40—50° for 30 min, filtered, and the precipitate was recrystallized from iso-PrOH to give colorless prisms, mp 164—166°. Yield, 10.59 g (95%). *Anal.* Calcd. for $C_{22}H_{26}O_6N_4$: C, 47.95; H, 7.60; N, 16.37. Found: C, 48.02; H, 7.59; N, 16.40. IR ν_{max}^{liquid} cm^{-1}: 1660 (C=O).

3,3′-Hexamethylene-bis[2,4(1H, 3H)-quinazolinedione] (XXXIII)——A solution of 3 g (0.01 mole) of XXXII in 8 ml of 10% NaOH was warmed at 50° for 30 min. When cooled, the reaction mixture was acidified with 10% HCl with stirring and the resulting crystals were collected. The crystals were washed with water and recrystallized from DMF–H_2O to colorless prisms, mp>300°. Yield, 3.2 g (78.8%). *Anal.* Calcd. for $C_{22}H_{22}O_4N_4$: C, 65.01; H, 5.45; N, 13.78. Found: C, 64.97; H, 5.44; N, 13.82.

Acknowledgement The authors express their deep gratitude to Professor Haruo Saikachi, Kobe Gakuin University, for his encouragement throughout the course of this work. Thanks are also due to the Analytical Center of Kyoto University for elemental analyses.

[Chem. Pharm. Bull. 23(3) 668—673 (1975)] *UDC 615.33.011.5*

Synthesis of New Antimicrobials. V.[1] Synthesis of Alkylenebis(thiosemicarbazides) and Their Related Compounds

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(Received June 29, 1974)

Several kinds of alkylenebis(thiosemicarbazide) and alkylenebis(bithiourea) derivatives were synthesized in order to examine their antimicrobial activity. 1,1′-Dibenzylidene-4,4′-alkylene-bis(thiosemicarbazides) were prepared from 4,4′-alkylene-bis(thiosemicarbazides) and arylaldehydes, and 1,1′-diaroyl-4,4′-hexamethylene-bis(thiosemicarbazides) were prepared by the reaction of 4′,4′-hexamethylene-bis(thiosemicarbazide) with aroyl chlorides. 1,1′-Dialkyl- or diaryl-6,6′-alkylene-bis(bithioureas) were synthesized from 4,4′-alkylene-bis(thiosemicarbazides) and alkyl or aryl isothiocyanates. N,N′-Hexamethylene-bis[2-amino-5-(2-methoxyphenyl)thiadiazole] was prepared by the ring closure of 1,1′-bis(2-methoxybenzylidene)-4,4′-hexamethylene-bis(thiosemicarbazide).

The potent antibacterial activity of thiosemicarbazones such as thioacetazone prompted our investigation for producing related compounds which might show improved therapeutic values either by increasing their activity or reducing their toxicity, or both. Alkylenebis(thiosemicarbazides) and their derivatives, 1,1′-dibenzylidene-4,4′-alkylene-bis(thiosemicarbazides), 1,1′-diaroyl-4,4′-alkylene-bis(thiosemicarbazides), and 1,1′-dialkyl- or 1,1′-diaryl-6,6′-alkylene-bis(bithioureas) were synthesized in our laboratory. N,N′-Hexamethylene-bis[2-amino-5-(2-methoxyphenyl)thiadiazole] was also synthesized.

Synthesis of 4,4′-alkylene-bis(thiosemicarbazides) (I to VIII) was initially carried out in good yield by the reaction between alkylene diisothiocyanate[1] with two equivalents of hydrazine or substituted hydrazines at about −10°. The reaction scheme and the compounds prepared are shown in Chart 1 and Table I, respectively.

1,1′-Dibenzylidene-4,4′-alkylene-bis(thiosemicarbazides) (IX to XXXI) were obtained by the reaction of 4,4′-alkylene-bis(thiosemicarbazides) (I, III, VI) with two moles equivalents of arylaldehyde, 1,1′-diaroyl-4,4′-hexamethylene-bis(thiosemicarbazides) (XXXII to XXXVIII) were prepared from 4,4′-hexamethylene-bis(thiosemicarbazide) (VI) and two moles equivalents of aroyl chlorides, and 1,1′-dialkyl- or 1,1′-diaryl-6,6′-alkylene-bis(thioureas)

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[1] Part IV: T. Yabuuchi, M. Hisaki, and R. Kimura, *Chem. Pharm. Bull.* (Tokyo), 23, 663 (1975).

