evaporated; the residue was dissolved in hot acetone and precipitated with *n*-hexane. The pentapeptide XIX was obtained as a white solid: 39.6 g (78%); mp 130–134°; $[\alpha]^{19}D$ +12.8° (*c* 2.13, DMF); mtlc (system A) homogeneous.

Anal. Calcd for $C_{59}H_{66}N_6O_8S$: S, 69.52; H, 6.53; N, 8.25; S, 3.15. Found: C, 69.54; H, 6.39; N, 8.41; S, 3.28.

***t*-Butyl *N*-Carbobenzoxy-*S*-trityl-L-cysteinylglycyl-N^{ϵ}-carbobenzoxy-L-lysylglycyl-*S*-benzhydryl-L-cysteinylglycinate (XXI).**

A. Generation of XX.—A solution of 10.88 g (0.0107 mole) of *N*-trityl ester XIX in 120 ml of acetic acid and 30 ml of water was heated for 2–3 min on a steam bath, diluted with 750 ml of water, evaporated *in vacuo*, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with hot saturated sodium chloride solution, dried, and the free base XX was precipitated as a gelatinous solid, 6.86 g (88%): mtlc (system A) homogeneous (iodine, ninhydrin, ultraviolet).

Treatment of XIX with a methanol–5 *N* hydrochloric acid (4:1) solution for 10–20 min at room temperature or at reflux for 1 min gave a product which was homogeneous (mtlc, ninhydrin, system A).

B. Coupling of XX with *N*-Carbobenzoxy-*S*-trityl-L-cysteine.—A solution of 7.05 g (0.0142 mole) of *N*-carbobenzoxy-*S*-trityl-L-cysteine[5] and 10.96 g (0.0142 mole) of XX in 20 ml of DMF was cooled to −10° and treated with 2.92 g (0.0142 mole) of DCC in 3 ml of DMF. The mixture was stirred for 9.5 hr, diluted with DMF, and filtered. The filtrate (*ca.* 125 ml) was diluted with 575 ml of water, cooled, and filtered to give 16 g (90%) of hexapeptide XXI: mtlc homogeneous (iodine, ultraviolet, system A). The peptide was dissolved in hot acetone containing a little DMF, the solution brought to the cloud point with *n*-hexane, and diluted to twice its volume with ether. The mixture was cooled, filtered, and the solid was washed with ether to provide 14.2 g (89% recovery) of XXI: mp 189–191°, $[\alpha]^{19}D$ −7.4° (*c* 0.19, DMF).

Anal. Calcd for $C_{70}H_{77}N_7O_{11}S_2$: C, 66.91; H, 6.18; N, 7.80; S, 5.10. Found: C, 67.08; H, 6.24; N, 7.78; S, 5.29.

Bis(*t*-Butyl *N*-Carbobenzoxy-L-cysteinylglycyl-N^{ϵ}-Carbobenzoxy-L-lysylglycyl-*S*-benzhydryl-L-cysteinylglycinate) (II).—To a solution of 1.26 g (0.001 mole) of XXI in 10 ml of DMF was added a solution of 0.17 g (0.001 mole) of silver nitrate and 0.081 ml (0.001 mole) of pyridine in 10 ml of ethanol. The reaction mixture was stored in the dark for 1 hr, treated with 50 ml of ether, and filtered. The gel was washed with methanol and ether, dried, and suspended in DMF. The suspension was treated with hydrogen sulfide for 15 min, warmed, and filtered. The thiol precipitated on addition of ether and petroleum ether; the solid was washed with ether to provide 0.4 g (40%) of thiol. The nitroprusside test was positive; mtlc (system A) homogeneous.

Air oxidation of the thiol was conducted in 10 ml of DMF containing 2 drops of triethylamine but was incomplete (positive nitroprusside test) after 2 days. Treatment of the solution with an ether solution of iodine provided the disulfide; after 0.5 min, II was precipitated by addition of ether and purified by two reprecipitations from DMF. The melting point was 192–202° dec; nitroprusside negative; mtlc homogeneous (system A); $[\alpha]^{19}D$ −60.2° (*c* 0.997, DMF).

Anal. Calcd for $C_{102}H_{124}N_{14}O_{22}S_4$: C, 60.46; H, 6.16; N, 9.68; S, 6.33. Found: C, 59.88; H, 6.35; N, 9.78; S, 6.62.

