

The Synthesis and Stereochemistry of
5*H*-1,2,3,4,5*a*,12*b*-Hexahydrocyclohepta[*b*]-10,11,12-trimethoxybenzo[*d*]thiepin-8(7*H*)-one

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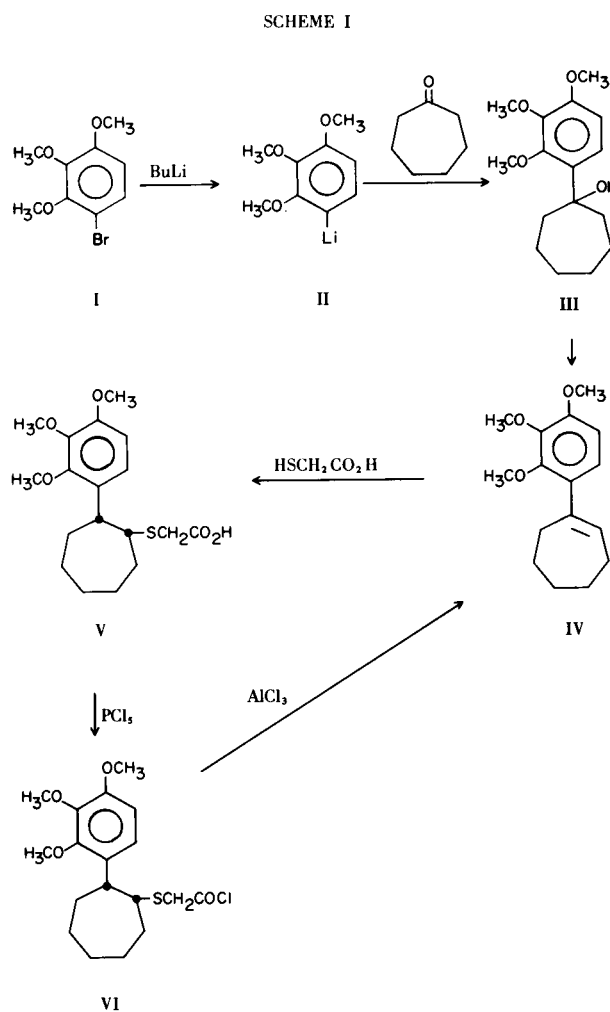
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The author previously reported the successful synthesis of *cis* and *trans* 1,2,3,4,4*a*,11*b*-hexahydro-9,10,11-trimethoxydibenzo[*b,d*]thiepin-7(6*H*)-one by the ring closure of *cis* and *trans*-2-(2',3',4'-trimethoxyphenyl)cyclohexanemercaptoacetyl chloride with aluminum chloride. In this paper we extend the study to the reaction of *cis* and *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetyl chloride with aluminum chloride.

The synthesis of *cis*-2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetyl chloride (VI) was achieved as outlined in Scheme I. The cyclization of 2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetyl chloride was attempted using the conditions reported for the cyclization of 2-(2',3',4'-trimethoxyphenyl)cyclohexanemercaptoacetyl chloride (1). The main product of this reaction was 1-(2',3',4'-trimethoxyphenyl)cycloheptene (IV). Attempts to obtain the desired cyclic compound by using milder Friedel-Craft catalysts, lower temperatures and other solvents were unsuccessful. The formation of 1-(2',3',4'-trimethoxyphenyl)cycloheptene can be rationalized as follows; the strong acid (aluminum chloride) complexes with the sulfur atom of the sulfide acid chloride thus creating a bulky group in the axial position. This results in increased strain in the seven-membered ring which is relieved by elimination of the mercaptoacetyl chloride residue resulting in the formation of a cation which loses a proton to give 1-(2',3',4'-trimethoxyphenyl)cycloheptene (IV).

