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Reduction of dimethyl sulfoxide by dihydrohalide salts of pharmaceuticals

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Summary

Dihydrohalide salts of pharmaceutical compounds effect reduction of dimethyl sulfoxide to give dimethyl sulfide under mild conditions. The reduction was initiated by the facile dissociation of HCl or HBr from the dihydrohalide salts and involved α-chloromethyl (or α-bromomethyl) methyl sulfide and α-chloromethyl (or α-bromomethyl) methyl sulfoxide as the intermediates. No reactions were observed with the monohydrohalide salts.

Introduction

The determination of residual solvents and other volatile process-related chemical contaminants in bulk pharmaceuticals is growing in importance in the development of pharmaceuticals owing to the increasingly severe regulations on the production of medicinals. Depending on the intended dosage form of the drug, as well as on the nature of the contaminants, the specifications for these process-related chemicals vary over the range of a few parts per billion for most injectibles to values of high parts per million for tablets. In addition to meeting the analytical requirements of these specifications, the quantitation of these process-related contaminants also contributes to the material balance analysis of a drug substance, a process that is of particular significance during the initial stages of drug development when primary reference standards as well as working standards are being characterized.

While these analyses are normally addressed through the development of methods specific for the type of drug and residual solvents or other process-related chemicals being analyzed, a general procedure for a variety of drugs and solvents that do not require specialized headspace techniques (which are not easily adaptable to common autosampling units) is clearly more desirable. According, Haky and Stickney (1985) have reported a generalized method employing a packed graphitized carbon-black stationary phase column and benzyl alcohol as the general dissolution solvent. Since commercial benzyl alcohol contains trace amounts of toluene, a common analyte in

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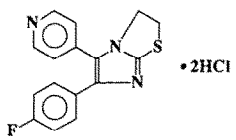
our laboratory, and most of our development compounds are not sufficiently soluble in benzyl alcohol to the necessary concentration for trace analysis, we have experimented with dimethyl sulfoxide (DMSO) being used as the superior alternative dissolution solvent in conjunction with the commercially available DB-624 bonded capillary column. We report here a general abnormality in these analyses, involving the deoxygenation of DMSO solvent by the dihydrohalide salts of pharmaceutical compounds, producing extraneous by-products that would elute in the chromatographic region of interest. No such reaction was observed with the monohydrohalide salts. The recognition of this abnormality is of utmost importance to the correct interpretation of assays involving DMSO as the dissolution solvent.

Materials and Methods

Materials

6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridyl) imidazole-(2,1-*b*)thiazole dihydrochloride (SK&F 86002-A_2, **1**), 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride (**2**), 2-methylpropanoic acid 4-[2-(methylamino)ethyl]-1,2-phenylene ester hydrochloride (**3**), 1-(4-methoxyphenyl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (**4**), 2,2′-decamethylene bis(isoquinolium bromide) (**5**), 2,2′-methylene-bis(7,8-dichloro-1,2,3,4-tetrahydroisoquinoline) dihydrochloride (**6**), 2-[*N*-2-(diethylamino)ethyl-*N*-methyl-*N*-2-(methylphenyl)]acetamide dihydrochloride (**7**), 2,2′-[1,2-ethanediylbis (thio)]bis[4,5-bis(4-chlorophenyl)-1H-imidazole]]



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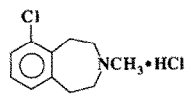

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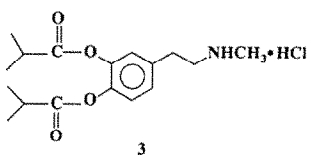

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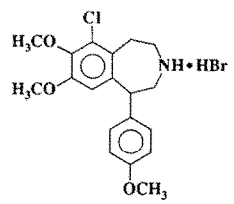

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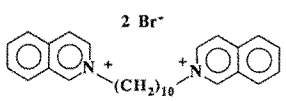

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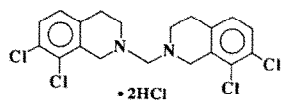

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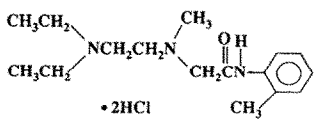

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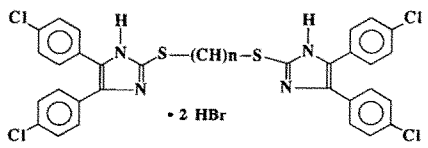