The Synthesis and Stereochemistry of 1,2,3,4,4a,11b-Hexahydro-9,10,11-trimethoxydibenzo[*b*,*d*]thiepin-7(6H)-one[1]

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The addition of mercaptoacetic acid to 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene under free-radical conditions yielded the *cis* acid IV. The resulting acid was converted to the acid chloride and cyclized with aluminum chloride to *cis*-1,2,3,4,4a,11b-hexahydro-9,10,11-trimethoxydibenzo[*b*,*d*]thiepin-7(6H)-one (VI). The corresponding *trans* compound XII was prepared by displacement of the *trans*-tosylate of 2-(2′,3′,4′-trimethoxyphenyl)cyclohexanol by the potassium salt of mercaptoacetic acid and subsequent cyclization of the acid chloride with aluminum chloride. Nucleophilic addition of mercaptoacetic acid to 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene could not be accomplished.

Although the antimitotic activity of the rather complex molecule colchicine has been known for many years its application in the treatment of cancer has been limited by its general toxicity. Some success has been achieved in synthesizing derivatives of colchicine having less toxicity but retaining a high antimitotic activity. The need for more effective antitumor agents with lower toxicity has prompted the investigation of the titled compounds.

Our approach to the preparation of the titled compounds is illustrated in Scheme I.

1-(2′,3′,4′-Trimethoxyphenyl)cyclohexanol (II) was prepared according to the procedure of Ginsburg and Pappo[2] which involved the condensation of 2,3,4-trimethoxyphenyllithium with cyclohexanone. The yield of II was considerably improved by using 1-bromo-2,3,4-trimethoxybenzene in place of 1,2,3-trimethoxybenzene. The method of Gutsche and Fleming[3] employing the Grignard in diethyl ether was unsuccessful in our hands. However, in later experiments a 50% yield of III was realized when tetrahydrofuran was used as a solvent and the product was distilled.

The tertiary alcohol II was dehydrated to 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene with oxalic acid in boiling toluene.[2] Addition of mercaptoacetic acid in the presence of benzoyl peroxide to 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene was extremely slow at 25°. This was in contrast to the findings with styrene[4] and 1-methylcyclohexene[5] where the free-radical addition of mercaptoacetic acid was rapid. Initial attempts to crystallize the oil resulting from the above reaction using various solvents were unsuccessful and identification of the acid was initially achieved by conversion to the crystalline sulfone ester. The oil did slowly crystallize on standing at room temperature and the resulting crystals could then be further purified by crystallization.

The conversion of acid IV to the cyclic keto sulfide VI was attempted using polyphosphoric acid and hydrogen fluoride since these reagents had been used successfully

(1) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965. The interpretation of the results in this paper which was presented at the American Chemical Society meeting has been revised to explain additional experimental evidence.

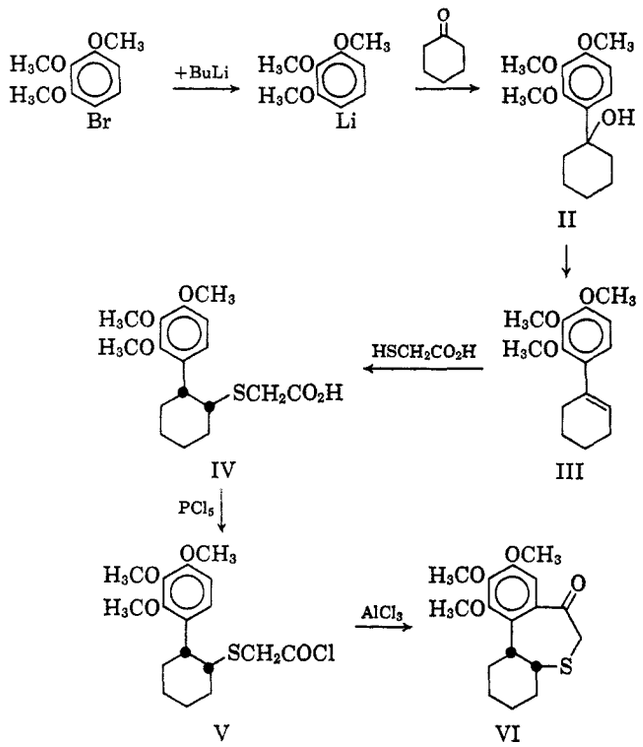
(2) D. Ginsburg and R. Pappo, *J. Am. Chem. Soc.*, **75**, 1094 (1953).

(3) C. D. Gutsche and F. A. Fleming, *ibid.*, **76**, 1771 (1954).

(4) B. Holmberg, *J. Prakt. Chem.*, **141**, 93 (1934).

(5) J. I. Cunneen, *J. Chem. Soc.*, **36** (1947).