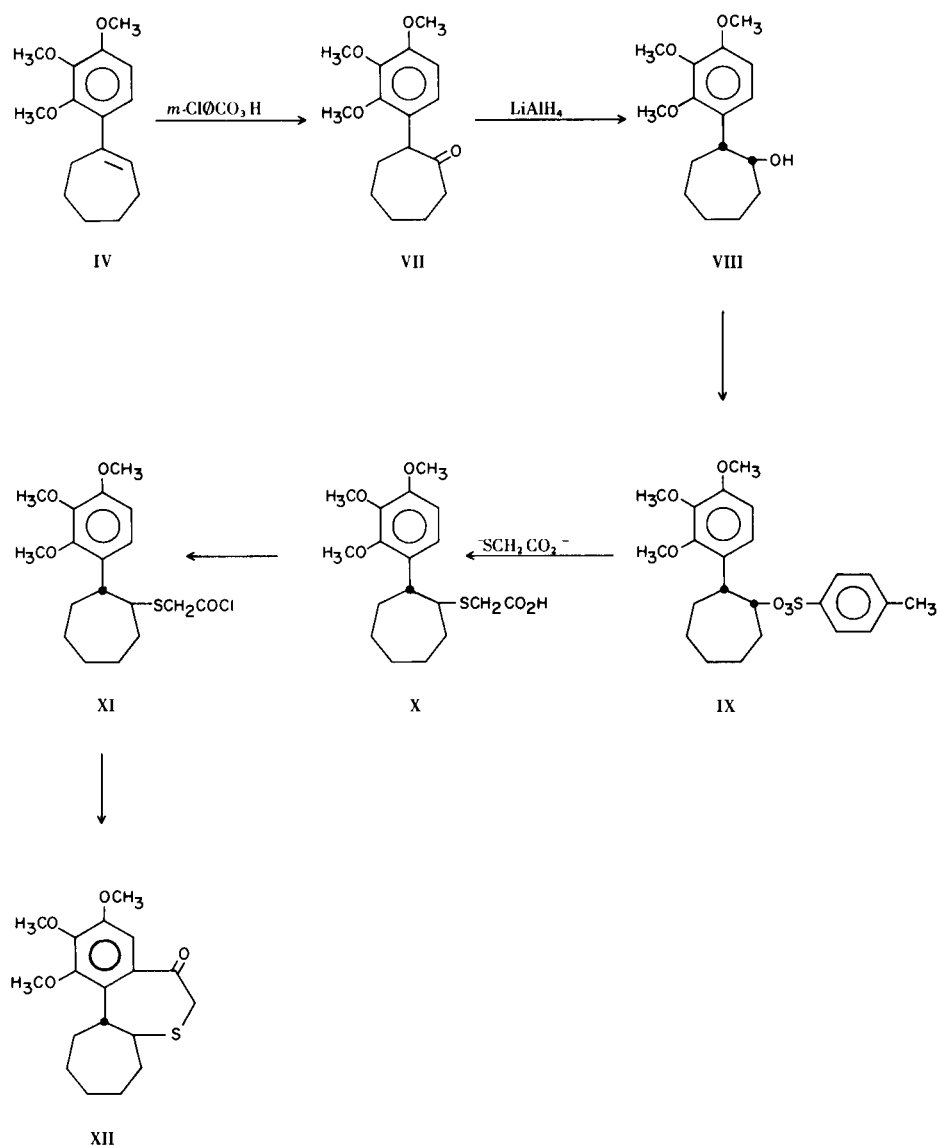
Since both the *cis* and *trans* cyclic compounds had been synthesized in the six-membered ring system (1) there appeared to be a strong possibility in the present situation that the *trans* sulfide acid chloride might be more stable in the presence of aluminum chloride and give the cyclized product since the mercaptoacetic acid group in the equatorial position should be more stable than in the axial position (2).

