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Studies on Hypoglycemic Agents. V.[1] A New Synthetic Method for Sulfonylurea Derivatives

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p-Chloro(trifluoromethyl)phenyl or *p*-tolylsulfonylurea derivatives were prepared by the reaction of 2-arylsulfonylimino-1,3-oxathiolanes(III) with various amines. The oxathiolanes(III) were prepared by treatment of 2-hydroxyethyl N-arylsulfonyldithiocarbamate (II), which were obtained from sodium arylsulfonyliminodithiocarbonate and ethylene chlorohydrin, with ethyl chloroformate. The compounds(II) were also converted to N-arylsulfonylimino-1,3-dithiolanes(IV) by treating with sulfuric acid. The preparation of N-*p*-chlorophenylsulfonylimino-1,3-dioxolane(VII) was also described. Further 1-*p*-chlorophenylsulfonyl-2-thio-3-*n*-propylurea(IX) was obtained by treatment of IV(X=Cl) with *n*-propylamine.

Some of arylsulfonylurea derivatives are well known as hypoglycemic agents. Methods for the general synthesis of the arylsulfonylureas have been widely investigated, mainly in patent literature, for example: by the reaction of sulfonylisocyanate,[3,4] sulfonylurea,[5] or sulfonylcarbamate[6] with appropriate amine; by the action of alkylisocyanate,[4] alkylurea,[5] or alkylcarbamate[5] on sulfonamide; by the desulfurization[7] of the corresponding sulfonylthiourea; by the oxidation of arylsulfonylurea[8]; from sulfonylcarbodiimide,[9] sulfonylpseudourea,[10] or sulfonylguanidine[10]; and others.[11] The present paper describes a new synthetic method for the sulfonylurea derivatives by the reaction of 2-arylsulfonylimino-1,3-oxathiolanes (III) with various amines.

1) Part IV: S. Suzue and T. Irikura, *Chem. Pharm. Bull.* (Tokyo), **16**, 806 (1968).
2) Location: *1-3, Ukima, Kita-ku, Tokyo.*
3) H. Ulrich, *Chem. Rev.*, **65**, 369 (1965).
4) B. Hökfelt and A. Jönsson, *J. Med. Pharm. Chem.*, **5**, 231 (1962).
5) F. Kurzer, *Chem. Rev.*, **50**, 1 (1952).
6) F.J. Marshall and M.V. Sigal, Jr., *J. Org. Chem.*, **23**, 927 (1958); D.R. Cassady, C. Answorth, N.R. Easton, M. Livezey, M.V. Sigal, Jr., and E. Van Heyningen, *ibid.*, **23**, 923 (1958).
7) S. Onishi, *Yakugaku Zasshi*, **79**, 559 (1950).
8) Y. Nitta, N. Ando, Y. Ikeda, M. Koizumi, and A. Shioya, *Yakugaku Zasshi*, **82**, 191 (1962).
9) B. Anders and E. Kühle, *Angew. Chem.*, **77**, 430 (1965).
10) E. Haack, W. Peschke, F.H. Schmidt, and H. Weber, Ger. Patent 1168415 (1964) [*C.A.*, **61**, 4272*c* (1964)].
11) W. Aumüller and H. Herr, Ger. Patent 1066575(1959)[*C. A.*, **55**, 13378*h*(1961)]; S. Toyoshima, S. Tanaka, and T. Komaki, *Yakugaku Zasshi*, **84**, 830 (1964).

Synthetic method for the sulfonylimino-1,3-oxathiolane analogue could not be found in previous reports, then the compounds(III) were first prepared by the route as illustrated in Chart 1.

