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41. Seishi Takagi, Hisashi Tanaka, Minoru Yano, and Katsunosuke Machida: Studies on the Syntheses of Polymethylenebisthioureas and their Derivatives. I.

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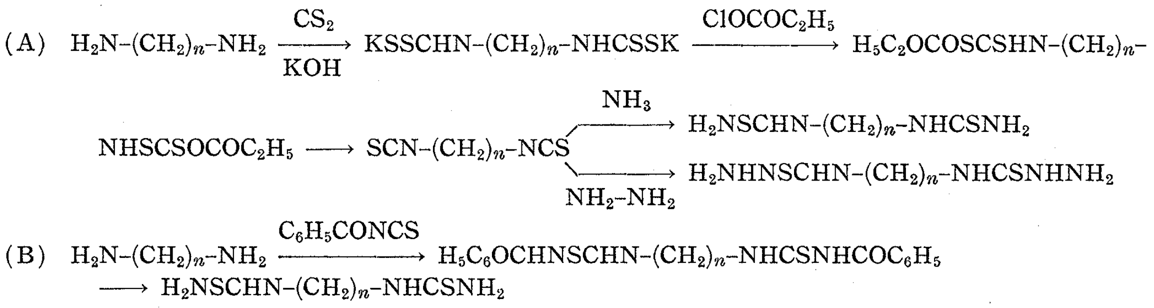
Some utilizable ganglion blockers have been found among the compounds which have two polar groups at both ends of polymethylene chain, such as polymethylenebisammonium or sulfonium salts.[1] In this research some polymethylenebisthiazolium and polymethylenebisthiuronium derivatives were synthesized and submitted to the pharmacological test. The present paper deals with the syntheses of polymethylenebisthioureas and polymethylenebisthiosemicarbazides which could be converted into bis-thiazolium and -thiuronium salts.

Nonsubstituted polymethylenebisthioureas were synthesized from diamines by the following two methods (A and B) and polymethylenebisthiosemicarbazides by method (A).



$$(A)\quad H_2N\text{-}(CH_2)_n\text{-}NH_2 \xrightarrow[KOH]{CS_2} KSSCHN\text{-}(CH_2)_n\text{-}NHCSSK \xrightarrow{ClOCOC_2H_5} H_5C_2OCOSCSHN\text{-}(CH_2)_n\text{-}NHSCSOCOC_2H_5 \longrightarrow SCN\text{-}(CH_2)_n\text{-}NCS \begin{cases} \xrightarrow{NH_3} H_2NSCHN\text{-}(CH_2)_n\text{-}NHCSNH_2 \\ \xrightarrow[NH_2\text{-}NH_2]{} H_2NHNSCHN\text{-}(CH_2)_n\text{-}NHCSNHNH_2 \end{cases}$$

$$(B)\quad H_2N\text{-}(CH_2)_n\text{-}NH_2 \xrightarrow{C_6H_5CONCS} H_5C_6OCHNSCHN\text{-}(CH_2)_n\text{-}NHCSNHCOC_6H_5 \longrightarrow H_2NSCHN\text{-}(CH_2)_n\text{-}NHCSNH_2$$

In method (A), carbon disulfide was added to a solution of diamine in acetone in the presence of potassium hydroxide and potassium dithiocarbamate obtained was treated with ethyl chlorocarbonate in acetone at 0°. Ethoxycarbonyl dithiocarbamate was obtained as colorless crystals but its purification failed. The ethoxycarbonyl derivatives were decomposed by heating to form diisothiocyanate, to which ammonia or hydrazine was added and converted into polymethylene-bisthioureas or -bisthiosemicarbazides.

In method (B), diamine was added to the reaction mixture of ammonium thiocyante and benzoyl chloride. N-Benzoyl-polymethylenebisthioureas were obtained with fairly good yield and the yield was better if purified benzoyl isothiocyanate was used. The hydrolysis of the N-benzoyl derivatives obtained could not be effected by long heating with acid or alkali under atmospheric pressure. Moreover, a long heating with ethanolic potassium hydroxide in a pressurized bottle failed to hydrolyze N-benzoyl derivatives, but by the action of sodium in ethanol, the decomposition proceeded smoothly with a good yield of the product.

N,N-Disubstituted polymethylene-bisthioureas were synthesized by the reaction of isothiocyanate and diamines.

