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Composition and Structure of 2-Methylpiperazine-Carbon Disulfide Complex

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It was found that 2-methylpiperazine–carbon disulfide complex (I) obtained by the reaction of 2-methylpiperazine (II) with carbon disulfide was not 2-methylpiperazine-1-carbodithioic acid, but a mixture composed of 3-methylpiperazine-1-carbodithioic acid (VIII) and 2-methylpiperazine salt of 2-methylpiperazine-1,4-dicarbodithioic acid (IX), and moreover that there was no possibility of disproportionation between VIII and IX during the treatment.

It has been generally known that some of the dithiocarbamates are useful as agricultural fungicides and bacteriocides and they have also anthelmintic and other interesting pharmacological activities. During the course of a search for biological active dithiocarbamates, it became desirable to determine the composition and structure of 2-methylpiperazine–carbon disulfide complex of formula $C_6H_{12}N_2S_2$ (I). Complex I has already been synthesized by Esch and Marckwald[2] as a substance of mp 193—194° (decomp.) which was recently reported as a hepatic and irradiation protective agent and moreover assigned as 2-methylpiperazine-1-carbodithioic acid[3], but no report investigated on the structure has been published. On

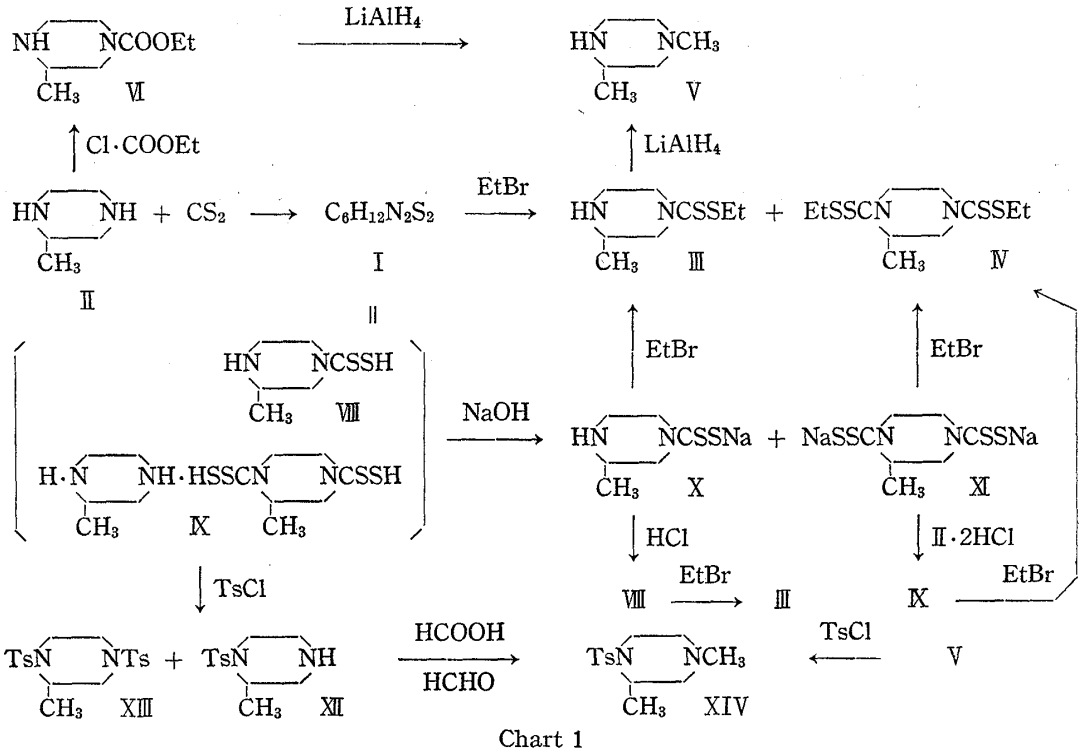

Chart 1

1) Location: *Ebie-kami-2-chome, Fukushima-ku, Osaka.*
2) W. Esch and W. Marckwald, *Chem. Ber.*, **33**, 761 (1900).
3) *a*) V. Palma, G. Galli, S. Garattini, R. Paoletti and R. Vertura, *Arzneimittel Forsch.*, **11**, 1034 (1967); *b*) *C.A.*, **64**, 19642[f], Span. Patent 318859 (Dec. 16, 1965); *c*) *C.A.*, **59**, 5451[d], R. Paolletti, *et al.*, *Rass. Intern. Elettron. Nucl., 7th, Congr. Nucl., 5th, Rome*, **1960**, 675—696.

