

as the least soluble species (1.7%; in addition to impure fractions, mp 240–260°, containing other isomers), followed by V, mp 145–146° (0.3%), and a fraction that, when rechromatographed, was separated into VI, mp 102–105° (0.2%; wide melting point range indicates presence of other isomers), and the oily mixture VII (3.0%). The third zone, mechanically removed from the column, extracted with ether, and rechromatographed in cyclohexane, produced two bands. The lower one, reprecipitated from hexane by partial vacuum evaporation, gave VIIIa, M_n 680 (10.1%); similarly, the upper one gave VIIIa, M_n 810 (3.2%). From the fourth zone, worked up as in the preceding case, two fractions VIIIb were isolated; the lower molecular fraction (1.6%), reprecipitated from cyclohexane solution by methanol, had M_n 1050; the higher molecular fraction (6.6%), reprecipitated from benzene solution by methanol, had M_n 1720. Analytical data for all new compounds are collected in Table I. The identities of III, V, and VI were established by elemental analysis and comparison of melting point, X-ray diffraction pattern, and ir spectra with those of authentic samples.^{9–11}

Registry No.—IIId, 12271-18-0; III, 12088-07-2; IV, 12271-17-9; V, 1317-11-9; VI, 12271-19-1; VII, 12271-20-4; aluminum chloride, 7446-70-0; dichloromethane, 75-09-2; ferrocene, 102-54-5.

Acknowledgment.—The author is greatly indebted to Miss K. Koda and Mr. E. Quo for their excellent contribution to the experimental work. Mr. R. K. Crossland, University of Southern California, obligingly recorded the pmr spectra.

The Novel Reaction of 2-(2',3',4'-Trimethoxyphenyl)cycloheptyl Methanesulfonate with Dipotassium Mercaptoacetate

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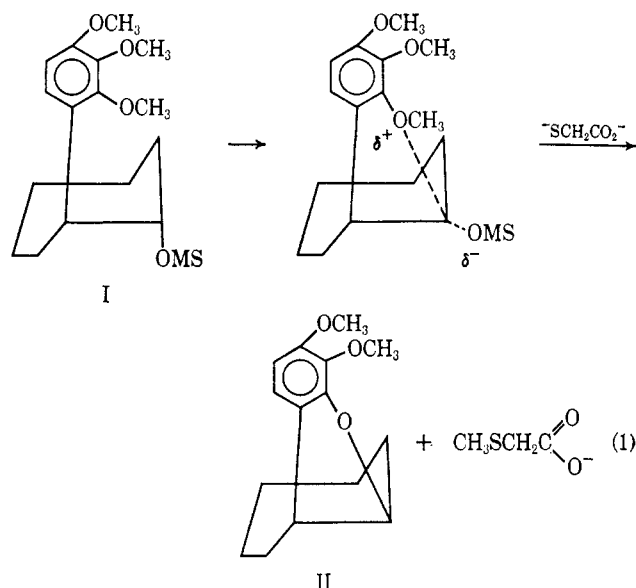
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Received December 22, 1967

While studying the stereochemistry of 2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetic acid obtained by the addition of mercaptoacetic acid to 1-(2',3',4'-trimethoxyphenyl)cycloheptene, it was necessary for the author to prepare *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptanemercaptoacetic acid. Because axial tosylates substituted in the axial 2 position by a phenyl group containing an electron-donating group in the *ortho* or *para* position retain their configuration when treated with nucleophilic reagents,¹ it was felt that in the present situation the desired compound could be obtained by treating *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptyl methanesulfonate with the dipotassium salt of mercaptoacetic acid.

Treatment of *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptyl methanesulfonate with the dipotassium salt of mercaptoacetic acid yielded only a small amount of the desired product. The major fraction was sulfur free and insoluble in base. The nmr spectrum of the base insoluble material showed single-proton absorptions at τ 5.0 and 6.5. These single proton absorptions were not in the region of the olefinic protons of a conjugated or unconjugated cyclic system² and were not in

the region of the ethylenic proton of 1-(2',3',4'-trimethoxyphenyl)cycloheptene which absorbed at τ 4.18. Absorptions at τ 6.08 and 6.17 integrated correctly for only six protons representing two methoxyl groups rather than the expected three methoxyl groups. Thus, a methyl group of one methoxyl group was evidently lost during the reaction. Since the infrared spectrum showed no absorption in the hydroxyl region for this compound, reaction 1 is believed to occur. The



structure of compound II is consistent with the nmr spectrum since the substitution pattern on the benzene ring remains unchanged, the seven-membered ring is intact, and the protons of one methoxy group are no longer present. The proton absorption at τ 5.0 is assigned to the hydrogen atom α to the oxygen of the cyclic ether. Although this value is approximately 0.57 ppm downfield from the absorption of the proton α to the ether oxygen in 2,3-dihydro-5-methoxybenzofuran (τ 5.57),³ Fulmor, *et al.*, have assigned a proton absorption at τ 5.02 to a proton α to the cyclic ether oxygen in the 6,14-*endo*-ethenotetrahydrothebaine system.⁴ The proton absorption at τ 6.5 is assigned to the benzyl proton. Structure II is also consistent with the elemental analysis and the infrared spectrum. The isolation of S-methylmercaptoacetic acid also supports the postulated reaction.