The best approach to the synthesis of the desired compound appeared to be through the displacement of *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptyl-*p*-toluenesulfonate by the dipotassium salt of mercaptoacetic acid (Scheme II). In a previous paper (1) we reported that



trans-2-(2',3',4'-trimethoxyphenyl)cyclohexyl-*p*-toluenesulfonate yielded *trans*-2-(2',3',4'-trimethoxyphenyl)cyclohexanemercaptoacetic acid when treated with the dipotassium salt of mercaptoacetic acid. However, the application of this reaction to *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptylmethanesulfonate yielded only a small amount of the desired product. The major product obtained was 6*H*-3,4-dimethoxybenzo[*b*]-5*a*,7,8,9,10,10*a*-

SCHEME II



hexahydrocyclohepta[*d*]furan (3). Since the *cis* tosylate (IX) should also give the desired sulfide acid by inversion during displacement it was decided to prepare the *cis* alcohol by reduction of the ketone.

2-(2',3',4'-trimethoxyphenyl)cycloheptanone (VII), prepared according to the procedure of Gutsche and Fleming (4), was reduced with lithium aluminum hydride. The resulting mixture was fractionated over neutral aluminum oxide to yield the *cis* alcohol (45%) and the *trans* alcohol (55%). The configurations of the alcohols were established by comparing the *p*-nitrobenzoates of these alcohols with the *p*-nitrobenzoate of the *trans*

alcohol obtained by the stereospecific method of hydroboration. The stereospecificity of the hydroboration reaction in the phenyl substituted seven-membered ring system was established by subjecting 1-phenylcycloheptane to hydroboration and comparing the melting points of the tosylate and *p*-nitrobenzoate derivatives of the resulting alcohol with the known values (5).

The *cis* alcohol (VIII) was converted to the tosylate (IX) which was treated with the dipotassium salt of mercaptoacetic acid in methanol. *trans*-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetic acid (X) was isolated as indicated by the nmr and infrared spectra.

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetic acid exhibited a singlet at τ 7.05 which represents the methylene hydrogens between the sulfur and the carboxyl group. The *trans* isomer formed by the displacement of the *cis* tosylate exhibited a doublet at τ 6.90 and 6.95 which also represents the methylene hydrogens between the sulfur and carboxyl group. This is similar to *trans*-2-(2',3',4'-trimethoxyphenyl)cyclohexanemercaptoacetic acid which showed absorptions at τ 6.90 and 6.97. In a series of methoxyphenyl substituted cyclohexanemercaptoacetic acid derivatives we have found that the methylene hydrogens between the sulfur atom and the carboxyl group always absorb at a lower field in the *trans* isomer than in the *cis* isomer.

Further evidence for the inversion of the *cis* tosylate was obtained by treating the *cis* tosylate with sodium acetate in glacial acetic acid and reducing the acetate with lithium aluminum hydride. *trans*-2-(2',3',4'-Trimethoxyphenyl)cycloheptanol was obtained as evidenced by the nmr and infrared spectra.

A mixture of base insoluble products was also obtained from the displacement reaction which consisted of the following compounds; 1-(2',3',4'-trimethoxyphenyl)cycloheptene, 2-(2',3',4'-trimethoxyphenyl)cycloheptyl methyl ether and 6*H*-3,4-dimethoxybenzo[*b*]-5*a*,7,8,9,10,10*a*-hexahydrocyclohepta[*d*]furan.

The *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetic acid (X) was converted to the acid chloride (XI) and treated with aluminum chloride to give a 47% yield of *trans*-5*H*-1,2,3,4,5*a*,12*b*-hexahydro-10,11,12-trimethoxybenzo[*b,d*]thiepin-6(7*H*)-one (XII), as evidenced by the analysis and the nmr and infrared spectra.

EXPERIMENTAL

Melting points were taken using a Nalge-Axelrod melting point apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 13-U spectrophotometer and nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer in deuterated chloroform solutions (ca. 10%) using tetramethylsilane as an internal standard. Gas liquid partition chromatographs were obtained with a Microtek 220 instrument.