8 n=2
9 n=3

dihydrobromide (**8**), and 2,2′-[1,3-propanediylbis (thio)]bis[4,5-bis(4-chlorophenyl)-1H-imidazole]] dihydrobromide (**9**) were obtained from Smith Kline & French Laboratories. The purities of these compounds were established by HPLC, TLC, NMR, IR, and elemental analysis. DMSO and methyl ethyl ketone (both AnalaR grade) were obtained from J.T. Baker Co. Chloromethyl methyl sulfide was obtained from Aldrich (Milwaukee, WI). Chloromethyl methyl sulfoxide and bromomethyl methyl sulfoxide were synthesized according to the method of Tsuchihashi and Ogura (1971).

Gas chromatography conditions

Gas chromatography was performed using an HP 5880 gas chromatograph equipped with a capillary injection system and a flame ionization detector. The reactions were followed on a bonded DB-624 capillary column (J&W, 30 m × 1.6 μm film thickness) using hydrogen as the carrier gas. The initial column temperature was set at 50 °C for 10 min, then programmed to 150 °C at 20 °C per min. The injection port temperature was held at 130 °C and a Jenning's inversion cup liner was used. The injection split ratio was set at 60 : 1. A sample (1 μl) of the reaction mixture was injected via an HP 7673A autosampler. Data were acquired and processed using a Beckman CIS-CALS laboratory management system. Cold, on column injection was performed on a Scientific Glass Engineering on-column injector.

GC-MS analysis

GC-MS analysis were performed in the electron-impact mode on a Finnigan Mat 700 Ion Trap. Full scan spectra from m/z 45 to 250 were recorded at a scan rate of 2.0 μs/scan. The reaction mixtures were analyzed on a similar bonded DB-624 column under the same GC conditions as above.

General method for the reaction of hydrohalide salts of pharmaceutical compounds with DMSO

To 30 mg of pharmaceutical compound salts in a 3 ml glass vial equipped with a Teflon-faced screw cap, 1 ml of dimethyl sulfoxide was added. The glass vial was stoppered and then sonicated in a water bath at 15 °C for 0–15 min to dissolve the compound. A volume of 1 μl of the reaction solution was then injected into the gas chromatograph. Chloromethyl methyl sulfide and chloromethyl methyl sulfoxide were identified by comparison of their respective GC retention times as well as mass spectral data with authentic compounds.

Reaction of DMSO with conc. HCl

To 1 ml of dimethyl sulfoxide placed in a 3 ml glass vial equipped with a Teflon-lined screw cap, 13.6 μl of conc. HCl (37.3%) was added. The solution was then sonicated and chromatographed as described above.

*Heated reaction of 2-methylpropanoic acid, 4-[2-(methylamino)-ethyl]-1,2-phenylene ester hydrochloride (**3**), and 1-(4-methoxyphenyl)-6-chloro-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (**4**) with DMSO.*

To 30 mg of the monohydrochloride salt **3** or monohydrobromide salt **4** placed in a 3 ml glass vial, 1 ml of DMSO was added. The reaction mixture was stoppered, vortex-mixed, and heated at 100 °C in a Pierce dry heating block for 30 min. A sample (1 μl) of the reaction mixture was then chromatographed as described above.

*Reaction of 6-(4-fluorophenyl)-2,3-dihydro-5-(4-pyridyl)imidazole-(2,1b)thiazole [(SK&F 86002 A_2) **1** free base] with DMSO*

To an aqueous solution of 20 mg **1** in an ice-water bath, solid sodium bicarbonate was added until a pH of 7 was obtained. The solution was then saturated with sodium chloride and extracted with three 700-μl portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate, filtered into a 3 ml glass vial, and blown-dried under a gentle stream of clean nitrogen to give the free base of **1**. The free base obtained was then treated with 1 ml of DMSO and analyzed under the same conditions.

Reaction of DMSO with conc. HCl in the presence of methyl ethyl ketone

To a 1 ml portion of a solution of DMSO containing 1% (w/w) of methyl ethyl ketone, 13.6

μl of conc. HCl was added. The resultant solution was then sonicated and chromatographed as described above. For comparison 1 ml of a DMSO solution containing a 1% (w/w) methyl ethyl ketone without added conc. HCl was analyzed under the same conditions.