the other hand, Dunderdale[4] and Psarrea[5] reported that the piperazine–carbon disulfide complex of empirical formula $C_5H_{10}N_2S_2$, which has been used widely for treatment of roundworms in pigs and poultry, was a mixture composed of piperazine-1-carbodithioic acid and the piperazine salt of piperazine-1,4-dicarbodithioic acid. Therefore, it may be mentioned that the composition of I is similar to that of piperazine–CS_2 complex. Compound I prepared by the reaction of 2-methylpiperazine (II) with an equimolar amount of carbon disulfide in methanol was decomposed to 2-methylpiperazine and carbon disulfide in acid solution, sensible to heat and partially degenerated on drying under heating.

When I was dissolved in aqueous sodium hydroxide followed by ethylation with ethyl bromide, ethyl 3-methylpiperazine-1-carbodithioate (III) and diethyl 2-methylpiperazine-1, 4-dicarbodithioate (IV) were obtained in 50.4 and 30.8% yields, respectively.

Beck[6] proved ethyl 3-methylpiperazine-1-carboxylate (VI) was obtained by the reaction of II with ethyl chloroformate at a pH of 3—3.5, and subsequently 1,2-dimethylpiperazine (VII) was given by methylation of VI followed by hydrolysis and decarboxylation. On reduction with lithium aluminum hydride, III gave dimethylpiperazine (V) which was identified with an authentic specimen, 1,3-dimethylpiperazine, prepared by the same reduction of VI synthesized according to Beck's method, whereas I was so insoluble in solvents that the same reduction was unsuccessful. From the above results, it was found that I was a mixture consisting of 3-methylpiperazine-1-carbodithioic acid (VIII) and 2-methylpiperazine salt of 2-methylpiperazine-1,4-dicarbodithioic acid (IX). However, there still remains the possibility of the disproportionation between VIII and IX during the above treatment. Complex I was then converted (to sodium dithiocarbamate) by treating with sodium hydroxide followed by the fractional precipitation from ethanol–ether to isolate the two kinds of sodium carbodithioates, sodium 3-methylpiperazine-1-carbodithioate (X) and disodium 2-methylpiperazine-1,4-dicarbodithioate (XI). X and XI were obtained also by the reaction of II with equimolar amount of carbon disulfide and sodium hydroxide followed by the treatment as described above. Compound XI was also obtainable from the reaction either of II with two equimolar amounts of carbon disulfide and sodium hydroxide, or of I with an equimolar amount of carbon disulfide and two equimolar amounts of sodium hydroxide. Treatment of X with an equimolar amount of hydrochloric acid yielded VIII. By ethylation of X or VIII with ethyl bromide, III was obtained in 61.1 and 71.4% yields, respectively, but in the case any of the diester IV could not be detected. Treatment of XI with II dihydrochloride afforded IX. On ethylation of XI or IX, IV was given in 65.8 or 61.5% yield, respectively, but III was not obtained. These experiments, thus, showed to eliminate the possibility of the disproportionation.

On treatment with tosyl chloride in aqueous sodium hydroxide followed by hydrolysis with dilute hydrochloric acid, I afforded 1-tosyl-2-methylpiperazine (XII) and 1,4-ditosyl-2-methylpiperazine (XIII) besides 2-methylpiperazine in 11.2 and 38.8% yields, respectively. In the reaction, a mixed anhydride, considered as a intermediate, tosyl 3-methyl-4-tosylpiperazine-1-carbodithioate, was not isolated, but it can be assumed that the anhydride formed would likely be hydrolyzed to give XII. Methylation of XII with formic acid and formaldehyde gave 1-tosyl-2,4-dimethylpiperazine (XIV) which was identical with the product obtained by tosylation of V. X was also similarly cnverted to XII in a rather lower yield, but in the case any of XIII was not detected. However, the reaction gave *p*-tolyl *p*-toluenethiolsulfonate as a by–product. XIII was also easily given by tosylating 2-methylpiperazine.