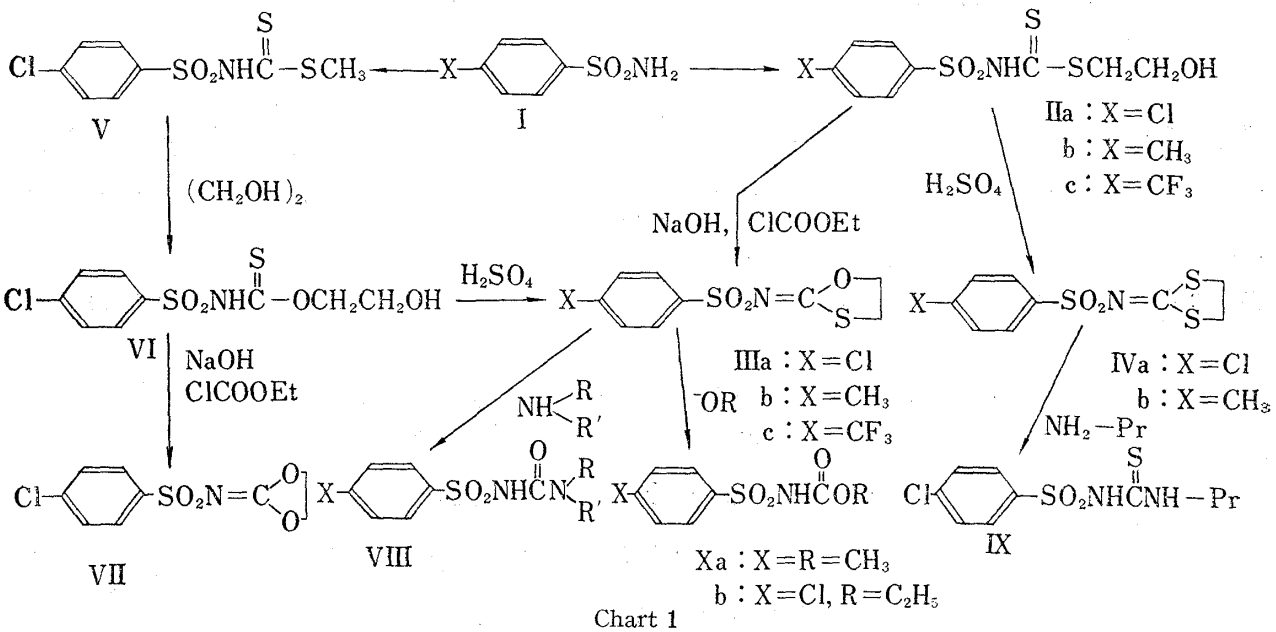


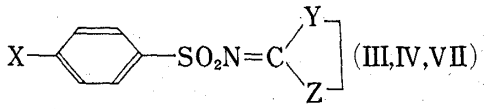
Chart 1

TABLE I. X—C6H4—SO2NHC(=S)—SCH2CH2OH (II)

Compound	Formula	mp (°C)	Recryst. solvt.	Appearance	Yield (%)	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	$C_9H_{10}O_3NS_3Cl$	118—120	MeCN	rods	77	34.71	3.21	4.50	34.76	3.20	4.59
IIb	$C_{10}H_{13}O_3NS_3$	137—140	MeCN	rods	69	41.24	4.50	4.81	41.35	4.65	4.99
IIc	$C_{10}H_{10}O_3NS_3F_3$	117—118	benzene	plates	71	—	—	4.07	—	—	4.16

By the application of the method by Gompper, *et al.*[12] 2-hydroxyethyl N-arylsulfonyldithiocarbamates(II) were obtained from sodium arylsulfonyldithiocarbamates by treating with ethylene chlorohydrin. Then the dithiocarbamates(II) were cyclodesulfurized to III by treating with desulfurized agents such as mercuric acetate and ethyl chloroformate. And consequently ethylchloroformate was the more useful reagent for this cyclodesulfurization. Further the compounds(II) could be converted to 2-arylsulfonylimino-1,3-dithiolanes(IV), which had been prepared by Gompper, *et al.*[12] with another route, in good yield by treating with dehydrating agent such as sulfuric acid. On the other hand, methyl N-*p*-chlorophenylsulfonyldithiocarbamate(V)[12] was converted to 2-hydroxyethyl ester(VI) by the alcoholysis[12] with ethyleneglycol. Then VI was also converted to IIIa with the treatment of sulfuric acid. Further, treating with ethyl chloroformate, VI was cyclodesulfurized to 2-*p*-chlorophenylsulfonylimino-1,3-dioxolane(VII). The structural proof of these cyclization products(III, IV and VII) was made by means of infrared spectroscopy and elementary analyses. The infrared (IR) spectra of III, IV, and VII showed that the absorption bands at near 3500, 3050, and 2800(broad) cm^{-1} attributed to OH and NH groups of II(or VI) had disappeared and that

12) R. Gompper and W. Hägele, *Chem. Ber.*, **99**, 2885 (1966).

