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Oxidation of 4-[3-(dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2H-1,4-benzothiazine, hydrochloride (I) with hydrogen peroxide yielded a mixture of two sulfoxides (II). Since this mixture exhibited antiinflammatory activity, the two components (Isomers A and B) were prepared in purified form by oxidation of I with *N*-chlorosuccinimide and hydrogen peroxide, respectively. Isomer A was more potent than Isomer B in the carrageenin-induced edema test.

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In previous papers, the synthesis (1), biological activity (2), and the metabolic studies (3) of 4-[3-(dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2H-1,4-benzothiazine, hydrochloride (I) were reported. Since the sulfoxide was one of the major metabolites of this benzothiazine, I was oxidized with hydrogen peroxide in aqueous solution to give a mixture of two sulfoxides (II). The latter showed significant activity when screened in the carrageenin-induced edema test in rats by the oral route. Subsequent tlc studies showed II was a mixture of about 30% Isomer A and 70% Isomer B (4).

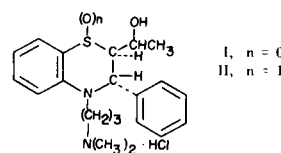


Figure 1. Structures of I and II.

The initial preparation of the isomers was achieved by selective crystallization of the oxalic acid salts of II. This method provided a practical method for obtaining a

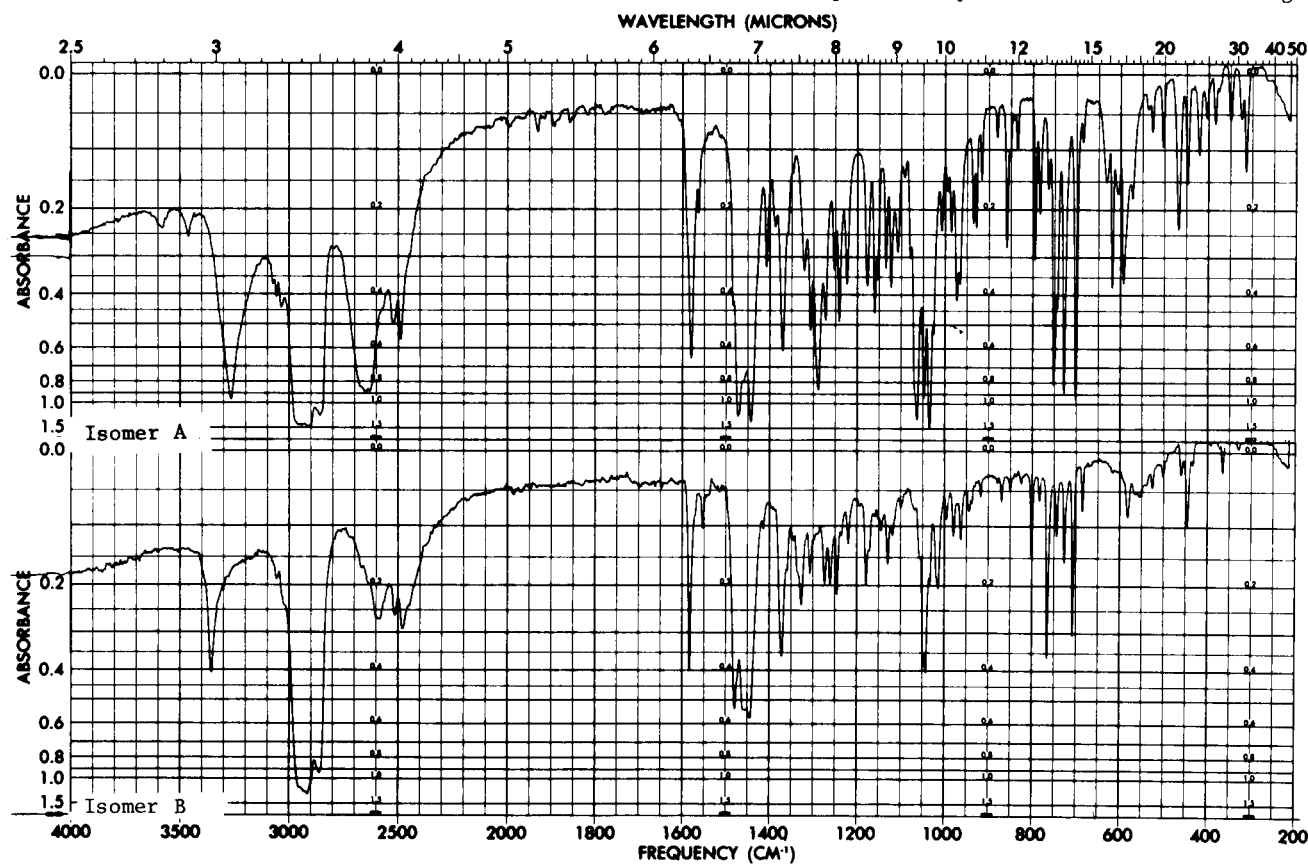


Figure 2. Ir spectral data for Isomers A and B.

large quantity of purified Isomer B; however, the isomer A prepared by this procedure still contained about 5% of Isomer B. Purified Isomer A was obtained by the oxidation of I with *N*-chlorosuccinimide (NCS). Utilizing tlc to study the products of the oxidation of I by sodium periodate, *m*-chloroperbenzoic acid, *t*-butyl hypochlorite, iodobenzene dichloride and NCS, we found that only the NCS oxidation gave Isomer A as the dominant component. The yield of Isomer B was increased when a solution of the free base of I in acetic acid was oxidized with hydrogen peroxide at room temperature. The sulfoxides are highly soluble in water (>10%), whereas I is less than 1% soluble.