1-(2',3',4'-Trimethoxyphenyl)cycloheptanol (III).

This compound was prepared according to the procedure of Ginsburg and Pappo (2) as modified by Lotspeich and Karickhoff (1) for the preparation of 1-(2',3',4'-trimethoxyphenyl)cyclohexanol.

1-(2',3',4'-Trimethoxyphenyl)cycloheptene (IV).

This preparation was achieved according to the procedure of Ginsburg and Pappo (6).

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetic Acid (V).

Mercaptoacetic acid (14.73 g., 0.16 mole) and 25.99 g. (0.099 mole) of 1-(2',3',4'-trimethoxyphenyl)cycloheptene were

allowed to react for 34 days at room temperature. The mixture was dissolved in diethyl ether and extracted with 5% sodium hydroxide until all acidic material was removed. The ether extract was washed with water and concentrated to yield 6.8 g. of 1-(2',3',4'-trimethoxyphenyl)cycloheptene. The basic solution was acidified with dilute hydrochloric acid and extracted with diethyl ether. The ether extract was washed with water, dried and concentrated to yield 25.9 g. (74%) of a solid which melted at 102-104° after recrystallization from aqueous ethanol.

The infrared spectrum (chloroform) had bands at 2890, 1705, 1587, 1488, 1478, 1412, 1294, 1096 and 1007 cm^{-1} ; nmr, τ 3.3 (center of two doublets, 2H), 6.08 and 6.20 (9H), 7.03 (2H), 7.65 (broad band, 4H), and 8.48 (8H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_5\text{S}$: C, 60.99; H, 7.39. Found: C, 60.81; H, 7.37.

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetyl Chloride (VI).

2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetic acid (5.00 g., 0.014 mole) was dissolved in 50 ml. of carbon disulfide. The mixture was cooled in an ice bath and phosphorus pentachloride (3.0 g., 0.014 mole) was added slowly with stirring. After 24 hours the carbon disulfide and phosphorus oxychloride were removed under vacuum (10 mm.). Extraction of the oily residue with petroleum ether (35-37°) yielded 4.1 g. (79%) of the acid chloride. Similar results were obtained when oxalyl chloride was used in place of phosphorus pentachloride. The infrared spectrum (neat) had bands at 2928, 2857, 1792, 1594, 1491, 1415, 1297, 1285, 1243, 1229, 1099, 1075, 1029, 989, 968, 914, 853, and 797 cm^{-1} .

Attempted Ring Closure of *cis*-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetyl Chloride (VI).

The acid chloride (5.00 g., 0.0134 mole) dissolved in spectra grade chloroform (50 ml.) was added dropwise with stirring to a slurry of aluminum chloride (1.9 g.) in 100 ml. of chloroform. The reaction was allowed to proceed for 4 hours and was then hydrolyzed with dilute hydrochloric acid and washed with water. The chloroform solution was evaporated and the resulting oil was extracted with petroleum ether (35-37°). The petroleum ether extract was washed with 5% sodium bicarbonate and then water. Evaporation of the petroleum ether left an oil (3.2 g.) which had an infrared spectrum very similar to that of 1-(2',3',4'-trimethoxyphenyl)cycloheptene. Attempts to crystallize the material from petroleum ether (35-37°) were unsuccessful. The oil (3.2 g.) was taken up in 10 ml. of petroleum ether (35-37°) and passed over a column of 76 g. of neutral aluminum oxide (Merck) prepared with hexane. The column was eluted with the indicated solvents: (1) 40 ml. pentane, nothing; (2) 80 ml. pentane-10% diethyl ether, 1.01 g.; (3) 40 ml. pentane-20% diethyl ether, 0.96 g.; (4) 120 ml. pentane-30% diethyl ether, 0.20 g.; (5) 120 ml. pentane-50% diethyl ether, 0.43 g.; (6) 180 ml. diethyl ether, 0.24 g.