SCHEME I



for the ring closure of β-[2-(2′,3′,4′-trimethoxyphenyl)-cyclohexane]propionic acid[3] and 2-(2′,3′,4′-trimethoxyphenyl)cyclohexaneacetic acid.[3] However, ring closure could not be achieved with these reagents in the present case, nor with acid chloride V and stannic chloride.

Although the 3′-methoxy group would be expected to activate the aromatic ring for closure with mild Friedel–Craft catalysts[6] our results would not appear to support this assumption. However, it is probable that the deactivating influence of the 2′- and 4′-methoxy groups[6] which are *meta* to the position of ring closure overshadow the activating influence of the 3′-methoxy group which is *para* to the position of ring closure. Acid chloride V was successfully cyclized with aluminum chloride in chloroform and the resulting material had an infrared and ultraviolet spectrum consistent with that expected of the desired product VI.

Since the free-radical addition of thiols to olefins has been shown in numerous cases to give principally the *cis* isomer,[7,8] it was initially assumed that compound VI was the *cis* isomer. To verify the configuration of compound VI a displacement reaction involving the *trans*-2-alcohol (IX) tosylate and the salt of mercaptoacetic acid was utilized. The *cis* acid should have resulted from the inversion in configuration at C-1.

The substituted cyclohexene derivative III (Scheme II) was oxidized with metachloroperbenzoic acid using a modified procedure of Gutsche and Fleming.[3] The resulting glycol VII was treated with sulfuric acid to yield the ketone VIII which was reduced with lithium aluminum hydride to alcohol IX. The tosylate of this alcohol was treated with the potassium salt of mercaptoacetic acid to yield the substituted mercaptoacetic acid derivative XI which was converted to the corresponding acid chloride and cyclized with aluminum chloride. The resulting crystalline material had an infrared and ultraviolet spectra similar to that of VI but a different melting point. A depression in melting point was observed when VI and XII were mixed. Since the reduction of 2-substituted cyclohexanones with lithium aluminum hydride generally produces high yields of the *trans* alcohols[9] it was assumed that *trans* alcohol IX was obtained in the present case.

trans alcohol IX was also prepared by the stereospecific reaction of 2,3,4-trimethoxyphenyllithium with cyclohexene oxide[10] and by the hydroboration method of Brown.[11,12] Although Bergmann, *et al.*,[10] reported that 2,3-dimethoxyphenyllithium gave a high yield of 2-(2′,3′-dimethoxyphenyl)cyclohexanol when allowed to react with cyclohexene oxide for 2 hr, it was necessary in the present case to reflux 2,3,4-trimethoxyphenyllithium with cyclohexene oxide in diethyl ether for 100 hr in order to obtain a reasonable yield. The hydroboration method of Brown yielded a crystalline alcohol. The tosylates of the alcohols prepared by the above two methods yielded cyclic keto sulfide XII when treated with the potassium salt of mercaptoacetic acid and the resulting acids cyclized.

Truce and Levy[13] have shown that nucleophilic addition of thiols to cyclohexene derivatives yield *cis* isomers. Our attempts to use this method for the preparation of acid IV were unsuccessful. Starting material was recovered in all cases. Since the *o*- and *p*-methoxy groups would tend to increase the electron density at position 2 it is probable that the attacking nucleophilic reagent was unable to react at this position of high electron density.

Since Cristol and Stermitz[14] had previously shown that 2-phenylcyclohexyl-*p*-toluenesulfonate underwent inversion on treatment with sodium methyl mercaptide it was reasonable to postulate that inversion occurred in the present case. However, the nmr spectra were not consistent with this reasoning. The spectrum of acid IV showed two broad peaks centered at τ 6.84 and 6.60 for the two tertiary protons. Acid XI had an unresolved peak centered at τ 7.85 and a broad peak centered at τ 7.00 partially obscured by the protons of the methylene group between the sulfur atom and carboxy group. When acid XI was oxidized to the corresponding sulfone the peak at τ 7.85 slightly shifted downfield to τ 7.80 while the peak formerly at τ 7.00 shifted to τ 6.70 indicating that this tertiary proton (τ 7.00) is α to the sulfur atom.[13] The tertiary proton α to the sulfur atom in acid IV shifted to τ 6.30 when the sulfide was converted to the sulfone while the peak at τ 6.84 shifted to τ 6.78. The steric requirement for a trimethoxyphenyl group is much larger than for a hydrogen atom and therefore the hydrogen atom α to the trimethoxyphenyl group should tend to occupy the axial position.[15] Since it

