The Synthesis of Methoxy Substituted Hexahydro[*b*,*d*]thiepine-7(6*H*)-ones (1)

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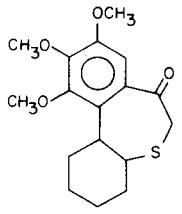
In 1966 (2) the author reported the synthesis of 1,2,3,4,4a,11b-hexahydro-9,10,11-trimethoxydibenzo-[*b*,*d*]thiepin-7(6*H*)-one (A).



A

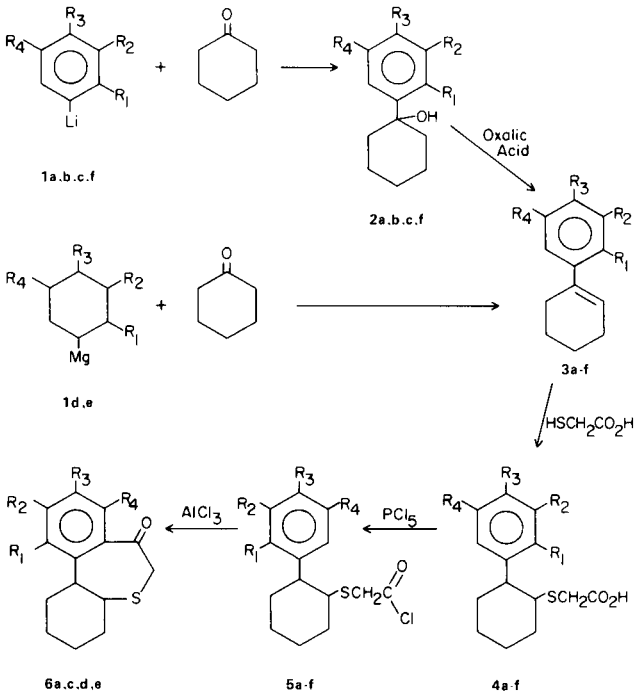
Our continuing interest in the general type compound A led us to synthesize a series of these compounds and to determine what effect the position and number of methoxy groups attached to the benzene ring might have on the course of ring formation.

The effect of the methoxyl group and methyl group on the formation of five and six-membered ring systems has been investigated (3). 6-Methoxytetralone-1 is obtained from γ-*m*-methoxyphenylbutyric acid in 96% yield (*para* cyclization). *m*-Methoxyhydrocinnamic acid which can undergo *para* or *ortho* cyclization yields mainly *para* cyclization. In some cases *ortho* cyclization is reported but generally the yields are low. To the authors' knowledge no study has been made on the sulfur system which is reported in this paper.

For this investigation the compounds listed in Chart I were selected for study. In general these compounds were synthesized as outlined in Scheme I.

The substituted phenylcyclohexenes were synthesized by allowing the substituted phenyllithium derivatives to react with cyclohexanone (2) followed by dehydration of the tertiary alcohol with oxalic acid or by allowing the substituted phenyl Grignard reagent to react with cyclohexanone (2). In the latter cases dehydration of the tertiary alcohol occurred spontaneously during distillation. The substituted phenylcyclohexanemercaptoacetic acids were prepared by allowing the unsaturated compounds to react with mercaptoacetic acid. Identification of these

SCHEME I



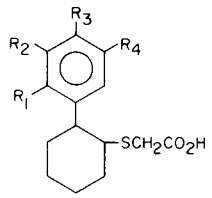
a. $R_1 = R_2 = OCH_3$, $R_3 = R_4 = H$
b. $R_1 = OCH_3$, $R_2 = R_3 = R_4 = H$
c. $R_1 = R_2 = R_3 = R_4 = H$
d. $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
e. $R_1 = R_4 = H$, $R_2 = R_3 = OCH_3$
f. $R_1 = R_4 = OCH_3$, $R_2 = R_3 = H$

acids was based on infrared (Chart IV) and nuclear magnetic resonance spectra (Chart III) and elemental analysis (Chart I) where possible. The acids were converted to their acid chlorides with phosphorus pentachloride. Identification of the acid chlorides was based on their infrared spectrum (carbonyl vibration - 1784 cm^{-1} - 1792 cm^{-1}).

cis-2-Phenylcyclohexanemercaptoacetyl chloride (**5c**) which contains no activating or deactivating groups yielded a base insoluble oil when treated with aluminum chloride in chloroform. The oil could not be crystallized but flash distillation of the oil gave a product which showed an infra-