[2] Location: *15-Morimoto-cho, Shimogamo, Sakyo-ku, Kyoto.*

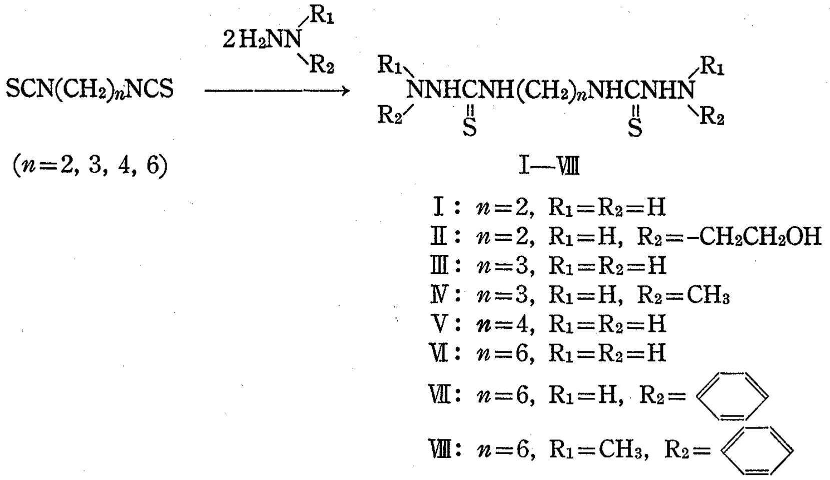


Chart 1

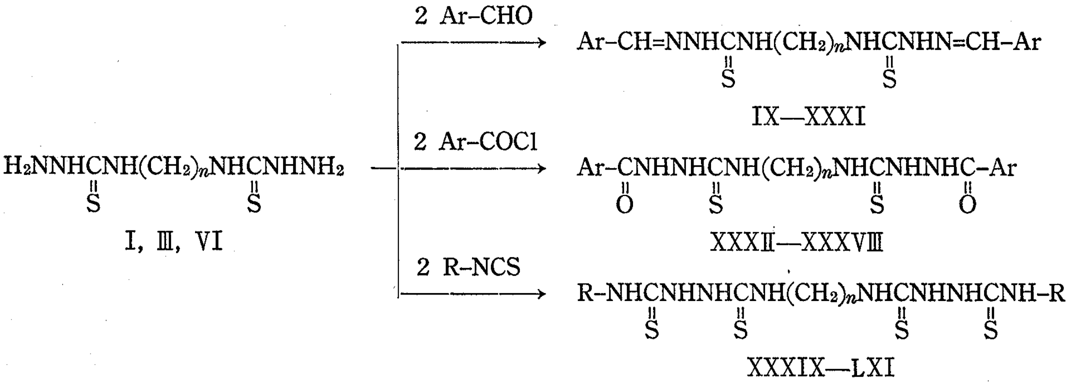
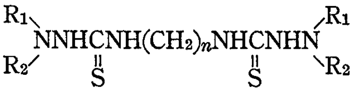
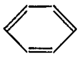


Chart 2

Table I. 4,4′-Alkylene-bis(thiosemicarbazides)

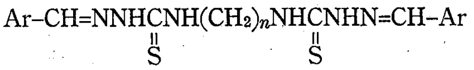


$$R_1R_2NNHC(=S)NH(CH_2)_nNHC(=S)NHNR_1R_2$$

Compd. No.	n	R_1	R_2	mp (°C)	Cryst. solvent	Appearance
I[a]	2	H	H	212—214	H_2O	colorless prisms
II[b]	2	H	$-CH_2CH_2OH$	169—170	H_2O	colorless prisms
III[a]	3	H	H	164	H_2O	colorless prisms
IV[b]	3	H	CH_3	144—145	iso-PrOH	colorless prisms
V[a]	4	H	H	177—178	H_2O	colorless prisms
VI[a]	6	H	H	145—146	H_2O	colorless prisms
VII[b]	6	H		145—146	H_2O	colorless prisms
VIII[b]	6	CH_3		126—127	dioxane	colorless prisms

[a] S. Takagi, H. Tanaka, M. Yano, and K. Machida, *Chem. Pharm. Bull.* (Tokyo), **7**, 206 (1959).
[b] new compounds