TABLE II.  (III,IV,VII)

Compound	X	Y	Z	mp (°C)	Recryst. solvent	Appearance	Yield (%)	Recovery of II (%)
IIIa	Cl	O	S	103—104	EtOH	needles	56	29
IIIb	CH_3	O	S	131—132	EtOH	needles	44	41
IIIc	CF_3	O	S	97— 99	EtOH	rods	49	21
IVa	Cl	S	S	122—123[a]	MeCN (EtOH)	needles	75	—
IVb	CH_3	S	S	128—129[b]	EtOH	rods	74	—
VII	Cl	O	O	178—179	MeCN+EtOH	plates	62	22 (VI)

Compound	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max}: cm^{-1} in KBr-tablet -C=N-
IIIa	$C_9H_8O_3NS_2Cl$	38.94	2.90	5.04	39.31	3.12	4.91	1550
IIIb	$C_{10}H_{11}O_3NS_2$	46.70	4.31	5.43	46.50	4.41	5.42	1540
IIIc	$C_{10}H_8O_3NS_2F_3$	—	—	4.51	—	—	4.94	1540
IVa	$C_9H_8O_2NS_3Cl$	36.85	2.75	4.68	37.02	2.94	4.76	1490
IVb	$C_{10}H_{11}O_2NS_3$	43.96	4.06	5.13	43.97	4.02	5.11	1485
VII	$C_9H_8O_4NSCl$	41.31	3.08	5.38	41.37	3.21	5.28	1610

a) lit[12]: mp 124° b) lit.[12]: mp 126—127°

the strong band between 1480 and 1610 cm^{-1} which was attributed to C=N stretching vibration appeared. Compound(VII) exhibited the C=N stretching vibration at higher wavenumber ($\delta\nu$=60 cm^{-1}) than that of IIIa and IIIa had the ν C=N at higher ($\delta\nu$=60 cm^{-1}) than that of IVa owing to mesomeric effect of S atom.

