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Arylthiation of Cyclohexanone Morpholine Enamine with Aryl Benzenethiosulfonates

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Sulfenylation of the nucleophilic β-carbon atom of 1-morpholino-1-cyclohexene with several thiosulfonates was attempted. Among these thiosulfonates, the reaction with alkyl alkanethiosulfonates and aralkyl benzenethiosulfonates were unsuccessful, but aryl benzenethiosulfonates in which an electron withdrawing group was substituted in the *ortho* or *para* position of the aryl group successfully reacted with 1-morpholino-1-cyclohexene to give the corresponding arylthio derivatives.

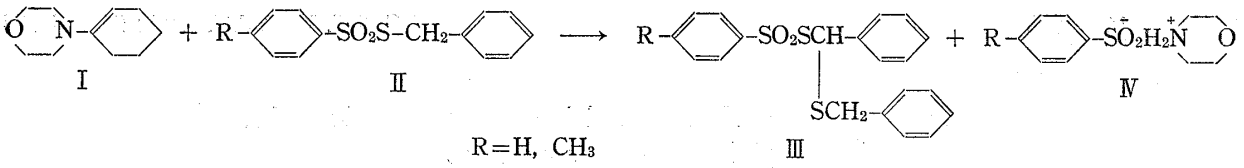
It has been reported that alkyl thiosulfonates react with thiols[2] and amines[2b,c,3] to give unsymmetrical disulfides and alkylsulfenamides. Recently we[4] have also found that alkyl thiosulfonates act as an efficient alkylthiation reagent for active methylene compounds to afford the alkylthio derivatives of active methylene compounds. These reactions are believed to occur by the nucleophilic attack on the sulfen sulfur atom of the thiosulfonates. In the meanwhile, enamines are well known to be represented by the following limiting structural

$$\backslash N-C=C- \longleftrightarrow \backslash \overset{+}{N}=C-\overset{-}{C}\ /$$

formula in which the β-carbon atom readily undergoes electrophilic attack with alkyl halides,[5] electrophilic olefines[6] and acyl halides[5,7] to give high yields of alkyl and acyl derivatives. These facts suggest that alkyl thiosulfonates might serve as an effective alkylthiation reagent for the nucleophilic β-carbon atom of enamines. This paper deals with the reaction of cyclohexanone morpholine enamine, 1-morpholino-1-cyclohexene (I), with thiosulfonates.

As the thiosulfonates, several different types of thiosulfonates shown by the following general formula, R-SO_2S-R′, in which R and R′ stand for alkyl or aryl group, were employed in this reaction. Among these thiosulfonates, the reaction of alkyl alkanethiosulfonates, such as butyl phenylmethanethiosulfonate, benzyl phenylmethanethiosulfonate and trimethylene bis-phenylmethanethiosulfonate, with I did not occur and the material was quantitatively recovered unchanged. When alkyl benzenethiosulfonates such as benzyl benzenethiosulfonate (II, R=H) and benzyl *p*-toluenethiosulfonate (II, R=CH_3) were, however, allowed

1) Location: *Oe-hon machi, Kumamoto.*
2) *a*) T.F. Parsons, J.D. Buckman, D.E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965); *b*) J.P. Weidner and S.S. Block, *J. Med. Chem.*, **10**, 1167 (1967); *c*) S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *Chem. Pharm. Bull.* (Tokyo), **17**, 954 (1969).
3) *a*) B.G. Boldyrev and S.A. Kolesnikova, *C.A.*, **62**, 13076e (1965); *b*) J.E. Dunbar and J.H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966); *idem*, *Tetrahedron Letters*, **1965**, 4291.
4) *a*) S. Hayashi, M. Furukawa, J. Yamamoto, and K. Niigata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1188 (1967); *b*) S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, *ibid.*, **17**, 419 (1969).
5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
6) G. Stork and H. Landesman, *J. Am. Chem. Soc.*, **78**, 5128 (1956).
7) *a*) G. Stork, R. Terrell, and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954); *b*) S. Hünig and E. Lücke, *Chem. Ber.*, **92**, 652 (1959); *c*) S. Hünig and W. Lendle, *ibid.*, **93**, 913 (1960); *d*) S. Yurugi, T. Fushimi, and M. Numata, *J. Pharm. Soc. Japan*, **80**, 1165 (1960).