CHART I

Substituted Phenyl Cyclohexanemercaptoacetic Acids

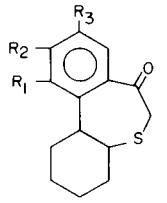


R_1	R_2	R_3	R_4	Melting Point	Yield %	Reaction Time Hr.	Solvent (b)	Acid/ Unsat.	Formula	Calcd.	Found
H	H	H	H	93-94	61	24	Cyclo-hexane	3/1	$C_{14}H_{18}O_2S$	C, 67.17 H, 7.25	66.98 7.36
OCH_3	H	H	H	128-130	85	24	Ethanol	3/1	$C_{15}H_{20}O_3S$	C, 64.26 H, 7.20	63.95 7.21
OCH_3	OCH_3	H	H		79	24		3/1	$C_{16}H_{22}O_4S$ (a)		
H	OCH_3	H	H	59-61.5	93	24	Carbon disulfide/ pentane	3/1	$C_{15}H_{20}O_3S$	C, 64.26 H, 7.20	64.45 7.21
H	OCH_3	OCH_3	H	121-124	85	48	Diethyl ether/ pentane	5/1	$C_{16}H_{22}O_4S$	C, 61.91 H, 7.14	61.71 7.12
OCH_3	H	H	OCH_3		84	65		3/1	$C_{16}H_{22}O_4S$		

(a) The sulfone methyl ester was analyzed. Calcd. for $C_{17}H_{24}SO_6$: C, 57.29; H, 6.79. Found: C, 57.29; H, 6.92. (b) Solvent used for recrystallization of the mercaptoacetic acid.

CHART II

1,2,3,4,4a,11b-Hexahydrodibenzo[*b*,*d*]thiepin-7(6*H*)-ones



R_1	R_2	R_3	Melting Point	Yield %	Formula	Calcd.	Found
H	H	H		17	$C_{14}H_{16}OS$ (a)		
H	OCH_3	OCH_3	104-106°	16	$C_{16}H_{20}O_3S$	C, 65.72 H, 6.89	65.77 6.78
OCH_3	OCH_3	H	123-126	21	$C_{16}H_{20}O_3S$	C, 65.72 H, 6.89	65.93 6.65
H	OCH_3	H	102-104	23	$C_{15}H_{18}O_2S$	C, 68.67 H, 6.91	68.72 6.82

(a) This Compound was analyzed as the 2,4-dinitrophenylhydrazone $C_{20}H_{20}SN_4O_4$ Calcd., C, 58.24, H, 4.89; Found, C, 57.91, H, 4.90.

CHART III

Proton Nmr Data for Substituted Mercaptoacetic Acids (a)

Compound	Aromatic	Cyclohexane	Tertiary	-S-CH_2-	-OCH_3
4a	3.2 (m, 3)	7.7 , 8.8 (8)	6.5 , 6.7 (2)	7.42 (q, 2)	6.18 (d, 6)
4b	3.0 (m, 4)	7.65, 8.65 (8)	6.6 , 6.9 (2)	7.55 (q, 2)	6.20 (d, 3)
4c	2.8 (s, 5)	7.65, 8.65 (8)	6.6 , 6.9 (2)	7.55 (q, 2)	
4d	2.9 (m, 4)	7.7 , 8.7 (8)	6.55, 6.82 (2)	7.35 (q, 2)	6.16 (d, 3)
4e	3.0 (m, 3)	7.8 , 8.7 (8)	6.58, 6.95 (2)	7.39 (q, 2)	6.18 (s, 3)
4f	2.9 (m, 3)	8.0 , 8.38 (8)	6.52, 6.75 (2)	7.50 (q, 2)	6.15 (s, 3)

(a) In τ values. The tertiary protons are broad singlets and the remaining cyclohexane protons appear in the spectrum as two broad peaks entered at the points indicated.

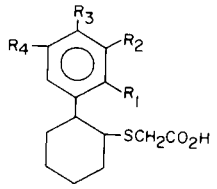
Proton Nmr Data for Thiepinones (a)

Compound	Aromatic	Cyclohexane	Tertiary	-S-CH_2	-OCH_3
6a	2.8 (d, 1) 3.25 (d, 1)	7.9, 8.8 (8)	6.20, 6.48 (2)	6.42 (q, 2)	6.18 (d, 6)
6c	2.7 (m, 4)	8.4 (8)	6.7 , 6.9 (2)	6.62 (q, 2)	
6d	3.10 (m, 2)	7.5, 8.6 (8)	6.3 , 6.9 (2)	6.56 (d, 2)	6.17 (s, 3)
6e	2.8 (s, 1)	8.4 (8)	6.5 , 6.7 (2)	6.54 (s, 2)	6.13 (d, 3)

(a) In τ values. The tertiary protons are broad singlets and the remaining cyclohexane protons generally appear in the spectrum as two broad peaks centered at the points indicated in the chart.