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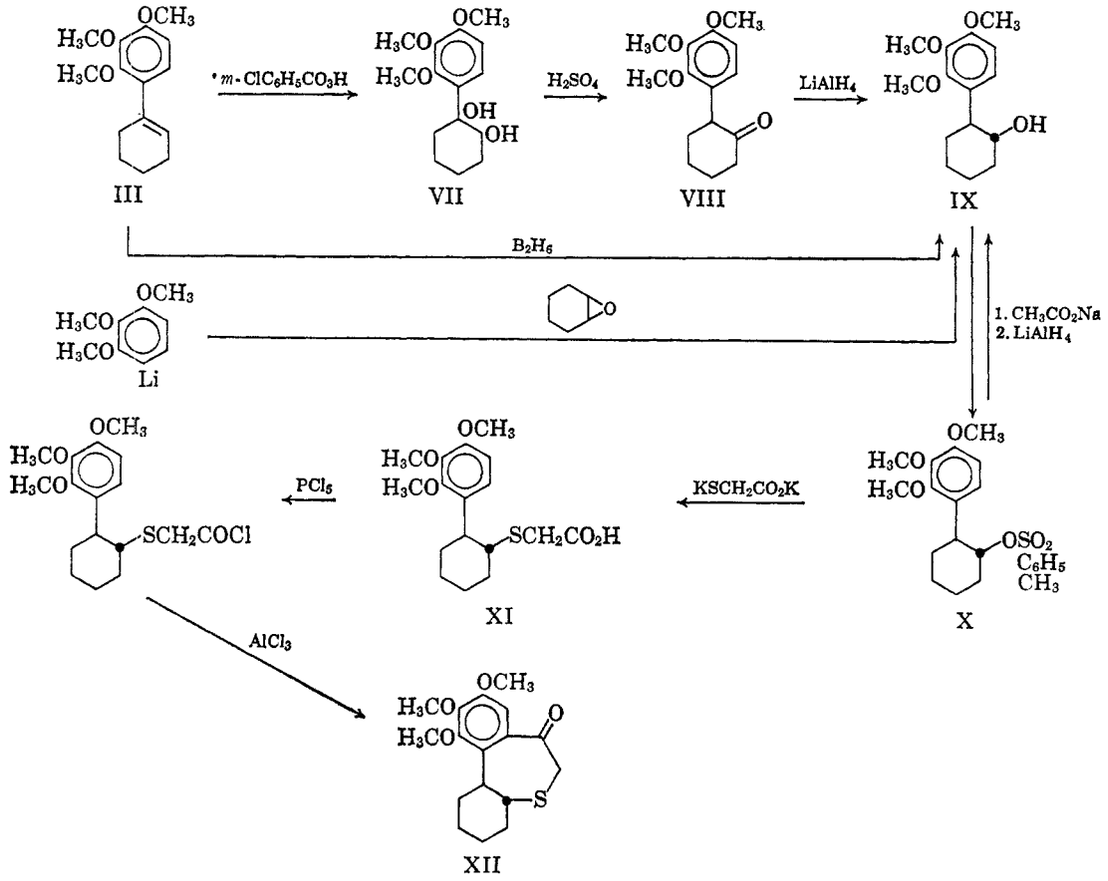
(7) H. L. Goering, D. I. Relyea, and D. W. Larsen, *J. Am. Chem. Soc.*, **78**, 348 (1956).
(8) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).
(9) L. F. Fieser and M. Fieser, "Topics in Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1963, pp 463.
(10) E. D. Bergmann, R. Pappo, and D. Ginsburg, *J. Chem. Soc.*, 1369 (1950).
(11) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6423 (1959).
(12) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6429 (1959).
(13) W. E. Truce and Alan J. Levy, *ibid.*, **83**, 4641 (1961).
(14) S. J. Cristol and F. R. Stermitz, *ibid.*, **82**, 4692 (1960).
(15) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 8.