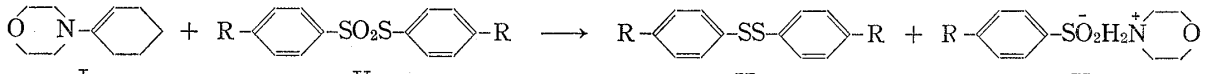


I II III IV

R=H, CH_3

to react with I in ether or benzene in the absence of any catalyst under reflux, α-benzylthiobenzyl benzenethiosulfonates (III, R=H and CH_3) were obtained in a low yield, accompanying a small amount of morpholinium benzenesulfinates (IV, R=H and CH_3). III was identified with an authentic sample[4a,8] prepared by the treatment of the thiosulfonate with sodium ethoxide by mixed melting point determination and comparison of the IR spectrum. The formation of III would be initiated by abstruction of the methylene hydrogen of II with morpholine formed from I. Nucleophilic attack of the resulting carbanion to the sulfen sulfur atom of unchanged II affords III with elimination of the benzenesulfonyl group. IV would be obtained from the resulting benzenesulfinic acid and morpholine. It is presumed that there is no direct participation of I in the reaction.

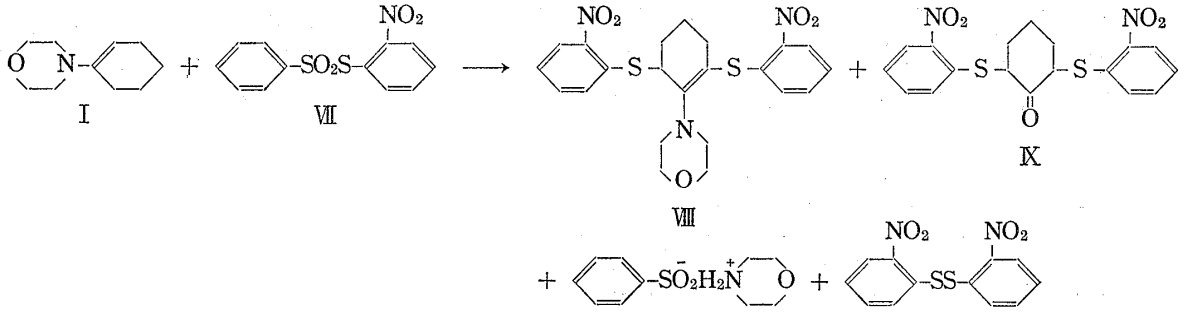
In the reaction of I with aryl benzenethiosulfonates, unequivocal effects of the substituent group in the aryl group were observed. Namely, phenyl benzenethiosulfonate (V, R=H) reacted with I under the similar conditions to give diphenyl disulfide (VI, R=H) and morpholinium benzenesulfinate (IV, R=H) in 20% and 10% yields, respectively. *p*-Tolyl *p*-toluenethiosulfonate (V, R=CH_3) also reacted analogously with I to give bis-*p*-tolyl disulfide (VI, R=CH_3) and morpholinium *p*-toluenesulfinate (IV, R=CH_3) in 33% and 12% yields, respectively. Alkaline hydrolysis of thiosulfonates is well known to give disulfides and sulfinic acids.[9] However, aryl benzenethiosulfonates in which an electron withdrawing group such



I V VI IV

R=H, CH_3

as nitro and chloro groups was substituted in the *ortho* or *para* position of the aryl group exhibited quite different behaviors toward I. When *o*-nitrophenyl benzenethiosulfonate (VII) was heated with two equivalent amounts of I in benzene in the absence of any catalyst for 13 hours under reflux, 1-morpholino-2,6-bis(*o*-nitrophenylthio)-1-cyclohexene (VIII), 2,6-bis-(*o*-nitrophenylthio)-cyclohexanone (IX), morpholinium benzenesulfinate and bis(*o*-nitrophenyl)-disulfide were obtained in 38%, 5%, 18% and 7% yields, respectively, as described in the previous communication.[10] It is presumed that the introduction of an electron withdrawing