Heated reaction of 6-(4-fluorophenyl)-2,3-dihydro-5(4-pyridyl)imidazole-(2,1-b)thiazole dihydrochloride (1) with DMSO for cold, on-column injection

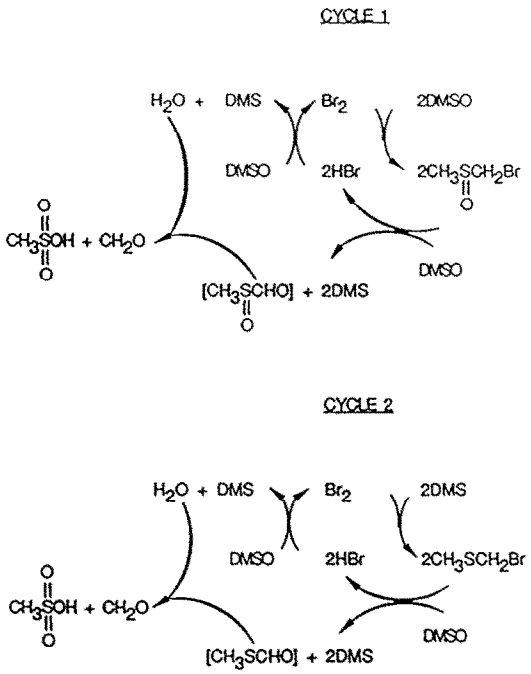
To 30 mg of the dihydrochloride salt **1** placed in a 3 ml glass vial equipped with a Teflon-lined screw cap, 1 ml DMSO was added. The reaction mixture was stoppered, sonicated as described above and then heated at 100 °C in a Pierce dry heating block for 5 min. Then, 1 μl solution was on-column injected into the gas chromatograph.

Reaction of chloromethyl methyl sulfide and chloromethyl methyl sulfoxide with DMSO

To 1 ml of DMSO in a 3-ml glass vial equipped with a Teflon-lined screw cap, 100 μl of chloromethyl methyl sulfide (or the sulfoxide) was added. The reaction mixture was then stoppered, vortex-mixed, and heated at 100 °C for 5 min. After cooling to room temperature, 1 μl of the reaction mixture was chromatographed as described above.

Results and Discussion

Recent reports of the reduction of sulfoxides to sulfides include the use of zinc/1,4-dibromobutane (Nagasawa et al., 1987), ferric chloride/sodium borohydride (Lin and Zhang, 1987), aluminum iodide (Babu and Bhatt, 1986) and *t*-butyl bromide (Tenca et al., 1981). Oae et al. (1974) reported that halide ions in DMSO in sealed tubes under conditions of elevated temperature and prolonged reaction time catalyzed both the Stevens-type rearrangement of sulfilimines and the reduction of dimethyl sulfoxides. The active species that triggered the reduction is believed to be either HBr or Br_2. The reduction of DMSO was postulated (Scheme 1) (Aida et al., 1973, 1976) to occur via a symbiotic combination of the reduction of DMSO by HBr and oxidation of the



Scheme 1.

transient α-bromomethyl methyl sulfide and α-bromomethyl methyl sulfoxide via the Kornblum reaction (Kornblum et al. 1959)(Scheme 1). A major factor in the oxidation-reduction mechanism of Aida et al. (1976) is therefore the α-bromination of dimethyl sulfide and DMSO to form the corresponding α-bromomethyl methyl sulfide and the sulfoxide (neither having been isolated), which then feed into the Kornblum oxidation cycle.

In conjunction with work aimed at developing a generalized method for the gas chromatographic analysis of residual solvents in pharmaceutical compound salts, we found that **1** dissolved in DMSO can similarly effect reduction of DMSO to yield dimethyl sulfide when injected into a gas chromatograph. Under these conditions, chloromethyl methyl sulfide and chloromethyl methyl sulfoxide, the chloro analogs of the postulated key intermediates in the oxidation-reduction system of Aida et al. (1976), were also obtained (Table 1). Other polar oxidation products observed by Aida et al. (1976), such as methanesulfonic acid and parafomaldehyde, were not investigated further,

TABLE 1

Product distribution of the reaction of dimethyl sulfoxides with dihydrochloride salt ***1****, conc. HCl, monohydrochloride* ***3*** *and monohydrobromide* ***4***