CHART IV

Infrared Data for Substituted Mercaptoacetic Acids



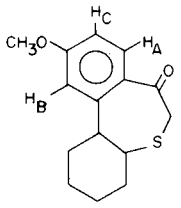
R_1	R_2	R_3	R_4	Wavelength (cm^{-1})						
H	H	H	H	3025M	2928S	2677W	2571W	1704S	1499W	1445M
				1427M	1294M	1208M				
OCH_3	H	H	H	3025M	2928S	2691W	2571W	1700S	1597W	1489M
				1456M	1292M	1232S	1108M	1050W	1029M	
OCH_3	OCH_3	H	H	3125M	2928S	2677W	2571W	1704S	1581W	1268S
				1242M	1288S	1268S	1218W	1088M	1001M	
H	OCH_3	H	H	3025M	2928S	2691W	2571W	1704S	1594M	1486W
				1440M	1287S	1258S	1152M	1044M		
H	OCH_3	OCH_3	H	3025M	2928S	2677W	2571W	1704S	1594W	1513M
				1454M	1415M	1294M	1252S	1228S	1149S	1026S
OCH_3	H	H	OCH_3	3125M	2928S	2691W	2558W	1704S	1587W	1491S
				1484M	1427M	1282S	1218S	1180M	1048S	1027M

red absorption band at 1673 cm^{-1} and had an nmr spectrum consistent with that expected on the basis of compound A. The elemental analysis and molecular weight of the 2,4-dinitrophenylhydrazone was in agreement with that expected for the cyclic compound.

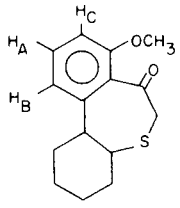
cis-2-(2′,3′-Dimethoxyphenyl)cyclohexanemercaptoacetyl chloride (**5a**) which possesses an activating group *para* to the position of ring closure was converted to a crystalline cyclic ketone upon treatment with aluminum chloride in 16% yield.

cis-2-(2′-Methoxyphenyl)cyclohexanemercaptoacetyl chloride (**5b**) in the presence of aluminum chloride gave an amorphous material which could not be crystallized, nor purified by chromatography over aluminum oxide. Although the material had a keto peak at 1660 cm^{-1}, it did not begin to melt until a temperature of 250° was reached. An attempt to obtain the cyclic compound by using a milder catalyst (stannic chloride) was unsuccessful as was the use of nitroethane with aluminum chloride. The methoxy group apparently deactivates the only position of ring closure so that intermolecular acylation takes preference over ring formation. Although ring closure *meta* to a methoxyl group has been noted (3) the deactivating influence of the methoxyl group in a position *meta* to ring closure has also been reported (3).

cis-2-(3′-Methoxyphenyl)cyclohexanemercaptoacetyl chloride (**5d**) when treated with aluminum chloride gave a crystalline ketosulfide (**6d**). The aromatic region of the nmr spectrum of this compound showed a doublet centered at τ 2.33 which represented one hydrogen and a multiplet centered at τ 3.10 which integrated correctly for two protons. It would appear that the one aromatic hydrogen is considerably different from the other two and would thus indicate that cyclization occurred mainly *para* to the methoxyl group yielding compound **6d**-1.



6d-1



6d-2

The coupling constants for JAC (8 cps) and JBC (3 cps) are consistent for *ortho* and *meta* coupling constants, respectively. The presence of only one *ortho* coupling constant is also compatible with structure **6d**-1 since the spectrum of compound **6d**-2 should contain two *ortho* coupling constants.

Additional evidence for the structure of **6d** can be deduced by examining the nmr of compound **6a** (Chart III) which has only two aromatic protons. One of these protons must be *ortho* to the electron attracting carbonyl group and consequently at lowest field (τ 2.8) since the other proton is *ortho* to an electron releasing methoxy group. Structure **6d**-1 which has a proton adjacent to the

carbonyl group can best explain the presence of the low field proton at τ 2.33 in the nmr spectrum of **6d**.

In the case of *cis*-2-(3′,4′-dimethoxyphenyl)cyclohexanemercaptoacetyl chloride (**5e**) cyclization can occur *ortho* or *para* to one methoxy group, but in either case it must be *meta* to one group. Cyclization of this acid chloride under conditions previously described gave a 21% yield of cyclic product (**6e**). In this case the ring closed *para* to the methoxyl group. This is indicated by the nmr spectrum in the aromatic region where two peaks are found; one at τ 2.8 and the other at τ 3.1. Each peak integrates correctly for one hydrogen. If cyclization had occurred *ortho* to a methoxy group then two aromatic hydrogens would have been adjacent and splitting would be expected. This is not observed in the spectrum. Furthermore, acylation *para* to a methoxy group accounts for the low field proton (τ 2.8) as previously discussed.