TABLE II. 1,1′-Dibenzylidene-4,4′-alkylene-bis(thiosemicarbazides)



$$Ar\text{-}CH{=}NNH\underset{\overset{\|}{S}}{C}NH(CH_2)_nNH\underset{\overset{\|}{S}}{C}NHN{=}CH\text{-}Ar$$

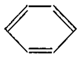
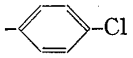
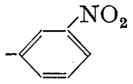
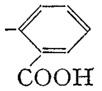
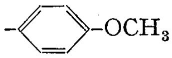
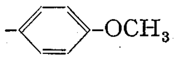
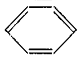
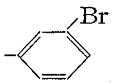
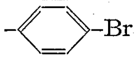
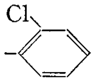
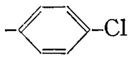
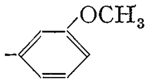
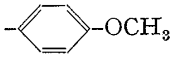
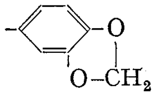
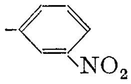
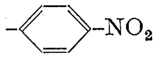
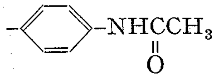
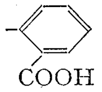
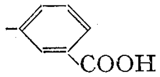
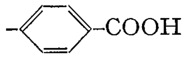
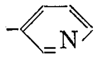
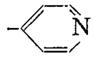
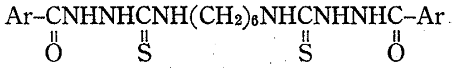
Compd. No.	n	Ar	mp (°C) ( ): Cryst. solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N
IX	2		212 (DMF-50% EtOH)	prisms	$C_{18}H_{20}N_6S_2$	52.40 (52.03)	4.89 (4.78)	27.16 (27.08)
X	2		226—228 (DMF-EtOH)	prisms	$C_{18}H_{18}N_6Cl_2S_2$	47.68 (47.41)	4.00 (3.96)	18.54 (18.71)
XI	2		234—235 (DMF-EtOH)	prisms	$C_{18}H_{18}O_4N_8S_2$	45.56 (45.53)	3.82 (3.99)	23.62 (24.20)
XII	2		233—236 (DMF)	prisms	$C_{20}H_{20}O_4N_6S_2$	50.38 (50.43)	4.21 (4.03)	17.79 (18.05)
XIII	2		227—229 (DMF)	prisms	$C_{20}H_{24}O_2N_6S_2$	54.03 (53.75)	5.44 (5.72)	18.90 (19.20)
XIV	3		197—199 (DMF-50%EtOH)	prisms	$C_{19}H_{22}N_6S_2$	57.26 (57.56)	5.56 (5.43)	21.09 (20.91)
XV	3		212—214 (DMF-50%EtOH)	prisms	$C_{21}H_{26}O_2N_6S_2$	55.00 (55.26)	5.71 (5.79)	18.33 (18.07)
XVI	6		198—200 (DMF-EtOH)	prisms	$C_{22}H_{28}N_6S_2$	59.96 (59.78)	6.40 (6.59)	19.07 (19.28)
XVII	6		235—236 (THF-MeOH)	prisms	$C_{22}H_{26}N_6Br_2S_2$	44.15 (44.24)	4.37 (4.48)	14.04 (14.31)
XVIII	6		226—227 (THF—MeOH)	prisms	$C_{22}H_{26}N_6Br_2S_2$	44.15 (44.30)	4.37 (4.48)	14.04 (14.06)
XIX	6		230—231 (DMF-MeOH)	prisms	$C_{22}H_{26}N_6Cl_2S_2$	51.92 (51.69)	5.41 (5.28)	16.51 (16.61)
XX	6		209—210 (DMF-MeOH)	prisms	$C_{22}H_{26}N_6Cl_2S_2$	51.92 (51.83)	5.41 (5.30)	16.51 (16.70)
XXI	6		197—198 (THF-MeOH)	prisms	$C_{24}H_{32}O_2N_6S_2$	57.57 (57.34)	6.44 (6.44)	16.78 (17.06)
XXII	6		181—183 (THF-MeOH)	prisms	$C_{24}H_{32}O_2N_6S_2$	57.57 (57.57)	6.44 (6.32)	16.78 (16.81)
XXIII	6		224—225 (THF-MeOH)	prisms	$C_{24}H_{28}O_4N_6S_2$	54.52 (54.52)	5.34 (5.09)	15.89 (15.79)
XXIV	6		240 (DMF-MeOH)	light yellow prisms	$C_{22}H_{26}O_4N_8S_2$	49.79 (49.52)	4.93 (5.06)	21.11 (20.88)
XXV	6		247.5 (DMF-MeOH)	light yellow prisms	$C_{22}H_{26}O_4N_8S_2$	49.79 (50.06)	4.93 (5.17)	21.11 (20.94)
XXVI	6		251—252 (DMF-MeOH)	prisms	$C_{26}H_{34}O_2N_8S_2$	56.29 (56.01)	6.18 (6.21)	20.20 (20.33)
XXVII	6		229—230 (DMF-MeOH)	prisms	$C_{24}H_{30}O_4N_6S_2$	54.32 (54.35)	5.69 (5.43)	15.83 (15.85)
XXVIII	6		258 (DMF-MeOH)	prisms	$C_{24}H_{30}O_4N_6S_2$	54.32 (54.04)	5.69 (5.42)	15.83 (16.11)
XXIX	6		253—254 (DMF-MeOH)	prisms	$C_{24}H_{30}O_4N_6S_2$	54.32 (54.13)	5.69 (5.73)	15.83 (15.39)
XXX	6		227—228 (DMF-MeOH)	prisms	$C_{20}H_{26}N_8S_2$	54.27 (54.18)	5.92 (6.06)	25.31 (25.23)
XXXI	6		213 (DMF-MeOH)	prisms	$C_{20}H_{26}N_8S_2$	54.27 (54.48)	5.92 (6.20)	25.31 (25.19)