Fractions 2,3, and 4 were combined and crystallized from petroleum ether (35-37°) to yield a solid, m.p. 36-38°. Admixture of the compound with 1-(2',3',4'-trimethoxyphenyl)cycloheptene showed no depression in melting point.

In additional cyclization reactions, anhydrous hydrogen fluoride was used for 48 hours (7), polyphosphoric acid (8) was used at 25° and 3° for 6 and 10 hours, respectively. The acid chloride was also used with aluminum chloride in *sym*-tetrachloroethane, aluminum chloride in carbon disulfide, and stannic chloride in chloroform.

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptanol (VIII).

2-(2',3',4'-Trimethoxyphenyl)cycloheptanone (3.20 g., 0.0115 mole) dissolved in 25 ml. of diethyl ether was added dropwise to a slurry of 0.114 g. (0.0030 mole) of lithium aluminum hydride in 50 ml. of diethyl ether. The solution was allowed to stand for 2 hours at room temperature. The mixture was decomposed by the dropwise addition of water followed by dilute hydrochloric acid. The resulting ether solution was washed with dilute hydrochloric acid and water. Evaporation of the ether yielded 3.1 g. of oil. This oil was chromatographed on 72 g. of neutral aluminum oxide (Merck). The aluminum oxide column (25 x 130 mm.) was prepared with hexane and eluted with the following mixtures: (1) 160 ml. pentane (37°); (2) 80 ml. 20% diethyl ether 80% pentane; (3) 80 ml. 40% diethyl ether-60% pentane; (4) 160 ml. 60% diethyl ether-40% pentane; (5) 560 ml. diethyl ether; (6) 340 ml. 10% methanol-90% pentane. The *cis* alcohol (1.63 g.) was eluted in fractions 1-5 while the *trans* alcohol was eluted in fraction 6. The *p*-nitrobenzoate of the *cis* alcohol was prepared using dry pyridine and *p*-nitrobenzoyl chloride. Repeated recrystallization of the *p*-nitrobenzoate from methanol yielded yellow crystals, m.p. 94-96°.

Anal. Calcd. for C₂₃H₂₇NO₇: C, 64.32; H, 6.34. Found: C, 64.11; H, 6.29.

The *p*-nitrobenzoate of the *trans*-alcohol was prepared and crystallized from ethanol to give a white crystalline solid, m.p. 95-97°.

Anal. Calcd. for C₂₃H₂₇NO₇: C, 64.32; H, 6.34. Found: C, 64.22. H, 6.37.

The *p*-nitrobenzoate of the *trans*-alcohol prepared by hydroboration (3) gave a melting point depression when mixed with the *p*-nitrobenzoate of the *cis*-alcohol but no depression when mixed with the ester of the *trans*-alcohol prepared by reduction of the ketone.

Nmr of *trans*-alcohol τ 3.22 (center of two doublets), 6.13, 6.15, 6.18 (sharp triplet superimposed on broad band, 10H), 7.05 (1H), and 8.34 (10H).

The *cis* *p*-nitrobenzoate (3.00 g.) was mixed with 2.00 g. of sodium hydroxide, 19 ml. of water and 45 ml. of dioxane and refluxed for 4 hours. The dioxane was evaporated, water was added and the solution was extracted with diethyl ether. Evaporation of the ether left an oil which distilled at 142-143° (0.05 mm), n_D^{23} 1.5382; nmr, τ 3.19 (center of two doublets 2H), 6.03, 6.09 and 6.12 (sharp triplet superimposed on broad band, 10H), 6.83 (center of doublet, 1H) and 8.17 (10H).

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptyl-*p*-toluene sulfonate (IX) was prepared by allowing 2.00 g. (0.00714 mole) of the *cis*-alcohol to react with 1.6 g. (0.0084 mole) of *p*-toluenesulfonyl chloride in 5 ml. of pyridine at 10° for 48 hours. The pyridine solution was poured into a mixture of ice and 10% hydrochloric acid. After vigorous stirring the resulting solid was filtered, washed with diethyl ether and recrystallized from methanol and then acetone to give 2.0 g. (65%) of crystals, m.p. 126-128°.