Although tlc was used as a primary method for estimation of the composition of the isomers during the stages of their separation, the ir spectra of these isomers (Figure 2) were remarkably different in the hydroxy, hydrochloride, sulfoxide and aromatic regions to also permit the estimation of the purity of each isomer. Similar differences in the ir spectra were also observed in the oxalic acid salts of these isomers.

Biological Results.

The isomers were evaluated in the carrageenin-induced edema test in rats by the oral route (2). The ID₅₀ values for Isomers A and B were 85 and 130 mg./kg., respectively. The ID₅₀ value for phenyl butazone is 120 mg./kg. In a subsequent toxicity study of the isomers in dogs (50 mg./kg. of a 2 or 5% solution in 0.15% agar, by gavage), Isomer A was given to two dogs and Isomer B to five dogs. All animals exhibited allergic reactions. These observations precluded further evaluation of the compounds.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra (as Nujol mulls) were determined with a Perkin-Elmer IR-621 spectrometer. Thin-layer chromatographic (tlc) assays were performed on silica gel plates (QIF). The samples were dissolved in methanol containing 1% ammonium hydroxide, developed with methanol and the components were visualized under a uv lamp.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine 1-Oxide Hydrochloride. (II).

A stirred suspension of 200.0 g. (0.51 mole) of 4-[3-(dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine hydrochloride (I) (1) in 2.0 l. of water was cooled to 15° and treated portionwise with 228.0 g. (2.0 moles) of 30% hydrogen peroxide while the temperature was maintained at 12-15°. After stirring for 90 minutes at room temperature, the mixture was slowly heated (75 minutes) to 70° and the resulting solution was maintained at 70-75° for 75 minutes. At this point a sample was subjected to tlc analysis (ethyl acetate on alumina) and showed no starting material was present. The solution was cooled to 20°, treated with 300 ml. of diethyl ether, and basified with a cold solution of 24.0 g. of sodium hydroxide in 500 ml. of water. The organic phase was separated and the aqueous phase was extracted with 300 ml. of diethyl ether

(three times). The organic phases were combined, washed with 500 ml. of water (twice), dried (magnesium sulfate), and the solvent evaporated to give 185.5 g. of pale yellow glass-like residue.

A solution of this base in 2.0 l. of methyl ethyl ketone was treated with 90 ml. of 5.8 *N* ethanolic hydrogen chloride. The product crystallized from the solution. After standing overnight at room temperature, the mixture was filtered to give 162.5 g. of colorless solid, m.p. 192-194°. This material was pulverized, suspended in 800 ml. of acetone, cooled and filtered to give 156 g. (75%) of colorless salt, m.p. 192-194°; tlc *Anal.*: Isomer A, 30%, Isomer B, 70%.

Anal. Calcd. for C₂₁H₂₈N₂O₂S·HCl: C, 61.67; H, 7.15; N, 6.85; Cl, 8.67; S, 7.84. Found: C, 61.46; H, 7.08; N, 6.67; Cl, 8.61; S, 7.88.

This material tended to solvate when crystallized from methanol, ethanol and dimethylformamide.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine, 1-Oxide Hydrochloride. Isomer A.

A stirred suspension of 25.0 g. (0.064 mole) of I (1) in 250 ml. of methanol and 250 ml. of water was cooled to 3° and treated portionwise with 8.8 g. (0.65 mole) of *N*-chlorosuccinimide (98% purity) to give a purple-brown colored solution. After stirring at 2-4° for 1 hour, the mixture was allowed to stand at room temperature overnight and concentrated to about 50% of the initial volume using a rotary evaporator. The residue was stirred, cooled, layered with 200 ml. of diethyl ether, and treated portionwise with 17.5 g. of potassium carbonate. The base was isolated from the mixture in the same manner as II to give 21.9 g. of pale yellow glass-like residue. The tlc analysis (methanol on silica gel) indicated only Isomer A was present. A solution of this base in 220 ml. of acetone was treated with a solution of 5.5 g. of oxalic acid in 110 ml. of acetone to give a gum-like material which then became granular. After standing overnight, the mixture was filtered to give 25.7 g. of the oxalic acid salt, m.p. 193-195°. This material was dissolved in 75 ml. of hot dimethylformamide (105-110°) and diluted with 225 ml. of ethanol to give 21.6 g. of the oxalate, m.p. 202-204°. After recrystallization from 60 ml. of hot dimethylformamide and 180 ml. of ethanol, the colorless product weighed 20.0 g., m.p. 202-204°. The tlc analysis (methanol on silica gel) indicated only Isomer A was present.