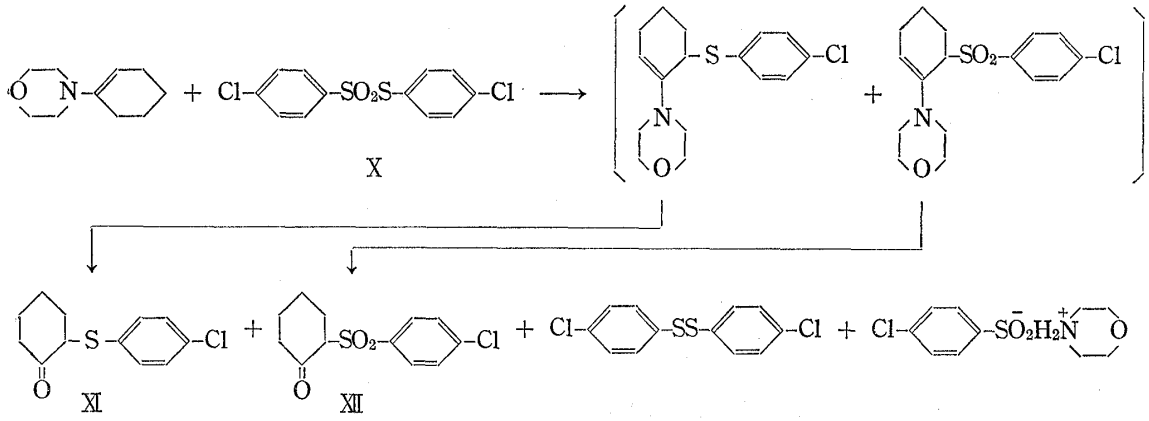
I VII VIII IX

substituent to the aryl group would result in the increased positive charge of the sulfen sulfur atom and therefore the facile attack of the nucleophilic β-carbon atom of I to the sulfur atom

8) S. Hayashi, M. Furukawa, Y. Fujino, and H. Okabe, *Chem. Pharm. Bull.* (Tokyo), **19**, 2252 (1971).
9) *a*) R. Otto and A. Rossing, *Chem. Ber.*, **19**, 1235 (1886); *b*) L. Bauer and J. Cymerman, *J. Chem. Soc.*, **1950**, 109.
10) M. Furukawa, Y. Kojima, S. Tsuiji, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2738 (1972).

would occur. The same reaction at room temperature for a long time directly gave IX in 38% yield, no trace of any VIII being isolated. The assigned structure of VIII was confirmed by the elemental analysis and the spectral data.[10] The introduction of two *o*-nitrophenylthio groups to I was evidently established by the molecular ion (M^+) observed at *m/e* 473 as the most abundant peak and by the abundant fragmentation peaks corresponding to $(M-\text{C}_6\text{H}_4(\text{NO}_2)\text{-S})^+$ and $(M-2\,\text{C}_6\text{H}_4(\text{NO}_2)\text{-S})^+$ in the mass spectrum. Support for the assigned structure VIII was also provided by facile hydrolysis to IX, whose structure was also established by the elemental analysis and the IR, NMR and mass spectra. In this reaction the product in which a nitrophenylthio group was introduced to the enamine (I) should be also anticipated to form, but no trace of such a product was isolated. It is of interest that two *o*-nitrophenylthio groups were introduced even in the presence of an excess of I, in spite of Williamson's suggestion[11] in the alkylation of α-substituted ketoenamine.

On the other hand, treatment of *p*-chlorophenyl *p*-chlorobenzene thiosulfonate (X) with two moles of I in benzene at room temperature for 16 hr directly gave a 45% yield of 2-*p*-chlorophenylthiocyclohexanone (XI) in addition to a small amount of 2-*p*-chlorophenylsulfonylcyclohexanone (XII), bis(*p*-chlorophenyl) disulfide (VI, R=Cl) and morpholinium *p*-chlorobenzenesulfinate (IV, R=Cl). The structure of these compounds were confirmed



by the elemental analyses and the spectral data. In this reaction, efforts for the isolation of the intermediates of XI and XII, 1-morpholino-6-*p*-chlorophenylthio-1-cyclohexene and 1-morpholino-6-*p*-chlorophenylsulfonyl-1-cyclohexene, resulted in failure. It should be worth noted that the sulfonyl compound (XII) was unexpectedly obtained. Generally, nucleophilic attack to thiosulfonates occurs on the sulfen sulfur atom and the attack on the sulfonyl sulfur atom is unknown, probably because of the electric repulsion and steric hindrance of the sulfonyl oxygen atoms and the predominant elimination of alkylsulfonyl anion rather than alkylthio anion. The fact that XII was formed, however, elucidates evidently that the nucleophilic attack on the sulfur atom of the sulfonyl group was also successfully carried out. Attempts to introduce two *p*-chlorophenylthio groups by using a great excess of X were unsuccessful, no trace of any such a product being observed to form even by TLC.