Anal. Calcd. for C₂₃H₃₀O₆S: C, 63.59; H, 6.92. Found: C, 63.52; H, 6.80.

Acetolysis of *cis*-2-(2',3',4'-Trimethoxyphenyl)cycloheptyl-*p*-toluenesulfonate.

A solution of 2.20 g. (0.00506 mole) of *cis*-2-(2',3',4'-trimethoxyphenyl)cycloheptyl-*p*-toluenesulfonate in 50 ml. of glacial acetic acid containing 0.620 g. (0.00756 mole) of sodium acetate at 90° for 4 hours. The acetic acid was evaporated and the remaining oil was diluted with water and extracted with diethyl

ether. The diethyl ether extract was washed with 5% sodium bicarbonate solution and water and dried over sodium sulfate; the ether was removed under vacuum. The resulting oil (1.3 g.) was dissolved in 50 ml. of diethyl ether and added to 0.300 g. (0.00791 mole) of lithium aluminum hydride dissolved in 100 ml. of diethyl ether. The reduction was allowed to proceed for 1 hour at room temperature. The reaction mixture was worked up in the usual manner and 1 g. of the product was chromatographed over 36 g. of aluminum oxide (Merck).

Successive elution with the indicated solvents gave fractions: (1) 100 ml. of pentane, nothing; (2) 200 ml. pentane-50% ether, 810 mg. and (3) 100 ml. of ether, 9 mg. both unsaturated hydrocarbon; (4) 200 ml. of pentane-5% methanol, 250 mg. of *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptanol; nmr, τ 3.22 (center of two doublets), 6.13, 6.15, 6.18 (sharp triplet superimposed on broad band, 10H), 7.05 (1H), and 8.34 (10H). The infrared spectrum was identical to that of the *trans*-alcohol prepared by hydroboration. *trans*-2-(2',3',4'-Trimethoxyphenyl)cycloheptanemercaptoacetic acid (X).

cis-2-(2',3',4'-Trimethoxyphenyl)cycloheptyl-*p*-toluenesulfonate (6.70 g., 0.0154 mole) was added to 100 ml. of anhydrous methanol containing 5.30 g. (0.0315 mole) of potassium mercaptoacetate. The mixture was heated at 55° for 60 hours and the solvent was evaporated. The resulting oil was dissolved in diethyl ether and washed with 5% sodium hydroxide until all of the base soluble material was extracted. The ether solution was dried and evaporated to yield 3.5 g. of oil which was shown by gas chromatography (6 ft. column, 3%, carbowax 30M on anachrome) to contain 1-(2',3',4'-trimethoxyphenyl)cycloheptene (retention time, 5.2 minutes, 71%), 2-(2',3',4'-Trimethoxyphenyl)cycloheptyl methyl ether (retention time, 8.4 minutes, 25%), 6*H*-3,4-dimethoxybenzo[*b*]-5*a*,7,8,9,10,10*a*-hexahydrocyclohepta[*d*]furan (retention time, 16.4 minutes, 4%).

Two grams of the base insoluble oil was placed on 25 g. of neutral aluminum oxide (Merck) prepared with hexane. Successive elution with the indicated solvents gave: (1) 100 ml. pentane (37°), nothing; (2) 100 ml. pentane-5% benzene, 0.15 g. of 1-(2',3',4'-trimethoxyphenyl)cycloheptene; (3) 300 ml. pentane-30% benzene, 1.2 g. of 1-(2',3',4'-trimethoxyphenyl)cycloheptene, (retention time, 5.2 minutes); (4) 150 ml. benzene, 0.38 g. of oil (two components, 1-(2',3',4'-trimethoxyphenyl)cycloheptene, and a compound (retention time, 16.4 minutes); (5) 150 ml. pentane-30% diethyl ether, 0.10 g. of oil (retention time, 8.4 minutes); nmr, τ 3.25 (quartet 2H), 6.13, 6.17 (9H), 6.92 (4H), 8.34 (10H).