These polymethylene-bisthioureas and -thiosemicarbazides showed violet or blue-violet color by sodium nitroprussidate, sodium hydroxide and hydroxylamine hydrochloride which is a characteristic color reaction of thioureas.[2] The polymethylenebisthioureas so obtained are listed in Tables I, II, III, and IV.

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[1] A. Gray: J. Am. Chem. Soc., **76**, 2792(1954); H. Barber: U. S. Pat., 261,370 (1953); A. D'amico: Brit. Pat., 754,884 (1956).

[2] S. Okuma: Yakugaku Zasshi, **74**, 220(1954).

Table I. Polymethylenebis(benzoylthioureas)

C_6H_5-CO-NH-CS-NH-$(CH_2)_n$-NH-CS-NH-CO-C_6H_5

n	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. N	Analysis (%) Found N
2	212	77.6 96.1*	$C_{18}H_{18}O_2N_4S_2$	14.50	14.37
3	159	56.2	$C_{19}H_{20}O_2N_4S_2$	14.00	14.19
4	197	62.0	$C_{20}H_{22}O_2N_4S_2$	13.52	13.28
5	184~185	70.1	$C_{21}H_{24}O_2N_4S_2$	12.91	13.09
6	178	82.6	$C_{22}H_{26}O_2N_4S_2$	12.47	12.67

* Prepared directly from benzoyl isothiocyanate. Others were prepared from ammonium isothiocyanate and benzoyl chloride.

Table II. Polymethylenebisthioureas

NH_2-CS-NH-$(CH_2)_n$-NH-CS-NH_2

n	m.p. (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Method	Yield (%)
2	202	H_2O	$C_4H_{10}N_4S_2$	26.96	5.66	31.45	26.62	5.64	31.21	A	1.1
										B	71.1
3	178	H_2O	$C_5H_{12}N_4S_2$			29.17			28.88	B	45.2
4	204	H_2O	$C_6H_{14}N_4S_2$			27.17			26.85	A	0.5
										B	46.3
5	156	EtOH	$C_7H_{16}N_4S_2$			25.44			25.15	A	0.5
										B	48.2
6	206	EtOH	$C_8H_{18}N_4S_2$	40.98	7.74	23.92	40.96	8.02	23.68	B	55.4

Yield : Calcd. from diamine in the case of method (A), and from benzoyl derivatives in the case of method (B).

Table III. Polymethylenebisthiosemicarbazides

RNH-NH-CS-NH-$(CH_2)_n$-NH-CS-NH-NHR

n	R	m.p. (°C)	Recrystn. solvent	Formula	Analysis Calcd. N	Analysis Found N	Starting material (diamine, g.)	Product (g.)
3	H	165	H_2O	$C_5H_{14}N_6S_2$	37.81	37.67	7.40	4.25
4	H	179	H_2O	$C_6H_{16}N_6S_2$	35.38	35.11	8.80	3.33
6	H	145	H_2O	$O_8H_{20}N_6S_2$	31.82	31.20	11.60	5.28
6	C_6H_5	121	EtOH	$C_{20}H_{28}N_6S_2$	20.19	20.12	11.60	6.12

Table IV. Hexamethylenebis(substituted thioureas)

RNH-CS-NH-$(CH_2)_n$-NH-CS-NHR

R	m.p. (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd. N	Analysis (%) Found N	Yield (%)
CH_3	133~134	EtOH	$C_{10}H_{22}N_4S_2$	21.35	21.15	81.8
C_6H_5	144	EtOH	$C_{20}H_{26}N_4S_2$	14.51	14.38	88.5
p-Cl-C_6H_5	173~174	EtOH	$C_{26}H_{24}N_4S_2$	12.31	12.58	81.9