Experimental

General Procedure for Synthesis of Thiosulfonate——Method I[12]: A mixture of 0.1 mole of anhyd. sodium alkanethiosulfonate, 0.1 mole of alkyl halide and 250 ml of abs. EtOH was heated for 10—15 hr

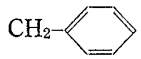
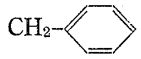
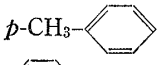
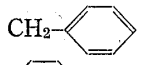
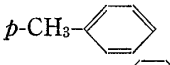
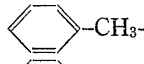
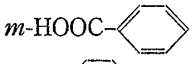
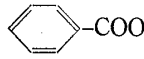
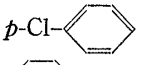
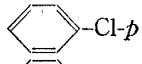
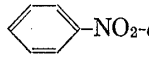
11) W.R.N. Williamson, *Tetrahedron*, 3, 314 (1958).
12) S. Hayashi, M. Furukawa, J. Yamamoto, and K. Hamamura, *Chem. Pharm. Bull.* (Tokyo), **15**, 1310 (1967).

under reflux. The hot mixture was filtered and the precipitates deposited on cooling were collected by filtration, washed with a large amount of H_2O and recrystallized from EtOH or AcOEt.

Method II[13]: To a mixture of 0.16 mole of substituted benzenesulfonyl chloride, 200 ml of ether and 32 g of Zn dust was added dropwise with stirring 100 ml of conc. HCl during 45 min. The mixture was then refluxed until the Zn dust disappeared. The ether layer was separated, washed with Na_2CO_3 solution and then H_2O, dried over Na_2SO_4, evaporated to dryness and the residue was recrystallized from MeOH–H_2O.

Method III[14]: A solution of 5 g of *o*-nitrophenylsulfenyl chloride in 30 ml of ether was gently refluxed with 5 g of dry powdered sodium benzenesulfinate in suspension for 15 min. After filtration, the filtrate was evaporated to dryness and the residue was recrystallized from EtOH. Details of the data were summarized in Table I.

TABLE I R–SO_2S–R′

R	R′	Method	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
	*n*-C_4H_9	I	94	43	$C_{11}H_{16}O_2S_2$	54.06	6.60	54.22	6.65
		I	106	52	$C_{14}H_{14}O_2S_2$	55.77	7.02	55.90	6.88
		I	43	56	$C_{13}H_{12}O_2S_2$	59.06	4.57	59.27	4.59
		I	60	52	$C_{14}H_{14}O_2S_2$	60.40	5.07	60.58	5.21
		II	45	80	$C_{12}H_{10}O_2S_2$	57.60	4.03	58.01	4.35
		II	76	60	$C_{14}H_{14}O_2S_2$	60.43	5.07	60.54	5.28
		II	229	20	$C_{14}H_{10}O_6S_2$	49.71	2.98	49.93	3.14
		II	134	25	$C_{12}H_{18}O_2S_2Cl_2$	45.15	2.53	45.06	2.25
		III	87	60	$C_{12}H_9O_4NS_2$	48.82	3.07	49.02	3.34

Reaction of 1-Morpholino-1-cyclohexane (I) with Thiosulfonate——With Benzyl Benzenethiosulfonate (II, R=H): A solution of 2.6 g (0.01 mole) of benzyl benzenethiosulfonate and 3.2 g (0.02 mole) of 1-morpholino-1-cyclohexene in 100 ml of dry benzene was heated for 10 hr under reflux. The precipitates deposited on allowing to stand overnight at room temperature were collected by filtration and recrystallized from benzene to give 0.2 g (10%) of morpholinium benzenesulfinate melting at 114—116°, which was identified with an authentic sample by mixed melting point determination and comparison of the IR spectrum.

The filtrate was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from EtOH to give 0.6 g (15%) of α-benzylthiobenzyl benzenethiosulfonate, which was identified with an authentic sample[4a,8] by mixed melting point determination and comparison of the IR spectrum.

