HCl (2 g, 4.9 mmol) in MeOH (15 ml) was added dropwise over 15 min a soln. of equimolar H_2O_2/SeO_2 (0.5 ml 30% aq. H_2O_2 and 0.6 g of SeO_2) in MeOH/H_2O 50:50 (10 ml) with stirring. The green-blue mixture was stirred for a further 5 min, and quenched with H_2O (50 ml). The product was extracted with CH_2Cl_2 (3 × 30 ml), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The resulting yellow oil consisted of **3** (68%), and side products and starting material (32%).

3.4. *Method D* [28]. To a soln. of *rac*-**1**·HCl (0.5 g, 1.23 mmol) in hexafluoroisopropanol (6 ml), 30% aq. H_2O_2 (0.15 ml, 1.48 mmol) was added dropwise over 15 min, whereupon a colour change to deep blue was observed. Then, the soln. was stirred for another 5 min, and quenched with 1M aq. Na_2SO_3 soln. (10 ml). The org. layer was separated, and the fluorinated solvent was distilled off[2]). The crude product was dissolved in CH_2Cl_2 (20 ml), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The resulting yellow oil consisted of **3** (78%), and some side products and starting material (22%).

3.5. *Literature Method* [21]. To a soln. of $NaIO_4$ (0.53 g, 2.5 mmol) in H_2O (25 ml) cooled to 0°, a soln. of *rac*-**1**·HCl (1 g, 2.45 mmol) in H_2O (25 ml) was added dropwise with stirring over 20 min. A colour change to blue was observed. The mixture was stirred at 0° for 2 h, and then at r.t. for 24 h. After completion of the reaction, H_2O was added (50 ml), the mixture was extracted with CH_2Cl_2 (3 × 30 ml), the org. layer was dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The crude product contained **3** (22%) and **2** (*ca.* 78% by HPLC).

3.6. *Sulforidazine* (=*10-[2-(1-Methylpiperidin-2-yl)ethyl]-2-(methylsulfonyl)-10*H*-phenothiazine*; **4**). 3.6.1. *Method A* [33][34]. An aq. soln. of $KMnO_4$ was added to a stirred soln. of *rac*-**3** (0.81 g, 2.1 mmol) in acetone (100 ml) at a temp. of 45°. As the reaction progressed, the purple colour of $KMnO_4$ disappeared, and a brown precipitate occurred (MnO_2). $KMnO_4$ was continually added over a period of 30 min, until a purple tinge remained in soln. The brown precipitate was then filtered off, and the acetone was evaporated *in vacuo*. The remaining aq. soln. was extracted with CH_2Cl_2 (3 × 20 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The crude product was isolated by FC (SiO_2; CH_3Cl/MeOH 95:5) to afford **4** (0.439 g) in 52% yield. M.p. 118–121° ([38]: 121–123°). IR (film): 1150, 1311, 1456, 3431. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.3–2.16 (*m*, 10 H); 2.22 (*s*, MeN); 2.81 (*m*, 1 H); 3.02 (*s*, MeSO); 3.9 (*m*, 2 H); 6.84–7.37 (*m*, 7 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 24.11, 25.59, 29.75, 30.78 (4 CH_2); 43.04 (MeN); 44.19, 56.82 (2 CH_2); 44.60 ($MeSO_2$); 61.96 (CH); 113.41, 116.02, 121.04, 123.02, 127.63, 127.83, 127.90 (7 arom.CH); 123.64, 132.97, 139.47, 144.04, 146.10 (5 arom.C). EI-MS: 402 (38, M^+), 290 (12), 277 (9), 211 (12), 197 (16), 149 (13), 126 (24), 98 (100), 70 (8), 43 (13). HR-EI-MS: 402.14308 (M^+, $C_{21}H_{26}N_2O_2S_2^+$; calc. 402.14357).

3.6.2. *Method B.* To a soln. of *rac*-**3** (0.82 g, 2.1 mmol) in MeOH (30 ml) was slowly added 6M aq. NaOH soln., until **3** began to precipitate. Then, some MeOH (*ca.* 5 ml) was added to redissolve the precipitate. To this sat. soln., a 70% *t*-BuOOH soln (0.35 ml) was added, and the mixture was refluxed for 6 h. Then, a further portion of *t*-BuOOH (0.15 ml) was added, and the mixture was heated to reflux for 16 h. After completion of the reaction, H_2O (100 ml) was added, the mixture was extracted with CH_2Cl_2 (3 × 20 ml), dried ($MgSO_4$), filtered, and evaporated to dryness *in vacuo*. The crude product was purified by FC (SiO_2; $CHCl_3$/MeOH 95:5) to afford **4** (0.31 g) in 37% yield.

*10-[2-(1-Methylpiperidin-2-yl)ethyl]-2-(methylsulfanyl)-10*H*-phenothiazine 5-Oxide* (**2**). A soln. of $NaIO_4$ (0.53 g, 2.5 mmol) in 70% aq. MeOH (20 ml) containing seven drops of conc. HCl was added dropwise to a stirred soln. of *rac*-**1**·HCl (1 g, 2.46 mmol) in MeOH (30 ml), whereupon the colour changed to red. After completion of the reaction (10 min), H_2O (50 ml) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 ml), dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The product was crystallised from EtOH to afford **2** in 96% yield (HPLC). M.p. 114–126° ([30]: 113.5–128.5°). IR (KBr): 1025, 1047, 1449, 1457, 1577. ^{1}H-NMR (500 MHz $CDCl_3$): 1.26–2.16 (*m*, 10 H); 2.342, 2.349 (2*s*, MeN); 2.563, 2.570 (2*s*, MeSO); 2.80 (*m*, 1 H); 3.95 (*m*, 2 H); 6.9–7.23 (*m*, 7 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.83 (MeS); 24.57, 25.89, 29.66, 31.15 (4 CH_2); 43.633, 43.736 (MeN); 45.63, 57.28 (2 CH_2); 62.441, 62.503 (CH); 112.63, 116.16, 119.40, 122.34, 132.11, 132.45, 133.25 (7 arom.CH); 121.45, 125.10, 138.52, 138.92 145.96 (5 arom. C). EI-MS: 386 (15, M^+), 370 (51), 369 (29),

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[2]) Hexafluoroisopropanol can be recovered and re-used.

258 (17), 245 (7), 185 (7), 126 (6), 98 (100), 87 (7), 69 (18), 41 (24). HR-EI-MS: 386.14813 (M^+, $C_{21}H_{26}N_2OS_2^+$; calc. 386.14866).

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