Compound		DMS	Cl(Br)-DMS	Cl(Br)-DMSO	Unreacted DMSO
1	GC Area %	0.6	trace [a]	0.2 [b]	99.2
	% w/w of **1** [c]	6.3	trace	2.0	–
HCl	GC Area %	0.5	trace [a]	0.2 [b]	99.3
3 [f]	GC Area %	0	0 [a]	0 [b]	100
4 [f]	GC Area %	0	0 [d]	0 [e]	100

DMS, dimethyl sulfide; Cl(Br)-DMS, chloromethyl (bromomethyl) methyl sulfide; Cl(Br)-DMSO, chloromethyl (bromomethyl) methyl sulfoxide; DMSO, dimethyl sulfoxide.

[a] Chloromethyl methyl sulfide.

[b] Chloromethyl methyl sulfoxide.

[c] Value (in % w/w) was calculated using methyl ethyl ketone as the internal standard.

[d] Bromomethyl methyl sulfide.

[e] Bromomethyl methyl sulfoxide.

[f] Includes both unheated and heated (100 °C, 30 min) samples.

since they do not elute from the GC column without prior derivatization nor do they interfere with the residual solvent analysis. The same extent of reduction in DMSO can be reproduced by replacing the dihydrochloride salt **1** with the same equivalent of conc. HCl. However, no reaction was observed when **1** was substituted with its free base. Representative monohydrohalide salts, such as **2**–**4** (chemical names given in Materials and Methods), or the dihalide salt **5** displayed no reaction.

The relatively mild reaction conditions for the reduction of DMSO in the present work stand in sharp contrast to those employed by Aida et al. (1976). With cold, on-column injection of an unheated solution of **1** in DMSO no reaction was observed. Cold, on-column injection of the same heated solution gave dimethyl sulfide, indicating that the reduction reaction of **1** with DMSO was thermally induced at the heated injection port of the gas chromatograph. In contrast, dimethyl sulfide was produced with the cold, on-column injection of an unheated reaction mixture of DMSO with conc. HCl. On the other hand, monohydrohalide salts, such as **3** and **4**, failed to yield any dimethyl sulfide even upon prolonged heating at 100 °C (Table 1). These results suggest that the reduction of DMSO was initiated by the thermally induced dissociation of HCl from **1**. No indication of HBr dissociation from the monohydrohalide salt **4** was obtained under the experimental conditions employed, and hence no dimethyl sulfide was observed to occur. The relative ease of dissociation of HCl from the dihydrohalide salt of the very weakly basic **1** ($pK_1 = 2.27$, $pK_2 = 4.04$) compared to the monohydrohalide salt of the more basic **4** ($pKa = 7.91$) accounted for the difference in behavior between the mono- and dihydrohalide salts towards dimethyl sulfide production. Dimethyl sulfide was also formed when chloromethyl methyl sulfide or chloromethyl methyl sulfoxide was heated in DMSO, in accordance with the postulate (Aida et al., 1976) as to their intermediacy in the oxidation-reduction cycle. Methyl ethyl ketone, a common analyte in our residual solvent assays, remained unaffected under the conditions used in the present study. The difference with respect to the system used by Furukawa et al. (1977) is that the latter involved oxidation of the active methylene group in a third component to the corresponding ketones, and methyl ethyl ketone to polymeric products.

Other representative dihydrohalide salts, namely the dihydrochloride salts **6** and **7** or dihydrobromide salts. **8** and **9**, behaved in a similar manner to **1** (data not shown; full chemical names in Materials and Methods).

The observed facile production of dimethyl sulfide via reduction of DMSO by means of the dihydrohalide salts of pharmaceutical compounds has important ramifications in pharmaceutical analysis. As seen in Table 1, extraneous dimethyl sulfide amounted to 6% w/w of the drug substance under analysis. Depending on the chromatography conditions used, dimethyl sulfide could also coelute with acetonitrile, acetone, or isopropanol. Dihydrohalide salts of pharmaceuticals are the substances most popularly chosen as

drugs due to their water solubility properties; however, none have been formulated with DMSO. The current study indicates that care must be taken to consider the possible contribution of dimethyl sulfide in the material balance analysis of hydrohalide salts of a drug substance dissolved in DMSO for analysis.

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