4) J. Dunderdale and T.I. Watkins, *Chem. Ind.* (London), **1956**, 174.
5) Mlle A. Psarrea, C. Sandris and G. Tsatsas, *Bull. Soc. Chim. France*, **1961**, 2145.
6) K.M. Beck, K.E. Hamlin and A.W. Weston, *J. Am. Chem. Soc.*, **74**, 605 (1952).

Experimental[7]

2-Methylpiperazine-Carbon Disulfide Complex (I)——7.7 g of II was treated with 5.86 g of CS_2 in MeOH. The precipitate was filtered, washed with H_2O and EtOH, and dried to yield 12.2 g of I, mp 191—193° (decomp.) (lit[2]., mp 193—194°). *Anal.* Calcd. for $C_6H_{12}N_2S_2 \cdot 2/3H_2O$: C, 38.26; H, 7.13; N, 14.88; S, 34.05. Found: C, 38.42; H, 6.90; N, 14.98; S, 34.11.

Diethyl 2-Methylpiperazine-1,4-dicarbodithioate (IV) and Ethyl 3-Methylpiperazine-1-carbodithioate (III)——*a*) To a solution of 3.53 g of I dissolved in aqueous NaOH was added 0.2 g of EtBr in EtOH, and the mixture was shaken for 10—15 min, and EtOH was removed *in vacuo*. An oil isolated was extracted with ether, and the ethereal layer was extracted with 10% HCl, dried over anhyd. Na_2SO_4. Removal of the ether gave 0.95 g (30.8%) of IV, mp 68—70° (from dil. EtOH). *Anal.* Calcd. for $C_{11}H_{20}N_2S_4$: C, 42.81; H, 6.53; N, 9.08; S, 41.57. Found: C, 42.79; H, 6.60; N, 9.14; S, 41.57. Acidic aqueous layer obtained above was made alkaline with NaOH and an oil separated was extracted with ether. The extract was washed with H_2O, and dried over anhyd. Na_2SO_4. Ether was evaporated and an oily residue distilled to give 2.13 g (50.4%) of III, bp 118—119° (0.08 mmHg). Picrate, mp 165—175° (from EtOH). *Anal.* Calcd. for $C_8H_{16}N_2S_2 \cdot C_6H_3O_7N_3$: C, 38.79; H, 4.42; N, 16.16; S, 14.80. Found: C, 39.14; H, 4.47; N, 16.29; S, 14.70.

b) To a solution of 1.98 g of X in water was added a solution of 1.09 g of EtBr in EtOH, and the mixture was shaken for 10—15 min. After removing EtOH, an oil separated was extracted with ether. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, evaporated, and then the residue distilled to give 1.25 g of III.

c) To a solution of 1.76 g of VIII and 0.40 g of NaOH in H_2O was added a solution of 1.09 g of EtBr in EtOH, the mixture treated as described above to give 1.50 g of III.

d) 3.68 g of XI in H_2O was added a solution of 2.18 g of EtBr in EtOH, and the mixture was treated as described above to yield 2.03 g of IV.

e) To 3.53 g of IX dissolved in a solution of 0.80 g of NaOH in H_2O was added 2.18 g of EtBr in EtOH, the solution was treated as described above and 1.90 g of IV was obtained.

Ethyl 3-methylpiperazine-1-carboxylate (VI)——VI was synthesized according to the method described in the literature.[6]

1,3-Dimethylpiperazine (V)——*a*) A solution of 7.4 g of VI in dry ether was added dropwise to a solution of 9.6 g of $LiAlH_4$ in dry ether. After the mixture was stirred for 0.5 hr at a room temperature and then for 3 hr under refluxing, to the resulted mixture H_2O was added under ice-cooling, and the precipitate filtered. The filtrate was acidified with HCl, concentrated *in vacuo*, the residue was made alkaline with 50% aqueous NaOH, and an oil isolated was extracted with ether. The extract was dried over anhyd. Na_2SO_4, ether evaporated, and then the residue distilled to yield 1.4 g of V, bp 138—140° (760 mmHg). Dipicrate, mp 253° (decomp.) (from H_2O–EtOH). *Anal.* Calcd. for $C_6H_4N_2 \cdot 2C_6H_3O_7N_3$: C, 37.77; H, 3.53; N, 19.58. Found: C, 37.37; H, 3.60; N, 19.48.

b) A solution of 2.4 g of III in dry ether was added dropwise to a solution of 2.28 g of $LiAlH_4$ in dry ether. The mixture was treated similarly as described above, to give 0.6 g of V (bp 138—140° (760 mmHg)) which was identified with the authentic specimen prepared from VI mentioned above by comparison of IR spectra. Dipicrate, mp 253° (decomp.) (from H_2O–EtOH). The picrate was identified with the picrate of the authentic specimen prepared from VI by comparison of IR spectra and mixed melting determination.