Attempts to cleave the cyclic ether with gaseous hydrogen chloride at 80 and 100° were unsuccessful. Hydrogen bromide (48%) in refluxing glacial acetic acid (8 hr) cleaved the methoxyl groups but apparently failed to open the cyclic ether ring since the resulting phenolic ether could be successfully converted back into the starting compound by treatment with dimethyl sulfate and base.

Although it is generally postulated that the phenyl ring itself participates in anchimeric assistance, it has been suggested that the methoxyl group can participate directly in anchimeric assistance. Noyce⁵ has postulated that the methoxyl group in 1,4-methoxycyclo-

(2) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 61.

(3) S. D. Darling and K. D. Wills, *J. Org. Chem.*, **32**, 2794 (1967).

(4) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Amer. Chem. Soc.*, **89**, 3322 (1967).

(5) D. S. Noyce and B. R. Thomas, *ibid.*, **79**, 755 (1957).

(1) F. J. Lotspeich and S. Karickhoff, *J. Org. Chem.*, **31**, 2183 (1966).

hexyl tosylate assists in the displacement of the tosylate through the boat-form intermediate. Allred and Winstein⁶ recently reported the participation of the 5-methoxyl group in the lithium aluminum hydride reduction of 5-methoxyl-2-pentyl *p*-bromobenzene-sulfonate. In this case the oxygen atom of the methoxyl group was incorporated into the ring of 2-methyltetrahydrofuran which was formed in this reaction. Framework molecular models do not rule out the postulated reaction in the present case since they indicate that the *o*-methoxyl group of *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptyl methanesulfonate is properly located for a backside displacement of the mesylate group. Further studies in this area are in progress.

Experimental Section

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.

1-(2',3',4'-Trimethoxyphenyl)cycloheptanol was prepared according to the procedure of Ginsburg and Pappo⁷ as modified by Lotspeich and Karickhoff¹ for the preparation of 1-(2',3',4'-trimethoxyphenyl)cyclohexanol.

1-(2',3',4'-Trimethoxyphenyl)cycloheptene.—This preparation was achieved according to the procedure of Ginsburg and Pappo.⁷

trans-2-(2',3',4'-Trimethoxyphenyl)cycloheptanol.—The procedure which was followed in this synthesis was that of Brown and Subba Rao.⁸ 1-(2',3',4'-Trimethoxyphenyl)cycloheptene (23.6 g) gave 21.4 g of oil, bp 135–147° (0.04 mm). This oil (3 g) was chromatographed over 108 g of neutral aluminum oxide (Merk) prepared with hexane. Successive elution with the indicated solvents gave four fractions: (1) 120 ml of pentane–25% diethyl ether, 1.26 g of mainly 1-(2',3',4'-trimethoxyphenyl)cycloheptene; (2) 400 ml of pentane–80% diethyl ether, nothing; (3) 160 ml of diethyl ether, 120 mg of 1-(2',3',4'-trimethoxyphenyl)cycloheptanol; (4) 200 ml of pentane–10% methanol, 1.44 g of *trans*-2-(2',3',4'-trimethoxyphenyl)cycloheptanol. Fraction 4 was distilled: bp 142–143° (0.05 mm); n_D^{20} 1.5380.

Anal. Calcd for C₁₆H₂₄O₄: C, 68.57; H, 8.57. Found: C, 68.63; H, 8.62.

trans-2-(2',3',4'-Trimethoxyphenyl)cycloheptyl methanesulfonate was prepared by allowing 2.00 g (0.0071 mol) of the above alcohol to react with 0.96 g (0.0084 mol) of methanesulfonyl chloride in 5 ml of pyridine at 10° for 48 hr. The pyridine solution was worked up in the usual manner to give 1.6 g (63%) of white crystals which were recrystallized twice from methanol, mp 88–90°.

Anal. Calcd for C₁₇H₂₆O₆S: C, 56.98; H, 7.26. Found: C, 57.07; H, 7.22.

6H-3,4-Dimethoxybenzo[b]-5a,7,8,9,10a-hexahydrocyclohepta[d]furan.—*trans*-2-(2',3',4'-Trimethoxyphenyl)cycloheptyl methanesulfonate (5.5 g, 0.015 mol) was added to 100 ml of anhydrous methanol containing 3.00 g (0.018 mol) of potassium mercaptoacetate. The solution was heated at 55° for 60 hr and the methanol evaporated. Water (5 ml) was added and the material extracted with diethyl ether. The diethyl ether was washed with water and evaporated to yield 3.3 g of oil which solidified upon standing. The solid was crystallized from diethyl ether to yield 3.0 g of 6H-3,4-dimethoxybenzo[b]-5a,7,8,9,10a-hexahydrocyclohepta[d]furan, mp 70–71.5°. Attempts to reduce this compound with Raney nickel in methanol at 40 psi of hydrogen were unsuccessful. The compound also failed to react with potassium permanganate in acetone and to undergo hydroboration according to the procedure previously described. The infrared spectrum had bands at 3010, 2930, 2860, 1620, 1492, 1460, 1268, 1150, 1088, 1055, and 972 cm⁻¹. The nmr spectrum showed absorption bands at τ 3.4 (doublet, 2 H), 5.0 (broad, 1 H), 6.08 and 6.17 (6 H), 6.5 (broad, 1-H), 8.3 (10-H).