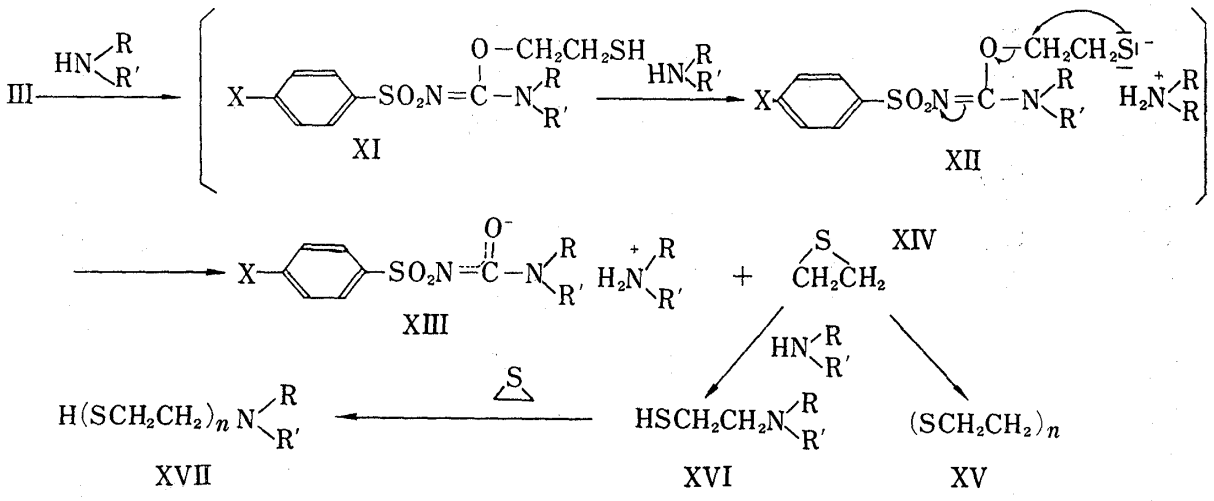


Chart 2

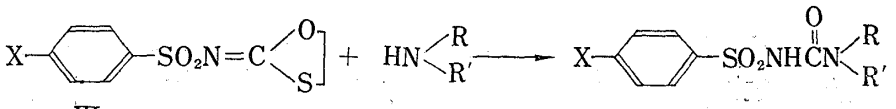
Generally, when one mole of III was allowed to react with three moles of amine, the amine salts(XIII) of VIII which separated from the reaction mixture were obtained in almost quantitative yield together with a small amount of solid which was identical with polyethylene-sulfide(XV) obtained from IIIa and sodium ethylate as described later by infrared spectra comparision. The reaction mixture, after removal of the precipitates(XIII and XV) and

the solvent, was distilled to afford N-2-mercaptoethylamine(XVI), leaving a large amount of undistillable viscous oil which seemed to be multimercaptoethylated amine(XVII), since its infrared spectra was almost identical with that of XVI. The reaction of two moles of amine per mole of III gave XIII in 80—98% yield with large amount of XV. Each equimoler amount reaction gave XIII and VIII in total 50—60% yield and 30—40% of III was recovered. The attempted equimolor reaction of III and amine in the presence of alkali such as triethylamine and sodium hydroxyde to avoid the consumption of the useful amine as the salts gave VIII in about 80% yield. The rates of formation of XV, XVI, and XVII were influenced by the properties and amounts of the used amine and reaction conditions. The detailed detection of them was not performed.

It was considered that, in this reaction, the thiol pseudourea(XI) was produced as an intermediate which would be very short lived and soon reacted with amine to form the strongly nucleophilic mercaptide ion(XII) which decomposed to XIII and ethylenesulfide(XIV).

The results obtained for the reaction of III with several amines under various conditions are tabulated in the Table III.

Table III. Reactions of III with Several Amines under Various Conditions



III VIII

Compound	X	$NH\langle^{R}_{R'}$	Ratio[a]	Reaction solvent	Temp.	Time (hr)	Yield (%)
VIIIa	Cl	HN⟨⟩	3	MeCN	rt[b]	16	98
VIIIb	CH_3	HN⟨⟩	3	MeCN	reflux	4	89
VIIIb	CH_3	HN⟨⟩	3	CH_2Cl_2	reflux	4	78
VIIIc	Cl	HN⟨⟩	2	MeCN	rt	16	96
VIIId	CH_3	$HN(Et)_2$	2	MeCN	rt	16	56
——	CH_3	$HN(iso\text{-}Pr)_2$	2	MeCN	rt	16	0
VIIIe	CH_3	H_2N-⟨H⟩	1	MeCN	rt	16	50
VIIIe	CH_3	H_2N-⟨H⟩	2	MeCN	rt	16	96
VIIIe	CH_3	H_2N-⟨H⟩	3	MeCN	rt	16	96
VIIIe	CH_3	H_2N-⟨H⟩	1+1.1 (NaOH)	MeOH+ H_2O (3:1)	60°	3	76
VIIIf	CH_3	H_2N-Bu	2	MeCN	rt	16	96
VIIIg	Cl	H_2N-Pr	1+2(Et_3N)	MeOH	rt	16	81
VIIIh	CH_3	$H_2N-iso\text{-}Pr$	2	MeOH	rt	16	99
VIIIi	CH_3	H_2NN⟨⟩	2	MeOH	rt	16	93
VIIIi	CH_3	H_2NN⟨⟩	1	MeCN	reflux	4	57
VIIIj	Cl	H_2NN⟨⟩	1+2(Et_3N)	MeCN	rt	16	72
VIIIj	Cl	H_2NN⟨⟩	2	MeCN	rt	16	90
VIIIj	Cl	H_2NN⟨⟩	1	MeCN	reflux	4	60
VIIIj	Cl	H_2NN⟨⟩	1	MeCN	reflux	4	59
VIIIk	CH_3	H_2NN⟨O⟩	2	MeCN	rt	16	82
VIIIl	CH_3	$H_2N-tert\text{-}Bu$	2	dioxane	100°	4	81
VIIIm	CH_3	H_2N-⟨⟩	1	dioxane	100°	4	23
VIIIn	CF_3	H_2N-⟨H⟩	2	MeCN	rt	18	89