SCHEME II

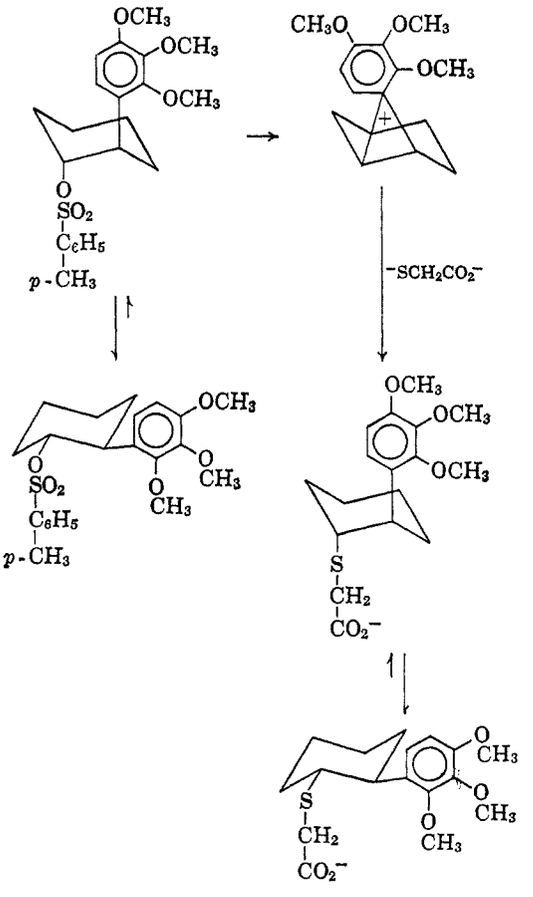


has been shown that axial protons generally absorb at higher frequencies than their equatorial counterparts[16] this evidence would suggest that acid XI, which has the proton α to the sulfur atom at a higher field than acid IV, is the *trans* isomer.

Additional evidence for this configurational assignment was obtained when *trans*-tosylate X was treated with sodium acetate in glacial acetic and the product was reduced with lithium aluminum hydride. *trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanol (IX) was obtained with a large amount of 2′,3′,4′-trimethoxyphenylcyclohexene. Thus, the chemical and physical evidence indicated that retention of configuration occurred rather than inversion which was expected from the work of Cristol and Stermitz. Reports that a *p*-methoxyphenyl group participates to a greater degree in anchimeric assistance than a phenyl group[17,18] make our results more tenable in view of Cristol's work since the benzene ring in our compound is substituted with both an *o*- and *p*-methoxy group and should be more effective in anchimeric assistance than the unsubstituted or the monosubstituted phenyl ring. Scheme III illustrates a possible pathway which explains our results.

On the basis of the configurations of the corresponding acids, cyclic keto sulfides XII and VI were assigned the *trans* and *cis* configurations, respectively. The nmr spectra were in accord with this assignment since the tertiary proton α to the sulfur atom in cyclic keto sulfide XII was at a higher field than the corresponding tertiary proton in keto sulfide VI.

SCHEME III



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(18) S. Winstein, M. Brown, K. C. Schreiber, and A. H. Schlesinger, *ibid.*, **74**, 1140 (1952).

Experimental Section[19]

1-(2′,3′,4′-Trimethoxyphenyl)cyclohexanol.—The hexane was removed under vacuum from 300 ml of butyllithium (15%) (Foote Mineral Co.). The solution was cooled to −10° and dry nitrogen was admitted to the flask. Diethyl ether (100 ml) was then added with stirring followed by 76.0 g (0.308 mole) of 1-bromo-2,3,4-trimethoxybenzene[20] dissolved in 300 ml of diethyl ether. This mixture was warmed to room temperature and refluxed for 2 hr. The mixture was cooled to −5° and 104 g (1.06 mole) of cyclohexanone was added dropwise over a period of 1 hr. The solution was then refluxed under nitrogen for 18 hr. The resulting ethereal solution was decomposed with ice–water, washed with 10% sodium hydroxide and water, dried over anhydrous sodium sulfate, and concentrated. The residue was distilled under vacuum to yield cyclohexanone, 1,2,3-trimethoxybenzene, an unidentified fraction, and 65 g of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol, bp 155–160° (0.5 mm). The alcohol was recrystallized from hexane: mp 65–67°, lit.[2] mp 66–67°; yield 51 g (62%).

In the same manner 1,2,3-trimethoxybenzene[21] and 1-iodo-2,3,4-trimethoxybenzene[22] gave 27% yields of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol.

Tetrahydrofuran (50 ml), 24.7 g. (0.10 mole) of 1-bromo-2,3,4-trimethoxybenzene, and 2.43 g (0.10g-atom) of magnesium turnings were heated at 60° until the reaction started. After the magnesium turnings disappeared the solution was cooled and 9.8 g (0.10 mole) of cyclohexanone dissolved in 100 ml of tetrahydrofuran was added dropwise to the reaction mixture. The resulting mixture was stirred for 15 hr at room temperature and slowly decomposed with ice–water. The ether extract of this material was washed with 10% sodium hydroxide and water, dried over anhydrous sodium sulfate, and concentrated. Distillation of the resulting oil yielded 13.4 g (54%) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene, bp 129–134° (0.6 mm).