Table III. 1.1′-Diaroyl-4,4′-hexamethylene-bis(thiosemicarbazides)



$\mathrm{Ar{-}\underset{\overset{\|}{O}}{C}NHNH\underset{\overset{\|}{S}}{C}NH(CH_2)_6NH\underset{\overset{\|}{S}}{C}NHNH\underset{\overset{\|}{O}}{C}{-}Ar}$

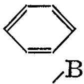
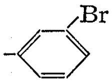
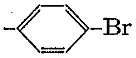
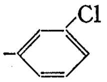
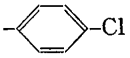
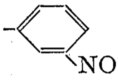
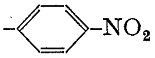
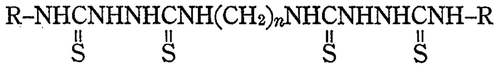
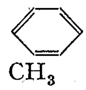
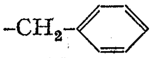
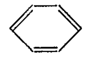
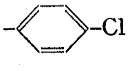
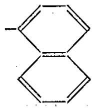
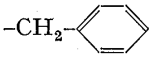
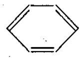
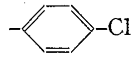
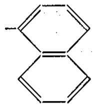
Compd. No.	n	Ar	mp (°C) ( ): Cryst. solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N
XXXII	6		245—246 (DMF)	prisms	$C_{22}H_{28}O_2N_6S_2$	55.92 (55.63)	5.97 (5.96)	17.97 (17.73)
XXXIII	6		205—206 (DMF–MeOH)	prisms	$C_{22}H_{26}O_2N_6Br_2S_2$	41.91 (41.65)	4.16 (4.25)	13.33 (13.25)
XXXIV	6		208—209 (DMF–MeOH)	prisms	$C_{22}H_{26}O_2N_6Br_2S_2$	41.91 (41.79)	4.16 (4.43)	13.33 (13.37)
XXXV	6		251—252 (DMF)	prisms	$C_{22}H_{26}O_2N_6Cl_2S_2$	48.79 (48.60)	4.84 (4.69)	15.52 (15.31)
XXXVI	6		194—196 (THF)	prisms	$C_{22}H_{26}O_2N_6Cl_2S_2$	48.79 (48.64)	4.84 (4.95)	15.52 (15.52)
XXXVII	6		211—212 (DMF–95%EtOH)	light yellow prisms	$C_{22}H_{26}O_6N_8S_2$	46.96 (47.20)	4.66 (4.67)	19.92 (19.78)
XXXVIII	6		202—204 (DMF)	light yellow prisms	$C_{22}H_{26}O_6N_8S_2$	46.96 (47.20)	4.66 (4.67)	19.92 (19.79)

Table IV. 1,1′-Dialkyl- or 1,1′-Diaryl-6,6′-alkylene-bis(bithioureas)