(6) E. L. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 4008 (1967).

(7) D. Ginsburg and R. Pappo, *ibid.*, **75**, 1094 (1953).

(8) H. G. Brown and B. C. Subba Rao, *ibid.*, **81**, 6423 (1959).

Anal. Calcd for C₁₅H₂₀O₃: C, 72.55; H, 8.12; mol wt, 248. Found: C, 72.86; H, 7.92; mol wt, 255.

The basic solution was acidified with concentrated hydrochloric acid and extracted with diethyl ether. Evaporation of the ether after washing with water yielded 1.8 g of material. Distillation of this material yielded 0.9 g of oil, bp 64–68° (0.7 mm). This material was converted into the acid chloride and treated with aniline to yield the anilide of S-methylmercaptoacetic acid, mp 77–78° (lit.⁹ mp 80°). This material did not depress the melting point of an authentic sample of the anilide of S-methylmercaptoacetic acid. The residue from the distillation was taken up in chloroform and the solid removed. The chloroform was evaporated and the liquid was taken up in a small amount of diethyl ether passed over a column (22 × 150 mm) containing 18 g of silicic acid. Elution with 20% diethyl ether in hexane yielded 0.40 g of an acidic oil which had an infrared and nmr spectra identical with the acid prepared by displacement of the *cis* tosylate.

The Reaction of 6H-3,4-Dimethoxybenzo[b]-5a,7,8,9,10,10a-hexahydrocyclohepta[d]furan with Hydrogen Bromide.—Hydrogen bromide (2.4 g of 48%), 5 ml of glacial acetic acid, and 2.0 g of 6H-3,4-dimethoxybenzo[b]-5a,7,8,9,10,10a-hexahydrocyclohepta[d]furan were refluxed for 8 hr. The solution was cooled, added to water, and extracted with diethyl ether. The ether extract was washed with 5% sodium bicarbonate solution and then water. Evaporation of the ether yielded 1.5 g of oil which solidified when treated with cold petroleum ether (bp 35–37°). This material melted at 160–166° after crystallization from methylene chloride–petroleum ether (bp 35–37°) (further recrystallization did not improve the melting point): nmr, τ 3.48 (center of two doublets), 4.55 (2-H), 4.48 (1-H), 6.50 (1-H), and 8.32 (10-H); the infrared spectrum (chloroform) had bands at 3633, 2925, 1641, 1486, 1013, and 1207 cm⁻¹.

Remethylation of 6H-3,4-Dihydroxybenzo[b]-5a,8,9,10,10a-hexahydrocyclohepta[d]furan.—6H-3,4-Dihydroxybenzo[b]-5a,7,8,9,10,10a-hexahydrocyclohepta[d]furan (1.00 g, 0.0040 mol) and 0.80 g (0.020 mol) of sodium hydroxide were treated with 0.63 g (0.0050 mol) of dimethyl sulfate at 80°. After stirring for 10 min an additional 0.80 g (0.020 mol) of sodium hydroxide and 0.63 g (0.0050 mol) of dimethyl sulfate were added and the solution was refluxed for 2 hr. The resulting solution was cooled and extracted with diethyl ether. The ether extract was washed with water and the ether was evaporated to yield dark yellow crystals. These crystals were recrystallized from petroleum ether (bp 35–37°), mp 70–71.5°. They showed no depression in melting point when mixed with a sample of 6H-3,4-dimethoxybenzo[b]-5a,7,8,9,10,10a-hexahydrocyclohepta[d]furan.

Registry No.—I, 16958-54-6; free base of I, 16958-55-7; II, 16958-56-8; dipotassium mercaptoacetate, 16958-57-9.

Acknowledgments.—The author wishes to thank Dr. Charles McCarty, Chemistry Department, West Virginia University, for assistance with the proton magnetic resonance spectra. This investigation was supported by Public Health Service Research Grant (GM 09342) from the National Institutes of Health.

(9) I. Heilbron, *Dictionary of Organic Compounds*, Vol. IV, Oxford University Press, New York, N. Y., 1953, p 2238.

Conformational Analysis of 1-Methylcyclohexanol

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Received February 7, 1968

The free-energy difference between the two chair forms of a monosubstituted cyclohexane is generally re-

(1) National Science Foundation Undergraduate Research Participant, summer, 1966.