Since the results to this point indicated that ring closure occurred mainly *para* to a methoxy group in this system *cis*-2-(2′,5′-dimethoxyphenyl)cyclohexanemercaptoacetyl chloride (**5f**) was used to further substantiate this observation. If ring closure was to occur in this compound, it must occur *ortho* to one methoxy group and *meta* to the other group. Ring closure of the acid chloride with aluminum chloride could not be demonstrated.

In conclusion it can be stated that cyclization occurs when a methoxyl substituent is *para* to the position of ring closure either in the presence or absence of a second methoxyl group *meta* to the position of acylation. Ring closure does not occur when one methoxyl substituent is present and *meta* to the position of ring closure or when acylation must occur *ortho* to a methoxyl substituent.

EXPERIMENTAL

In all experimental procedures, the reported melting points and boiling points are uncorrected. Melting points were determined on a Nalge-Axelrod aluminum block. Infrared spectra were run on a Perkin-Elmer 13U, using chloroform as the solvent unless otherwise specified.

All elemental and molecular weight analyses were carried out by Galbraith Laboratories, Inc., and NMR spectra were determined on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard.

1-(3′-Methoxyphenyl)cyclohexene and 1-(3′,4′-dimethoxyphenyl)cyclohexene were prepared by condensing 3-methoxyphenylmagnesium bromide and 3′,4′-dimethoxyphenylmagnesium bromide with cyclohexanone, respectively. 2-Phenylcyclohexanol, 2-(2′,3′-dimethoxyphenyl)cyclohexanol, 2-(2′-methoxyphenyl)-cyclohexanol and 2-(2′,5′-dimethoxyphenyl)cyclohexanol were prepared by condensing phenyllithium, 2,3-dimethoxyphenyllithium, 2-methoxyphenyllithium and 2,5-dimethoxyphenyllithium, respectively, with cyclohexanone according to the procedure of Lotspeich and Karickhoff (2). These compounds were dehydrated to the corresponding substituted phenyl cyclohexenes by the method of Ginsburg and Pappo (4) using oxalic acid and toluene.

Preparation of Phenyl Substituted Cyclohexanemercaptoacetic Acids.

General Procedure.

The appropriate substituted phenyl cyclohexene was mixed with mercaptoacetic acid in the ratio indicated in Chart I and allowed to react for the period indicated. The mixture was taken up in diethyl ether and extracted with 5% sodium hydroxide until all of the acidic material was removed. The basic solution was made acidic and the acid was extracted with chloroform. The chloroform solution was washed 6 to 8 times with 50 ml. portions of water to remove the excess mercaptoacetic acid. The chloroform was evaporated and the remaining acid was dissolved in base and reprecipitated with acid to remove the last traces of mercaptoacetic acid. The acid was recrystallized from the solvent indicated in Chart I. In the one case where the acid was an oil it was converted to the acid chloride without further purification.

Cyclization of the Phenyl Substituted Thioacetyl Chlorides.

General Procedure.

The appropriately substituted phenyl cyclohexanemercaptoacetic acid was converted to the acetyl chloride with phosphorus pentachloride using a 1/1 molar ratio of the acid and phosphorus pentachloride in carbon disulfide. The reaction was allowed to proceed for 5 hours at room temperature. The volatile components were removed by means of a water aspirator. The resulting acid chloride was taken up in chloroform (50 ml./6 g. of acid chloride) and added dropwise to 100 ml. of chloroform containing 2.5 g. of aluminum chloride. The reaction mixture was stirred for 4 hours and decomposed with dilute hydrochloric acid. The chloroform layer was washed with water and the chloroform evaporated. The resulting oil was taken up in diethyl ether and extracted with 5% sodium hydroxide. The diethyl ether extract was washed with water and evaporated to yield an oil. In most cases the oil would solidify on being washed with petroleum ether (37°). However, the resulting solid was generally difficult to purify by recrystallization. A better procedure was to add the oil dissolved in benzene to an aluminum oxide column containing 50 g. of aluminum oxide (Merck) (20 x 150 mm). The column was eluted with benzene and then diethyl ether. Evaporation of these solvents yielded the desired product which could be recrystallized from methanol to give a relatively pure material. It was impossible to obtain a crystalline product in the case of 1,2,3,4,4a,11b-hexahydrodibenzo[*b*,*d*]thiepin-7(6*H*)-one. The oil was flash distilled and the 2,4-dinitrophenylhydrazone prepared.

REFERENCES

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