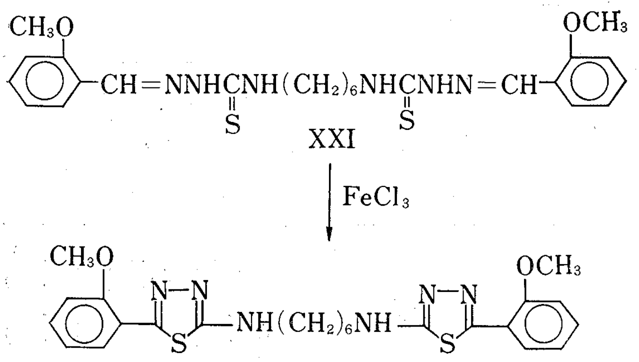
$\mathrm{R{-}NH\underset{\overset{\|}{S}}{C}NHNH\underset{\overset{\|}{S}}{C}NH(CH_2)_{\mathit{n}}NH\underset{\overset{\|}{S}}{C}NHNH\underset{\overset{\|}{S}}{C}NH{-}R}$

Compd. No.	n	R	mp (°C) ( ): Cryst. solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	F
XXXIX	2	CH_3	204—205 (DMF)	prisms	$C_8H_{18}N_8S_4$	27.09 (26.98)	5.11 (5.08)	31.60 (31.25)
XL	2	$-CH_2CH_3$	211 (DMF)	prisms	$C_{10}H_{22}N_8S_4$	31.39 (31.08)	5.79 (5.77)	29.28 (29.20)
XLI	2	$-CH_2CH=CH_2$	207—208 (DMF)	prisms	$C_{12}H_{22}N_8S_4$	35.44 (35.60)	5.45 (5.44)	27.56 (27.56)
XLII	2	$-C_4H_9$-iso	214—215 (DMF)	prisms	$C_{14}H_{30}N_8S_4$	38.33 (38.30)	6.89 (6.88)	25.54 (25.40)
XLIII	2		196—198 (DMF–H_2O)	prisms	$C_{18}H_{22}N_8S_4$	45.16 (45.08)	4.63 (4.55)	23.41 (23.40)
XLIV	3	CH_3	199—200 (DMF–EtOH)	prisms	$C_9H_{20}N_8S_4$	29.33 (29.41)	5.47 (5.30)	30.40 (30.21)
XLV	3	$-CH_2CH_3$	202—203 (DMF–EtOH)	prisms	$C_{11}H_{24}N_8S_4$	33.31 (33.94)	6.10 (6.10)	28.25 (28.10)
XLVI	3	$-CH_2CH=CH_2$	201—202 (DMF–EtOH)	prisms	$C_{13}H_{24}N_8S_4$	37.12 (37.40)	5.75 (5.88)	26.64 (26.44)
XLVII	3	$-C_4H_9$-iso	203—204 (DMF–EtOH)	prisms	$C_{15}H_{32}N_8S_4$	39.79 (39.89)	7.13 (7.18)	24.75 (25.05)
XLVIII	3		204—205 (DMF–EtOH)	prisms	$C_{21}H_{28}N_8S_4$	48.43 (48.20)	5.42 (5.67)	21.52 (21.40)
IL	3		202—202.5 (DMF–EtOH)	prisms	$C_{19}H_{34}N_8S_4$	45.38 (45.35)	6.82 (7.11)	22.29 (21.81)
L	3		185 (DMF–EtOH)	prisms	$C_{19}H_{24}N_8S_4$	46.31 (46.28)	4.91 (5.16)	22.74 (22.66)
LI	3		197—198 (DMF–EtOH)	prisms	$C_{19}H_{22}N_8Cl_2S_4$	40.63 (40.91)	3.95 (3.99)	19.95 (19.80)