When the same reaction was carried out with stirring at room temperature for 20 hr, morpholinium benzenesulfinate, α-benzylthiobenzyl benzenethiosulfonate and dibenzyl disulfide melting at 71° were obtained 4.5%, 5%, and 8% yields, respectively.

With Benzyl *p*-Toluenethiosulfonate (II, R=CH_3): A solution of 1.4 g (0.005 mole) of benzyl *p*-toluenethiosulfonate and 1.6 g (0.01 mole) of 1-morpholino-1-cyclohexene in 50 ml of dry benzene was heated for 10 hr under reflux. The precipitates deposited on cooling were collected by filtration and recrystallized from benzene to give 0.3 g (25%) of morpholinium *p*-toluenesulfinate melting at 126—127°. The filtrate was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from EtOH to give 0.4 g (20%) of α-benzylthiobenzyl *p*-toluenethiosulfonate melting at 147.5—148.5°. These products were identified with the respective authentic samples by mixed melting point determination and comparison of the IR spectra.

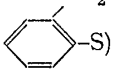
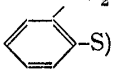
With Phenyl Benzenethiosulfonate (V, R=H): A solution of 1.25 g (0.005 mole) of phenyl benzenethiosulfonate and 1.6 g (0.01 mole) of 1-morpholino-1-cyclohexane in 50 ml of dry benzene was heated for

13) E. Vinkler and F. Klivenyi, *C.A.*, **49**, 2346 (1955).
14) J.D. Loudon and A. Livingston, *J. Chem. Soc.*, **1935**, 896.

20 hr under reflux. After allowing to stand at room temperature overnight, the precipitates deposited were collected by filtration and recrystallized from benzene to give 0.1 g (10%) of morpholinium benzenesulfinate melting at 114—116°. The filtrate was concentrated and chromatographed on silica gel. Development with benzene gave 0.2 g (20%) of diphenyl disulfide melting at 60—61° after recrystallization from MeOH. These products were identified with the respective authentic samples by mixed melting point determination and comparison of the IR spectra.

With *p*-Tolyl *p*-Toluenethiosulfonate (V, R=CH_3): A solution of 1.4 g (0.005 mole) of *p*-tolyl *p*-toluenethiosulfonate and 1.6 g (0.01 mole) of 1-morpholino-1-cyclohexene in 50 ml of dry ether was stirred at room temperature for 20 hr. The precipitates deposited were collected by filtration and recrystallized from benzene to give 0.15 g (10%) of morpholinium *p*-toluenesulfinate melting at 126—127°. The filtrate was concentrated and chromatographed on silica gel. Development with benzene gave 0.4 g (33%) of bis(*p*-tolyl) disulfide melting at 44—46° after recrystallization from MeOH. These products were identified with the respective authentic samples by mixed melting point determination and comparison of the IR spectrum.

With *o*-Nitrophenyl Benzenethiosulfonate (VII): A solution of 1.45 g (0.005 mole) of *o*-nitrophenyl benzenethiosulfonate and 1.6 g (0.01 mole) of 1-morpholino-1-cyclohexene in 50 ml of dry benzene was heated for 13 hr under reflux and allowed to stand at room temperature overnight. Resulted precipitates were collected by filtration and recrystallized from benzene to give 0.2 g (18%) of morpholinium benzenesulfinate.

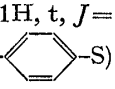
The filtrate was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from MeOH–$CHCl_3$ to give 0.9 g (38%) of 1-morpholino-2,6-bis(*o*-nitrophenylthio)-1-cyclohexene melting at 171—173°. *Anal.* Calcd. for $C_{22}H_{23}O_5N_3S_2$: C, 55.81; H, 4.90; N, 8.88. Found: C, 55.48; H, 4.83; N, 9.09. IR ν_{max}^{KBr} cm^{-1}: 1335, 1507 (NO_2), 1117 (–O–). NMR ($CDCl_3$) τ: 8.45—7.55 (6H, m, 3,4,5-methylene hydrogens), 7.10—6.75 (4H, m, CH_2–N–CH_2), 6.34 (4H, t, J=5 Hz, CH_2–O–CH_2), 5.55 (1H, broad s, 6-proton), 2.80—2.25 (6H, m, aromatic 4,4′,5,5′, 6,6′-hydrogens), 1.90—1.70 (2H, m, aromatic 3,3′-hydrogens). Mass Spectrum *m/e*: 473 (M^+), 319 (M^+–  -S), 155 (M^+–2  -S).