a) mol. of amine/ mol. of III b) rt= room temperature

Table IV. Analytical Data of VIII

Compound	mp (°C)	(mp of lit.) (°C)	Appearance[a]	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VIIIa	151—153	—	needles[b]	$C_{12}H_{15}O_3N_2SCl$	47.72	4.98	9.26	47.36	5.13	9.38
VIIIb	148—149	(147—149[13])	rods[c]	$C_{13}H_{18}O_3N_2S$	55.31	6.43	9.92	55.41	6.43	9.97
VIIIc	227—228	(242[13])	rods[c]	$C_{11}H_{13}O_3N_2SCl$	45.71	4.53	9.70	45.81	4.48	9.79
VIIId	130—134	(136—138[13])	needles[b]	$C_{12}H_{18}O_3N_2S$	53.32	6.71	10.37	53.23	6.62	9.95
VIIIe	175—176	(172—173[14])	needles[d]	$C_{14}H_{20}O_3N_2S$	56.74	6.80	9.45	56.63	6.83	9.50
VIIIf	127—129	(127—129[14])	needles[e]	$C_{12}H_{18}O_3N_2S$	53.32	6.71	10.37	53.76	6.61	10.23
VIIIg	128—129	(126—128[14])	rods[f]	$C_{10}H_{13}O_3N_2SCl$	43.41	4.73	10.12	43.53	4.66	9.85
VIIIh	148—150	(141—143[14]) (144—145[6])	rods[e]	$C_{11}H_{16}O_3N_2S$	51.56	6.29	10.93	51.46	6.03	10.76
VIIIi	181—182	(180—182[15])	needles[b]	$C_{12}H_{17}O_3N_3S$	50.84	6.03	14.82	50.81	6.03	14.61
VIIIj	199—201	(201[16])	plates[b]	$C_{11}H_{14}O_3N_3SCl$	43.51	4.65	13.83	43.88	4.96	13.87
VIIIk	205—207	(203—205[15])	rods[b]	$C_{12}H_{17}O_4N_3S$	48.16	5.73	14.04	47.95	5.67	13.89
VIIIl	164—166	(165—166[6])	needles[g]	$C_{12}H_{18}O_3N_2S$	53.32	6.71	10.37	53.61	6.61	10.16
VIIIm	172—174	(178—179[17])	needles[b]	$C_{18}H_{24}O_3N_2S$	62.05	6.94	8.04	62.23	6.93	8.11
VIIIn	174—178	(177—178[18])	needles[e]	$C_{14}H_{17}O_3N_2SF_3$	—	—	8.00	—	—	8.11

a) recryst. solvent b) EtOH+H_2O c) MeCN d) EtOH e) iso-PrOH f) MeOH

As can be noted in Table III, the rates of formation of VIII are influenced by the steric requirement of the attacking amine. The reactions by secondary amine such as diethylamine except for cyclic amine such as piperidine and pyrrolidine were quite slower than that of primary one. No reaction occured with the sterically bulky diisopropylamine. Refluxing with diisopropylamine in methanol, IIIb gave methyl arylsulfonylcarbamate(Xa). The reaction of IIIa with sodium ethylate also gave the corresponding sulfonylcarbamic ester(Xb) and polyethylenesulfide(XV) in good yield.

On the other hand, IV was made to react with propylamine to give the corresponding thiourea(IX) which was identical with authentic sample[19] by the infrared spectral comparison, a mixed melting point determination, and elementary analysis.

Some compounds in a series of the derivatives of III, IV, VII, and IX demonstrated antitumor activity.