Fraction 4 was recrystallized several times from petroleum ether to yield a solid, m.p. 58-60° (retention time 16.4 minutes); nmr, τ 3.45 (quartet-2H), 5.6 (1H), 6.08 (3H), 6.18 (3H), 6.7 (1H) and 8.38 (10H). This nmr spectrum is in accordance with the structure of 6*H*-3,4-dimethoxybenzo[*b*]-5*a*,7,8,9,10,10*a*-hexahydrocyclohepta[*d*]furan.

Anal. Calcd. for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.41; H, 8.15.

The base extract was acidified with dilute hydrochloric acid to give 1.5 g. of a yellow oil. The oil (1.5 g.) dissolved in 3 ml. of diethyl ether was placed on a silicic acid column (20 x 180 mm) containing 20 g. of silicic acid (Mallinckrodt 100 mesh) prepared in hexane and washed with 10 ml. of diethyl ether. Elution of the column gave the following results: (1) 50 ml. pentane, nothing; (2) 350 ml. of pentane (35-37°)-20% diethyl ether, 1.06 g. of oil.

The infrared spectrum (neat) of the oil had bands at 2890, 1707, 1587, 1488, 1478, 1405, 1277, 1091, and 1013 cm⁻¹; nmr,

τ 3.25 (center of two doublets, 2H), 6.13 and 6.23 (9H), 6.90 and 6.95 (doublet superimposed on broad band, 3H), 8.0 (1H) and 8.33 (10H).

trans-2-(2',3',4'-Trimethoxyphenyl) cycloheptanemercaptoacetyl chloride (XI).

This material was prepared as previously described for the *cis* compound. The infrared spectrum (neat) had bands at 2928, 2857, 1784, 1597, 1491, 1459, 1415, 1281, 1228, 1096, 1013, 979, 955, 912, 797 cm^{-1} .

5*H*-1,2,3,4,5a,12*b*-Hexahydrocyclohepta[*b*]-10,11,12-Trimethoxybenzo[*d*]thiepin-8(7*H*)-one (XII).

The above *trans* acid chloride (XI) (4.6 g., 0.012 mole) dissolved in 50 ml. of spectra grade chloroform was added dropwise with stirring to a slurry of aluminum chloride (1.9 g.) in 100 ml. of chloroform. The reaction was allowed to proceed for 6 hours and was then hydrolyzed with dilute hydrochloric acid and washed with water. The chloroform solution was evaporated and the resulting oil was extracted with petroleum ether (35-37°). The petroleum ether extract was washed with a 5% sodium bicarbonate solution and then water. Evaporation of the petroleum ether left an oil (2.3 g.) which was dissolved in 5 ml. of benzene and placed on a column (25 x 150 mm.) containing 36 g. of neutral aluminum oxide (Merck) which was prepared with hexane. The column was eluted as follows: (1) 80 ml. pentane (35-37°), nothing; (2) 80 ml. pentane-50% benzene, 0.07 g.; (3) 600 ml. of pentane-75% benzene, 1.8 g. solid. The 1.8 g. (45%) of solid after two recrystallizations from methanol melted at 79-82°. The infrared spectrum

(chloroform) of the solid had bands at 2890, 1666, 1588, 1447, 1406, 1308, 1131, 1099, 1016 and 960 cm^{-1} ; nmr, τ 3.34 (1H), 6.1 and 6.17 (sharp doublet, 9H), 6.31 (2H), 6.9 (broad band, 2H), 8.31 (10H).

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{S}$: C, 64.26; H, 7.19. Found: C, 64.25; H, 7.28.

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