Sodium 3-Methylpiperazine-1-carbodithioate (X) and Disodium 2-Methylpiperazine-1,4-dicarbodithioate (XI)——*a*) 53.8 g of I was dissolved in 102.05 ml of aqueous 3N NaOH(F=0.997) and the mixture concentrated *in vacuo*. The residue was extracted with acetone under refluxing to remove 2-methylpiperazine. The acetone-insoluble Na salts were precipitated fractionally from EtOH–ether, separated into four fractions. Disodium 2-methylpiperazine-1,4-dicarbodithioate (XI) was obtained from the first and second, a mixture composed of X and XI from the third, and 7.4 g of sodium 3-methylpiperazine-1-carbodithioate (X) from the fourth. X, mp 316° (decomp.). *Anal.* Calcd. for $C_6H_{11}N_2NaS_2 \cdot 1/3H_2O$: C, 35.27; H, 5.76; N, 13.71; Na, 11.25; S(3/4S), 23.54. Found: C, 35.46; H, 5.89; N, 13.51; Na, 10.92; S, 23.61. IX, mp 317° (decomp.). *Anal.* Calcd. for $C_7H_{10}N_2Na_2S_4 \cdot 4H_2O$: C, 22.82; H, 4.92; N, 7.60; Na, 12.48; H_2O, 19.56. Found: C, 22.79; H, 4.93; N, 7.82; Na, 12.41; H_2O, 19.32.

b) 77.0 g of II was dissolved in a solution of 30.76 g of NaOH in H_2O, to the solution were added 600 ml of acetone and then 58.6 g of CS_2. After standing for a minute, the mixture was concentrated. The residue was treated as described above to give 37.9 g of XI and 19.4 g of X which were identified with the products described in *a*) by IR comparison, respectively.

c) To a solution of 61.6 g of 2-methylpiperazine and 49.2 g of NaOH in H_2O was added acetone, and then 93.6 g of CS_2 in acetone added. After standing for a minute, acetone was added till the mixture became turbid. The mixture was cooled and the crystals isolated were collected by filtration to yield 170.9 g of XI.

d) 8.5 g of I was dissolved in 92.27 ml of aqueous 1N NaOH (F=1.02), to the solution were added acetone and 7.67 g of CS_2 successively. The mixture was treated as mentioned in *c*) to give 10 g of XI.

7) All melting points are uncorrected.

3-Methylpiperazine-1-carbodithioic Acid (VIII)——To a solution of 5.95 g of X in H_2O was added 26 ml of 1N HCl (F=1.048). The precipitate was filtered, washed with H_2O and EtOH successively to yield 3.4 g of VIII, mp 190° (decomp.). *Anal.* Calcd. for $C_6H_{12}N_2S_2 \cdot 2/3H_2O$: C, 38.26; H, 7.13; N, 14.88; S, 34.05. Found: C, 38.42; H, 6.90; N, 14.98; S, 34.11.

2-Methylpiperazine Salt of 2-Methylpiperazine-1,4-dicarbodithioic Acid (IX)——To a solution of 15 g of XI in H_2O was added a solution of 8.76 g of II dihydrochloride in H_2O, the precipitate filtered, washed with H_2O and EtOH to yield 13.4 g of IX, mp 189° (decomp.). *Anal.* Calcd. for $C_{12}H_{24}N_4S_4$: C, 40.87; H, 7.17; N, 15.89; S, 36.37. Found: C, 40.43; H, 7.17; N, 16.22; S, 35.78.