Experimental[20]

N-*p*-Substituted Phenylsulfonyldithiocarbamic Acid 2-Hydroxyethyl Ester(II)——To a solution of 0.1 mole of I in 75 ml of dimethylformamide was added portionwise a solution of 8 g of NaOH in 10 ml of H_2O with stirring during which time sodium salts of the sulfonamide separated. To the resulting suspension was added 6.5 ml of CS_2 at 20—30° to give clear red solution. After stirring for 30 min, 8.1 g of ethylene chlorohydrin was added during an interval of about one hr. The mixture was stirred at room temperature for 3 hr after the addition was completed and then poured onto 500 ml of cooled water. The solution was acidified with conc. aq. HCl to congo red paper to give an oily product which gradually solidified. The solid was separated on a filter and recrystallized. Experimental data are summarized in Table I.

13) Farbwerke Hoechst Akt.-Ges., Brit. Patent 863451 (1961) [*C.A.*, **55**, 22347*i* (1961)].
14) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, A. Bänder, and J. Scholz, *Arzneimittel-Forsch.*, **8**, 448 (1958).
15) J.B. Wright and R.W. Willette, *J. Med. Pharm. Chem.*, **5**, 815 (1962).
16) T. Irikura and S. Suzue, *Yakugaku Zasshi*, **84**, 1017 (1964).
17) K. Gerzon, E.V. Krumkalns, R.L. Brindle, F. J. Marshall, and J.A. Root, *J. Med. Chem.*, **6**, 760 (1963).
18) H.L. Yale and F. Sominski, *J. Org. Chem.*, **25**, 1824 (1960).
19) C.V. Deliwara, M.H. Shah, and M.Y. Mhasalkar, Indian Patent 71880 (1962) [*C. A.*, **58**, 4472*a*(1963)].
20) All melting points were uncorrected.

2-Arylsulfonylimino-1,3-oxathiolane(III)——a) To a stirred solution of 0.1 mole of II in 100 ml of 1N NaOH aq. solution was added 0.1 mole of ethyl chloroformate at room temperature within 30 min and the stirring was continued until the separated oil solidified. The solid was collected by filtration and triturated with 5% aq. Na_2CO_3 and the insoluble material was recrystallized from the solvent indicated in Table II. The aq. Na_2CO_3 solution was acidified with 35% HCl to recover II in the yield shown in Table II.

b) One gram of VI(described later) was treated with 2.5 ml of conc. H_2SO_4 by the same manner described in IV to give 0.3 g of IIIa.

2-Arylsulfonylimino-1,3-dithiolane(IV)——Twenty grams of II were dissolved in 60 ml of conc. H_2SO_4 below 20° with morderate cooling and vigorous stirring. After stirring for 2 hr at room temperature, the mixture was poured onto 500 g of crushed ice. The oil which separated gradually solidified. The solid was collected on a filter, washed with water and recrystallized from the solvent shown in Table II.

N-*p*-Chlorophenylsulfonylthiocarbamic Acid O-2-Hydroxyethyl Ester(VI)——A stirred mixture of 5.6 g of methyl N-*p*-chlorophenylsulfonyldithiocarbamate[12] in each 8 ml of benzene and ethyleneglycol was heated on a water bath for 1 hr during which time methylmercaptane was evolved. After removal of benzene *in vacuo*, the mixture was poured into 50 ml of H_2O. The separated oil gradually solidified and solid was collected by filtration and recrystallized from benzene to give colourless scales, mp 132—134°, weighing 3.9 g. *Anal.* Calcd for $C_9H_{10}O_4NS_2Cl$: C, 36.65; H, 3.39; N, 4.75. Found: C, 36.66; H, 3.59; N, 4.71.

2-*p*-Chlorophenylsulfonylimino-1,3-dioxolane(VII)——This was obtained by the same way described for III(method a) except that VI was used instead of II. Experimental data are described in Table II.