***cis*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetic Acid.**—A mixture of 20.0 g (0.081 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene, prepared by refluxing 1-(2′,3′,4′-trimethoxyphenyl)cyclohexanol with oxalic acid,[2] 9.0 g (0.098 mole) of mercaptoacetic acid, and 0.1 g of benzoyl peroxide was allowed to stand 1 month at room temperature. The resulting oil was dissolved in diethyl ether and extracted with 5% sodium hydroxide until all acidic material was removed. The diethyl ether was washed with water, dried, and evaporated. Unreacted 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene (6 g) was recovered. The basic solution was acidified with hydrochloric acid and extracted with diethyl ether. The diethyl ether extract was washed with water, dried, and concentrated. The oil decomposed on attempted distillation. Attempts to crystallize the oil from hexane, methanol, benzene, petroleum ether, and carbon disulfide at 0° were unsuccessful. The acid spontaneously crystallized on standing at room temperature for 3 weeks. The resulting crystals (13.5 g, 69%) melted at 77–79° after recrystallization from a mixture of petroleum ether (bp 37°) and carbon disulfide.

In a second experiment the experimental conditions were as described above except a reaction period of 336 hr was employed. A 50% yield of the *cis* acid was realized.

In a third experiment a mixture of 6.00 g (0.0242 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene, 2.23 g (0.0242 mole) of mercaptoacetic acid, and 0.1 g of benzoyl peroxide was heated at 42° for 48 hr. The reaction mixture was worked up as described above. At 37% yield (3.0 g) was realized.

***cis*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetyl Chloride.**—A solution of 4.00 g (0.0118 mole) of *cis*-2-(2′,3′,4′-trimethoxyphenyl)cyclohexanemercaptoacetic acid and 50 ml of carbon disulfide was cooled in an ice bath and 2.49 g (0.0120 mole) of phosphorus pentachloride was slowly added to the solution. The solution was allowed to stand for 24 hr at room temperature and the carbon disulfide and phosphorus oxychloride were removed under vacuum. The material decomposed when distillation was attempted. For the cyclization experiments the acid chloride was extracted with petroleum ether, the petroleum ether was removed under vacuum at 50°, and the remaining acid chloride was taken up in the solvent used for the particular cyclization experiment.

cis-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetic acid (10.0 g, 0.0294 mole) was dissolved in 50 ml of carbon disulfide and treated with 9.5 g (0.075 mole) of oxalyl chloride. The solution was maintained at 0° during the addition and was then allowed to stand at room temperature for 12 hr. The excess oxalyl chloride and carbon disulfide were removed under vacuum and the acid chloride was extracted with petroleum ether. The petroleum ether was removed under vacuum and the acid chloride was used in the cyclization reactions.

Ethyl *cis*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanesulfonylacetate.—A solution of 3.0 g (0.0084 mole) of 2-(2′,3′,4′-trimethoxyphenyl)cyclohexanemercaptoacetyl chloride and 20 g of anhydrous ethanol was allowed to react for 2 hr. The excess ethanol was evaporated and the remaining oil was taken up in 30 ml of glacial acetic acid and cooled to 10°. Hydrogen peroxide (10 ml) (30%) was added to the solution and the solution was allowed to stand for 4 days in the refrigerator. The excess hydrogen peroxide was decomposed with solid potassium permanganate and the volume of acetic acid reduced with an air jet. The remaining solution was diluted with water and extracted with benzene. The benzene extract was washed with 5% sodium hydroxide and water. Evaporation of the benzene left an oil (2.4 g) which crystallized as a white solid (2.0 g, 60%) from 95% ethanol: mp 84–86°.

Anal. Calcd for $C_{19}H_{28}O_7S$: C, 56.98; H, 7.04; S, 8.0; mol wt, 400. Found: C, 57.11, 57.05; H, 7.10, 7.05; S, 7.79, 7.92; mol wt, 400, 410.

Cyclization of *cis*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetyl Chloride.—A solution of 5.00 g (0.0139 mole) of *cis*-2-(2′,3′,4′-trimethoxyphenyl)cyclohexanemercaptoacetyl chloride and 80 ml of anhydrous chloroform was added dropwise to a stirred suspension of 1.86 g (0.014 mole) of anhydrous aluminum chloride and 200 ml of chloroform. The reaction mixture was stirred for 5 hr and decomposed with ice and hydrochloric acid. The chloroform was removed with an air jet and the remaining oil was taken up in diethyl ether, washed with 5% sodium hydroxide and water, and dried over anhydrous sodium sulfate. Evaporation of the diethyl ether yielded an oil which solidified in some cases when treated with petroleum ether. In most experiments the oil was chromatographed as follows.