Anal. Calcd. for C₂₁H₂₈N₂O₂S·C₂H₂O₄: C, 59.71; H, 6.54; N, 6.06. Found: C, 59.56; H, 6.73; N, 5.98.

A stirred suspension of the above purified oxalate in 300 ml. of water and 150 ml. of chloroform was cooled and basified with 12 g. of potassium carbonate. The organic phase was separated and the aqueous phase was extracted with 75 ml. of chloroform (three times). The organic phases were combined, dried (magnesium sulfate), filtered, and the filtrate treated with 5.3 ml. of 8.2 *N* ethanolic hydrogen chloride. The solvent was removed on a rotary evaporator until crystallization began and the mixture was diluted with 450 ml. of acetone. After standing overnight at room temperature, the mixture was filtered to give 15.2 g. (58%) of the hydrochloride salt, m.p. 225-227°. After recrystallization from 550 ml. of acetonitrile, the colorless salt weighed 10.7 g. (41%), m.p. 226-228°; R_f 0.34, methanol on silica gel; tlc Assay, >99% of Isomer A.

Anal. Calcd. for C₂₁H₂₈N₂O₂S·HCl: C, 61.67; H, 7.15; N, 6.85; Cl, 8.67; S, 7.84. Found: C, 61.55; H, 7.43; N, 7.15; Cl, 8.68; S, 7.67.

Preparation of I-Base.

A stirred suspension of 50.0 g. (0.13 mole) of I in 750 ml. of water and 200 ml. of chloroform was treated portionwise with

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18.5 g. of potassium carbonate and stirred until two clear layers separated. The organic phase was separated and the aqueous phase was extracted twice with 100 ml. portions of chloroform. The organic phases were combined, dried (magnesium sulfate), and the solvent evaporated to give a semi-crystalline residue. The latter was triturated with 400 ml. of hexane, cooled, and filtered to give 41.0 g. (91%) of the colorless base, m.p. 105-107°.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2H-1,4-benzothiazine 1-Oxide Hydrochloride. Isomer B.

A stirred solution of 50.0 g. (0.14 mole) of the above base in 250 ml. of acetic acid was cooled to 20° and treated portionwise with 50 ml. of 30% hydrogen peroxide. The temperature of the solution dropped to 12° and was maintained at 15-24° for 3 hours. At this point a sample was subjected to tlc analysis (ethyl acetate on alumina) and showed no starting material was present. The colorless solution was poured into 1.0 l. of cold water, added 300 ml. of diethyl ether, stirred, cooled and basified slowly with a cold solution of 200 g. of sodium hydroxide in 1.0 l. of water. The organic phase was removed and the aqueous was extracted with 300 ml. of diethyl ether (three times). The organic phases were combined, dried (magnesium sulfate), and the solvent evaporated to give 51.4 g. of colorless, glass-like base. The tlc analysis (methanol on silica gel) showed a high proportion of Isomer B (about 80%).

This base was converted to the oxalic acid salt (60.8 g. m.p. 188-190°) and crystallized twice from dimethylformamide-ethanol as in the Isomer A preparation to give 42.5 g. of colorless product, m.p. 196-198°. The tlc analysis (methanol on silica gel) indicated only Isomer B was present.

Anal. Calcd. for $C_{21}H_{28}N_2O_2S \cdot C_2H_2O_4$: C, 59.71; H, 6.54; N, 6.06. Found: C, 59.81; H, 6.44; N, 6.32.

A stirred suspension of the above purified oxalate in 250 ml. of water and 250 ml. of diethyl ether was cooled and basified with 25 g. of potassium carbonate. The organic phase was separated and the aqueous phase was extracted with 250 ml. of diethyl ether (three times). The organic phases were combined, dried

(magnesium sulfate), and solvent evaporated to give 34.2 g. of colorless, glass-like base. This material was dissolved in 300 ml. of chloroform, cooled, and treated with 12 ml. of 7.65 N ethanolic hydrogen chloride. The solvent was removed on a rotary evaporator and the resulting syrup (65 g.) was dissolved in 450 ml. of acetone. The solution was seeded and the hydrochloride salt rapidly crystallized. After standing overnight at room temperature, the mixture was filtered to give 33.5 g. (58%) of solid, m.p. 185-187°. This material was dissolved in 400 ml. of acetonitrile, seeded and rubbed to induce rapid crystallization (to avoid solvation), and allowed to stand overnight to give 27.5 g. (48%) of colorless product, m.p. 189-191°; R_f 0.26, methanol on silica gel; tlc assay, >99% Isomer B.

Anal. Calcd. for $C_{21}H_{28}N_2O_2S \cdot HCl$: C, 61.67; H, 7.15; N, 6.85; Cl, 8.67; S, 7.84. Found: C, 61.44; H, 7.07; N, 7.08; Cl, 8.57; S, 7.81.

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