1-Arylsulfonyl-3-substituted Urea(VIII)——The following preparation illustrates the general procedure for the products summerized in Table III. A mixture of 11 g of IIIa and 10 g of piperidine in 50 ml of MeCN was allowed to stand at room temperature for 16 hr. The colourless rods which precipitated were collected by filtration and recrystallized from MeCN to give the piperidine salts of VIIIa as colourless rods, mp 159—161°, weighing 13.1 g. On this recrystallization, there was a trace of insoluble crystalline powder and it was seemed to be polyethylenesulfide with comparision of its infrared spectrum with XV obtained in the preparation of Xb. The filtrate of the reaction mixture was concentrated in reduced pressure under the stream of N_2 and the residue was dissolved in 30 ml of benzene and the mixture was washed with 30 ml of H_2O. The aq. layer was acidified with AcOH to give 1.6 g of VIIIa. The benzene solution, on evaporation after drying over anhyd. Na_2SO_4, gave on oily mixture which was distilled under reduced pressure, bp 63—64° (6 mmHg), to give 1.1 g of N-2-mercaptoethylpiperidine (XVI), reaving the residure (3.5 g) seemed to be high-boiling higher mercaptoethylated piperidine (XVII) because its infrared spectrum was almost identical with that of XVI. *Anal.* Calcd. for $C_7H_{15}NS$; C, 57.92; H, 10.41; N, 9.65. Found: C, 57.87; H, 10.44; N, 9.48. The above obtained piperidine salts of VIIIa was dissolved in 150 ml of H_2O and the solution was acidified with AcOH to give 10.2 g of VIIIa which was recrystallized from 50% aq. EtOH to colourless needles, mp 151—153°. Total yield of VIIIa was 11.8 g.

1-*p*-Chlorophenylsulfonyl-2-thio-3-propylurea(IX)——A mixture of 2.9 g of $PrNH_2$ and 2.9 g of IVa in 30 ml of MeCN was allowed to stand at room temperature for 16 hr. After removal of the solvent, the oily residue was dissolved in 30 ml of $CHCl_3$ and the $CHCl_3$ solution was washed with dil. aq. HCl, then H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the solvent gave somewhat viscous solid which was dissolved in 25 ml of aq. 1N NaOH. After removal of the insoluble oily material by the extraction with $CHCl_3$, the aq. solution was treated with active carbon and acidified with AcOH to give 1.6 g of solid mass, which was recrystallized from EtOH to give 1.43 g of colourless rods, mp 136—137° (lit.[19] 135—136°). *Anal.* Calcd. for $C_{10}H_{13}O_2N_2S_2Cl$: C, 41.07; H, 4.47; N, 9.61. Found: C, 40.83; H, 4.41; N, 9.53.

Ethyl N-*p*-Chlorophenylsulfonylcarbamate (Xb)——A mixture of IIIa(2.7 g) and NaOEt–EtOH (Na, 0.23 g, in 30 ml of EtOH) was warmed on a water bath (60°) for 2.5 hr. After cooling, a white crystalline polymer (XV) which separated during the reaction was filtered off and dried *in vacuo* over $CaCl_2$. The material was insoluble in most organic solvent and melted at 156—162°. Yield, 0.37 g. *Anal.* Calcd. for $(C_2H_4S)_n$: C, 40.00; H, 6.71. Found: C, 40.14; H, 6.52. The filtrate was concentrated *in vacuo* and the residue was dissolved in H_2O (30 ml). After treating with active C, the solution was acidified to congo red paper with dil. aq. HCl to deposite an oil which solidified on standing. Recrystallized from $CHCl_3$–petr. ether gave colourless rods, mp 92—93°, weighing 2.3 g. The material was identical with the authentic sample[4] by the mixture mp and infrared absorption spectra comparison.

Reaction of IIIb with Diisopropylamine in MeOH——A mixture of IIIb (1.25 g) and diiso-Pr-NH_2 (1.5 g) in MeOH (10 ml) was refluxed for 3 hr. After cooled and filtered from white precipitates (XV), the solution was concentrated *in vacuo* and the residue was dissolved in H_2O (30 ml). The solution filtered over carbon was acidified to congored paper with dil. HCl to separate an oil which solidified on standing. It was recrystallized from $CHCl_3$–petr. ether to give colourless scales, mp 108—109°, weighing 1.0 g. This was proved to be methyl N-*p*-toluenesulfonylcarbamate (Xa) by its infrared spectrum and elementary analysis. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1760(COO–). *Anal.* Calcd. for $C_9H_{11}O_4NS$: C, 47.16; H, 4.84; N, 6.11. Found: C, 47.52; H, 5.08; N, 6.07.

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