1-Tosyl-2-methylpiperazine (XII) and 1,4-Ditosyl-2-methylpiperazine (XIII)——*a*) To a solution of 27.0 g of tosylchloride in dioxane was added dropwise a solution of 10.0 g of I in 112.5 ml of 10% aqueous NaOH, the mixture was shaken for a minute, and a separated oily product was extracted with $CHCl_3$. The extract was washed with dil-HCl, dil-NaOH and H_2O successively, dried over anhyd. Na_2SO_4 and evaporated. To the residual oil was added 10% HCl in EtOH, the mixture was refluxed for 5 hr, concentrated, and the residue was extracted with $CHCl_3$. The extract was washed with dil-HCl and H_2O, dried over anhyd. Na_2SO_4, evaporated to give 2.7 g of XIII, whose picrate was identified with the authentic specimen prepared in *b*) by mixed melting point determination. The aqueous layer was made alkaline with NaOH, a separated oil was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give 1.6 g of XII. Picrate of XII, mp 197—202° (from EtOH). *Anal.* Calcd. for $C_{12}H_{18}O_2N_2S \cdot C_6H_3O_7N_3$: C, 44.72; H, 4.35; N, 14.49; S, 6.63. Found: C, 45.05; H, 4.49; N, 14.45; S, 6.56. XII (derived from the picrate described above); *Anal.* Calcd. for $C_{12}H_{18}O_2N_2S$: C, 56.67; H, 7.13; N, 11.01; S, 12.58. Found: C, 55.69; H, 7.42; N, 10.46; S, 12.17.

b) To 0.5 g of II dihydrochloride was added 2.35 g of tosyl chloride and 12.4 ml of 10% aq. NaOH, and the mixture was shaken, heated on water bath, cooled, and then the isolated precipitate was filtered. Yield, 0.95 g, mp 169—171° (from EtOH) (lit.,[8] mp 173—174.5°).

c) To a solution of 3.0 g of X dissolved in 68 ml of 10% NaOH was added gradually 12.98 g of tosyl chloride in dioxane under stirring. The reaction mixture was acidified and evaporated, the residue was dissolved in H_2O, and the insoluble substance was extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was added to a HCl–EtOH solution and the mixture was heated on a water bath for 5 hr and evaporated *in vacuo*. To the residue was added H_2O, and the insoluble material was extracted with $CHCl_3$. The aqueous solution was made alkaline and an oily product isolated was extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give 0.45 g of XII which was identified with the compound (XII) prepared in *a*) by IR spectrum. On the other hand, the $CHCl_3$ layer described above was washed with H_2O, dried over Na_2SO_4 and evaporated to give 1.7 g of *p*-tolyl *p*-toluenethiolsulfonate, mp 75° (EtOH–H_2O) (lit.,[9] mp 77—78°). *Anal.* Calcd. for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.07; S, 23.04. Found: C, 59.65; H, 5.07; S, 22.90.

1-Tosyl-2,4-dimethylpiperazine (XIV)——*a*) To 0.5 g of XII was added 0.11 ml of HCOOH (80%) and 0.17 ml of HCHO (37% aq.), and the mixture was refluxed for 4 hr, and evaporated *in vacuo*. To the residue was added H_2O, and the solution was made alkaline with NaOH, and an isolated oil extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to give 0.5 g of XIV. The compound was identified with the product obtained from V by IR spectra. Picrate, mp 174—176° (from EtOH). *Anal.* Calcd. for $C_{13}H_{20}O_2N_2 \cdot C_6H_3O_7N_3$: C, 45.87; H, 4.66; N, 14.08; S, 6.49. Found: C, 46.22; H, 4.82; N, 14.24; S, 6.34. The picrate was identified with the picrate derived from V by IR spectral comparison and mixed melting point determination.

b) To 1.3 g of V was added 3.3 g of tosyl chloride and 18 ml of 10% aq. NaOH, and the mixture was shaken, heated on water bath, cooled, and an isolated oil was extracted with ether. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to give 2.5 g of XIV. Picrate, mp 179—181° (from EtOH). *Anal.* Calcd. for $C_{13}H_{20}O_2N_2 \cdot C_6H_3O_7N_3$: C, 45.87; H, 4.66; N, 14.08; S, 6.49. Found: C, 45.66; H, 4.74; N, 13.94; S, 6.52.

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8) T. Ishiguro, E. Kitamura and M. Matsumura, *J. Pharm. Soc. Japan*, **77**, 1051 (1957).
9) F. Klivényi, J. Szabó and E. Vinkler, *Acta Chim. Acad. Sci. Hung.*, **6**, 378—380 (1955) [*C.A.*, **51**, 1882^f (1957)].