A column of aluminum oxide (Merck) was prepared from a slurry of aluminum oxide and hexane. The oil from the cyclization reaction dissolved in benzene was placed on the column and eluted with diethyl ether. The diethyl ether was evaporated and the remaining material was washed with petroleum ether to yield a solid. This solid after recrystallization from methanol melted at 103–105°, yield 2.5 g (56%).

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.32; H, 6.87; S, 9.94; mol wt, 322. Found: C, 62.82; H, 6.82; S, 9.67; mol wt 326.

2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanone.—A solution of 6.56 g (0.038 mole) of *m*-chloroperbenzoic acid dissolved in 50 ml of ethyl acetate was added dropwise to a stirred solution of 10.0 g (0.0403 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene in 50 ml of ethyl acetate at 0°. The reaction mixture was stirred at 0° for 1.05 hr and at 25° for 1 hr. When the reaction was complete as evidenced by a negative iodine test, the solution was extracted with base and washed with water, and the ethyl acetate was evaporated. The resulting oil was dissolved in 50 ml of ethanol and treated with 2.2 ml of concentrated sulfuric acid dissolved in 2.1 ml of water and 50 ml of ethanol.[3] The solution was refluxed for 2 hr and the volume was reduced. The resulting material was extracted with diethyl ether and washed with 5% sodium bicarbonate and water. Evaporation of the ether and distillation of the resulting oil at 4 mm yielded 7.0 g (65%) of the ketone, bp 182–184°, $n^{25}D$ 1.5292 [lit.[3] bp 178–190° (5 mm), $n^{25}D$ 1.5390].

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanol.**—A solution of 10.0 g (0.038 mole) of 2-(2′,3′,4′-trimethoxyphenyl)cyclohexanone in 30 ml of diethyl ether was added dropwise to 0.400 g (0.0105 mole) of lithium aluminum hydride. The mixture was allowed to stand 1 hr at room temperature and was decomposed with water and then acid. The water phase was extracted with diethyl ether and the diethyl ether fractions were combined and washed with water. The ether was evaporated and 7.0 g (69%) of oil distilled at 135–137° (0.12 mm), $n^{25}D$ 1.5365.

trans-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanol was also prepared as follows. The hexane from 300 ml of Foote butyllithium (15%) was removed under vacuum. Diethyl ether (100

(19) Melting points were taken using a Nalge–Axelrod melting point apparatus and are uncorrected.

(20) D. Freedman and D. Ginsburg, *J. Org. Chem.*, **23**, 16 (1958).

(21) M. T. Bogert and B. B. Coyne, *J. Am. Chem. Soc.*, **51**, 571 (1929).

(22) W. Baker, A. W. Kirley, and L. V. Montgomery, *J. Chem. Soc.*, 2876 (1932).

ml) was added at −10° to the butyllithium. A solution of 76.0 g (0.308 mole) of 1-bromo-2,3,4-trimethoxybenzene dissolved in 300 ml of diethyl ether was then added to the butyllithium at −10°. The mixture was refluxed for 2.5 hr and cooled to 10°; 50.0 g (0.509 mole) of cyclohexene oxide was added. The solution was refluxed for 100 hr, decomposed with water, and washed with 10% sodium hydroxide. The ether was evaporated and the oil was distilled at 141–147° (0.19 mm), $n^{25}D$ 1.5363, 26 g (32%).

Anal. Calcd for $C_{15}H_{22}O_4$; C, 67.64; H, 8.32. Found: C, 67.67; H, 8.45.

Following the general procedure of Brown and Subba Rao[12] a solution of 2.55 g (0.018 mole) of boron trifluoride etherate in 17.7 ml of bis(2-methoxyethyl) ether was slowly added to a stirred solution of 10.0 g (0.0403 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene, 0.600 g (0.0159 mole) of sodium borohydride, and 21.5 ml of bis(2-methoxyethyl) ether in an atmosphere of nitrogen. The reaction mixture was stirred for 1 hr at room temperature and treated first with 3 ml of water, then 10 ml of sodium hydroxide, and finally 6 ml of 30% hydrogen peroxide. After standing for 16 hr at room temperature the mixture was diluted with water and extracted with diethyl ether. The extract was washed with dilute hydrochloric acid and water, and dried. Distillation of the oil remaining after evaporation of the ether yielded 5.0 g (47%) of oil, bp 134–144° (0.08 mm). This oil was crystallized from petroleum ether upon standing at 6° for 3 weeks, mp 36–38°.