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Experimental

Polymethylenebisthioureas—Method (A) : To a solution of 0.2 mole of KOH in a little water, 0.1 mole of CS_2 in 50 cc. acetone was added and to this mixture, a solution of 0.1 mole of polymethylenediamine in 20 cc. of acetone was added drop by drop, with vigorous stirring during 15 mins. at 30~40°. After the addition of diamine was completed, acetone and water were driven off *in vacuo* and the residue (potassium polymethylenebisdithiocarbamate) was washed with dehyd. EtOH and ether. To a mixture of 0.1 mole of potassium polymethylenebisdithiocarbamate and 100 cc. of dehyd. acetone, 0.2 mole of chloroethyl carbonate was added drop by drop, with vigorous stirring at 0°. After the addition was over, stirring was continued for further 30 mins., insoluble substance was filtered off, and acetone was distilled off *in vacuo*. Ethoxycarbonyl derivatives were obtained as a white crystalline powder. This ethoxycarbonyl derivative was mixed with a little water and heated at 80~90° on a water bath, when it decomposed with foaming and yellow oil (polymethylene diisothiocyanate) separated. To a solution containing 0.4 mole of NH_3, diisothiocyanate was added drop by drop and white crystals separated (bisthiourea), but considerable resinification occurred and yield was very low.

Polymethylenebisthiosemicarbazides—0.1 mole of polymethylene diisothiocyanate was added to 0.4 mole of hydrazine hydrate under ice-cooling. White crystals that separated (bisthiosemicarbazides) were collected.

Hexamethylenebis(phenylthiosemicarbazides)—16 g. of phenylhydrazine was dissolved and 16 g. of hexamethylene diisothiocyanate was added to it drop by drop under ice-cooling. Oily substance separated, which crystallized on cooling, were recrystallized from EtOH. m.p. 121°; yield, 5.2 g. *Anal.* Calcd. for $C_{20}H_{28}N_6S_2$: N, 20.19. Found : N, 20.12.

Polymethylenebisthioureas—Method (B) : a) Polymethylenebis(benzoylthioureas) : i) From BzCl and ammonium thiocyanate : To a solution of 0.2 mole of NH_4CNS in 150 cc. of dehyd. acetone, 0.2 mole of BzCl was added drop by drop and the mixture was refluxed for 15 mins. Then a solution of 0.1 mole of diamine in acetone was added to the reaction mixture, which was cooled to room temperature, and poured into 500 cc. of water. Yellow precipitate was collected, washed with water, and recrystallized from AcOEt.

ii) From benzoyl isothiocyanate : To a solution of 0.2 mole of benzoyl isothiocyanate in 70 cc. of EtOH, a solution of 0.1 mole of diamine in 20 cc. of EtOH was added under ice-cooling. The reaction mixture was refluxed for 30 mins., the precipitate was collected, and recrystallized from AcOEt.

b) Polymethylenebisthioureas : i) Hydrolysis of N-benzoyl derivatives with KOH : 0.01 mole of polymethylenebis(benzoylthiourea) was dissolved in a little EtOH and 0.04 mole of KOH was added and dissolved. The mixture was placed in a pressurized bottle and heated on a water bath for 10 hrs. EtOH was distilled off, the residue was dissolved in water with heating, insoluble substance was filtered off, and the filtrate was acidified with conc. HCl. Benzoic acid was extracted with ether and the aqueous layer was concentrated *in vacuo*. Colorless crystalline powder was collected.

ii) Decomposition of N-benzoyl derivatives with Na : To a suspension of 0.1 mole of polymethylenebis(benzoylthiourea) in 100 cc. of dehyd. EtOH, 0.4 mole of Na was added little by little and this mixture was shaken for a few mins. After N-benzoyl derivative dissolved completely, the reaction mixture was refluxed for 15 mins. on a water bath. EtOH was distilled off, the residue was dissolved in hot water, filtered, and the filtrate was concentrated to about ⅓ the original volume. The precipitate was collected, dissolved in water, and the solution was acidified with conc. HCl. Polymethylenebisthiourea thus obtained was recrystallized from a suitable solvent.

Hexamethylenebis(substituted thioureas)—To a solution of 0.2 mole of alkyl or aryl isothiocyanate dissolved in 30 cc. of EtOH, 0.1 mole of hexamethylenediamine was added under ice-cooling, and the mixture was refluxed for 15 mins. EtOH was distilled off and the residue was recrystallized from EtOH.

Summary

Polymethylenebisthioureas were synthesized from diamines by two methods. In one method, diamines were converted into corresponding bisisothiocyante and then treated with ammonia. In the other method, benzoyl isothiocyanate was reacted with diamines and N-benzoyl derivatives obtained were decomposed to form bisthioureas. Better yield was achieved by the latter method. Polymethylenebisthiosemicarbazides and polymethylene-bis-thioureas were also synthesized. These compounds were submitted to pharmacological test as a possible ganglion blocker.

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