The filtrate was chromatographed on silica gel and development with pet. ether gave 0.1 g (6.6%) of bis(*o*-nitrophenyl) disulfide melting at 193—195° after recrystallization from EtOH. This compound was identified with an authentic sample[15] prepared from *o*-chloronitrobenzene and sodium disulfide by mixed melting point determination and comparison of the IR spectrum. Development with benzene gave 0.1 g (5%) of 2,6-bis(*o*-nitrophenylthio)-cyclohexanone melting at 109—110° after recrystallization from pyridine–MeOH. *Anal.* Calcd. for $C_{18}H_{16}O_5N_2S_2$: C, 53.47; H, 3.99; N, 6.93. Found: C, 53.54; H, 4.07; N, 6.55. IR ν_{max}^{KBr} cm^{-1}: 1705 (CO), 1345, 1515 (NO_2). Mass Specrum *m/e*: 404 (M^+), 250 (M^+ –  -S), 96 (M^+–2  -S).

This compound was also obtained by hydrolysis of 1-morpholino-2,6-bis(*o*-nitrophenylthio)-1-cyclohexane with 10% HCl.

When the same reaction was carried out with stirring at room temperature for 20 hr, 2,6-bis(*o*-nitrophenylthio)-cyclohexanone was directly obtained in 33% yield, but no trace of 1-morpholino-2,6-bis(*o*-nitrophenylthio)-1-cyclohexene could be observed by TLC.

With *p*-Chlorophenyl *p*-Chlorobenzenethiosulfonate (X): A solution of 3.2 g (0.01 mole) of *p*-chlorophenyl *p*-chlorobenzenethiosulfonate and 3.2 g (0.02 mole) of 1-morpholino-1-cyclohexane in 100 ml of dry benzene was stirred at room temperature for 16 hr and the precipitates deposited on cooling were collected by filtration and recrystallized from benzene to give 0.4 g (15%) morpholinium *p*-chlorobenzenesulfinate melting at 135—136°.

The filtrate was concentrated and the precipitates deposited on cooling were collected by filtration and recrystallized from MeOH–$CHCl_3$ to give 1.1 g (45%) of 2-*p*-chlorophenylthiocyclohexanone melting at 46—48°. *Anal.* Calcd. for $C_{12}H_{13}OSCl$: C, 59.90; H, 5.03. Found: C, 60.13; H, 5.15. IR ν_{max}^{KBr} cm^{-1}: 1707 (CO). NMR ($CDCl_3$) τ: 8.50—6.90 (8H, m, 4 CH_2), 6.20 (1H, t, J=5 Hz, CH), 2.95—2.50 (4H, m, aromatic hydrogens). Mass Spectrum *m/e*: 241 (M^+), 107 (M^+–Cl–  -S).

The filtrate was chromatographed on silica gel and development with pet. ether gave 0.1 g (3.5%) of bis(*p*-chlorophenyl) disulfide melting at 71—72° after recrystallization from EtOH. This compound was identified with an authentic sample[16] prepared by reduction of *p*-chlorobenzenesulfonyl chloride with phosphor and iodine by mixed melting point determination and comparison of the IR spectrum.

Development with benzene gave 0.2 g (7%) of 2-*p*-chlorophenylsulfonylcyclohexanone melting at 72—74° after recrystallization from MeOH. *Anal.* Calcd. for $C_{12}H_{13}O_3SCl$: C, 52.84; H, 4.81. Found: C, 53.19; H, 4.86. IR ν_{max}^{KBr} cm^{-1}: 1706 (CO), 1145, 1323 (SO_2). NMR ($CDCl_3$) τ: 8.50—7.00 (8H, m, 4 CH_2),

15) M.T. Bogert and A. Stull, *Org. Synth.*, Col. Vol. 1, 220 (1956).
16) K. Kawahara, *Yakugaku Zasshi*, 77, 965 (1957).

6.12 (1H, t, $J=5$ Hz, CH), 2.70—1.95 (4H, m, aromatic hydrogens). Mass Spectrum *m/e*, 272 (M^+), 97 (M^+-Cl-  $-SO_2$).

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