To a stirred solution of 0.025 mole of sodium borohydride (20 ml of 1.25 *M* solution in bis(2-methoxyethyl) ether and 0.084 mole of aluminum chloride (5 ml of 1.7 *M* solution in bis(2-methoxyethyl) ether in a 200-ml flask flushed with nitrogen and maintained under nitrogen was added 12.4 g (0.050 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene over a period of 1 hr. The reaction mixture was stirred for 3 hr at room temperature and heated for 1 hr at 95°. The reaction mixture was hydrolyzed by the slow addition of 2 ml of water and then 10 ml of 3 *N* sodium hydroxide. Hydrogen peroxide (30%)(7g) was slowly added. The mixture was allowed to stand 4 hr, diluted with water, and extracted with diethyl ether. The extract was washed with dilute hydrochloric acid, water, and dried. Distillation of the oil remaining after evaporation of the ether yielded 4.5 g of oil, bp 133–145° (0.08 mm).

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexyl-*p*-toluenesulfonate.**—A solution of 24.0 g (0.0901 mole) of 2-(2′,3′,4′-trimethoxyphenyl)cyclohexanol and 28 g of pyridine was treated with 18.3 g (0.0960 mole) of *p*-toluenesulfonyl chloride at 0°.[23] The resulting mixture was allowed to stand for 32 hr at room temperature and was then decomposed with ice and hydrochloric acid. The resulting solid was filtered and washed with 5% sodium bicarbonate and ice–water. After recrystallization from methanol the solid melted at 119–121°, 30 g (79%).

Anal. Calcd for $C_{22}H_{28}O_6S$: C, 62.82; H, 6.72. Found: C, 62.66; H, 6.70.

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetic Acid.**—*trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexyl-*p*-toluenesulfonate (17.6 g, 0.042 mole) was dissolved in 250 ml of 96% methanol along with 7.00 g (0.0416 mole) of potassium mercaptoacetate. The solution was refluxed for 24 hr and the solvent was evaporated. The resulting oil was washed with 5% sodium hydroxide until all of the base-soluble material was extracted. The base-insoluble oil (10 g) distilled at 122–130° (0.2 mm), $n^{25}D$ 1.5385. Acidification of the basic extract yielded 2.5 g of oil which gave a positive test for sulfur. The oil could not be distilled. The infrared spectrum of this oil was similar to the infrared spectrum of an equimolar mixture of mercaptoacetic acid and 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene and to the spectrum of the *cis* acid.

Anhydrous methanol and a reaction temperature of 56° for 24 hr gave the best results out of a series of reaction conditions. A 50% yield was obtained under these conditions.

***trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetyl Chloride.**—The *trans* acid was treated as described for the preparation of the *cis*-2-(2′,3′,4′-trimethoxyphenyl)cyclohexanemercaptoacetyl chloride.

Cyclization of *trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexanemercaptoacetyl Chloride.—The *trans* acid chloride was cyclized using the conditions found best for the *cis* acid chloride. A 50% yield of crystalline material was obtained, mp 119–124°, depressed on admixture with compound VI.

Anal. Calcd for $C_{17}H_{22}O_4S$: C, 63.32; H, 6.87. Found: C, 63.51; H, 6.72.

The Attempted Nucleophilic Addition of Mercaptoacetic Acid to 1-(2′,3′,4′-Trimethoxyphenyl)cyclohexene.—Following the procedure of Truce and Levy[13] 0.92 g (0.040 mole) of sodium was dissolved in 200 ml of methanol. To this solution was slowly added 1.92 g (0.02 mole) of mercaptoacetic acid followed by 5.00 g (0.0201 mole) of 1-(2′,3′,4′-trimethoxyphenyl)cyclohexene. The solution was refluxed for 24 hr. The methanol was evaporated and the resulting solid was treated with water and extracted with diethyl ether. The ether extracted was washed with water, dried over anhydrous sodium sulfate, and evaporated to yield 4.8 g of starting material.

Acetolysis of *trans*-2-(2′,3′,4′-Trimethoxyphenyl)cyclohexyl-*p*-toluenesulfonate.—A solution of 2.20 g (0.0120 mole) of *trans*-2-(2′,3′,3′-trimethoxyphenyl)cyclohexyl-*p*-toluenesulfonate in 50 ml of glacial acetic acid containing 0.374 g (0.00456 mole) of sodium acetate was heated at 100° for 7 hr. 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 (1.4 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 hr 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 Merck aluminum oxide.

Successive elution with the indicated solvents gave fractions: (1) 50 ml of pentane, nothing; (2) 100 ml of pentane–25% ether, 520 mg of unsaturated hydrocarbon; (3) 200 ml of ether, nothing; (3) 200 ml of pentane–4% methanol, 360 mg of IX, mp 38–40°.

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