Compd. No.	n	R	mp (°C) ( ): Cryst. solvent	Appearance (colorless)	Formula	Analysis (%) Calcd. (Found) C	H	N
LII	3		188 (DMF–EtOH)	prisms	$C_{27}H_{28}N_8S_4$	54.70 (54.95)	4.76 (4.60)	18.90 (18.90)
LIII	6	CH_3	204—205 (DMF)	prisms	$C_{12}H_{26}N_8S_4$	35.10 (35.52)	6.38 (6.64)	27.29 (27.07)
LIV	6	$-CH_2CH_3$	212—213 (DMF)	prisms	$C_{14}H_{30}N_8S_4$	38.33 (38.70)	6.89 (7.06)	25.54 (25.33)
LV	6	$-CH_2CH=CH_2$	203.5—204 (DMF–EtOH)	prisms	$C_{16}H_{30}N_8S_4$	41.53 (41.25)	6.54 (6.31)	24.22 (24.32)
LVI	6	C_4H_9-iso	207.5—208 (DMF)	prisms	$C_{18}H_{38}N_8S_4$	43.69 (43.81)	7.74 (7.62)	22.65 (22.66)
LVII	6		214—215 (DMF)	prisms	$C_{24}H_{34}N_8S_4$	51.21 (51.22)	6.09 (6.19)	19.91 (19.97)
LVIII	6		214—215 (DMF)	prisms	$C_{22}H_{42}N_8S_4$	48.31 (48.02)	7.74 (7.81)	20.49 (20.27)
LIX	6		182—183 (DMF)	prisms	$C_{22}H_{30}N_8S_4$	49.41 (48.94)	5.66 (5.77)	20.96 (21.05)
LX	6		191—192 (DMF)	prisms	$C_{22}H_{28}N_8Cl_2S_2$	43.77 (43.60)	4.68 (4.70)	18.56 (18.36)
LXI	6		193—193.5 (DMF)	prisms	$C_{30}H_{34}N_8S_4$	56.71 (56.68)	5.39 (5.20)	17.64 (17.73)

(XLIII to LXV) accomplished by treating 4,4'-alkylene-bis(thiosemicarbazides)(I, II, III, VI) with two equivalent of alkyl or aryl isothiocyanate. The reaction scheme and the resulting compounds are shown in Chart 2 and Table II, III and IV.

Since the thiadiazole group has been of great interest for antimicrobials according to the report of Schreus,[3] the ring closure of 1,1'-bis(2-methoxybenzylidene)-4,4'-hexamethylene-bis(thiosemicarbazide) (XXI) was attempted by reaction of XXI with ferric chloride by refluxing in tetrahydrofuran to afford N,N'-hexamethylene-bis[2-amino-5-(2-methoxyphenyl)thiadiazole] (LXII) in a good yield (see Chart 3).



LXII

Chart 3

Experimental

All melting points are determined in open capillary tubes and are uncorrected. Infrared spectra are measured on Shimadzu Model IR-60 spectrophotometer.

4,4'-Alkylene-bis(thiosemicarbazides) (I to VIII)——To a solution of alkylene diisothiocyanate (1 mole) in $CHCl_3$ a solution of hydrazines or substituted hydrazines (2 moles) in $CHCl_3$ was added dropwise under ice-cooling. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent (see Table I).

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[3] H. th. Schreus, *Klin. Woch*, **21**, 14 (1949).

1,1′-Dibenzylidene-4,4′-alkylene-bis(thiosemicarbazides) (IX to XXXI)——A solution of arylaldehyde (2 mole) in DMF was added to a solution of 4,4′-alkylene-bis(thiosemicarbazides) (1 mole) in DMF, and the mixture was warmed at 40—50° for 2—5 hr. The resulting precipitate was collected by filtration and recrystallized from a suitable solvent (see Table II).

1,1′-Diaroyl-4,4′-hexamethylene-bis(thiosemicarbazides) (XXXII to XXXVIII)——A solution of aroyl chloride (2 mole) in DMF was added to a solution of VI (2 mole) in DMF at 0°, the mixture was warmed at 40—45° for 1—3 hr, and concentrated under reduced pressure. The residue obtained was recrystallized from a suitable solvent (see Table III).

1,1′-Dialkyl- or 1,1′-Diaryl-6,6′-alkylene-bis(bithioureas) (XXXIX to LXI)——To a solution of 0.1 mole of 4,4′-alkylene-bis(thiosemicarbazides) dissolved in 50 ml of DMF, 0.2 mole of alkyl or aryl isothiocyanates was added under ice-cooling and the mixture was kept at room temperature for 24—48 hr. The solvent was removed by distillation under reduced pressure and the residue was recrystallized from an appropriate solvent (see Table IV).

N,N′-Hexamethylene-bis[2-amino-5-(2-methoxyphenyl)thiadiazole] (LXII)——To a solution of 1.1 g (0.025 mole) of XXI in 50 ml of THF and 10 ml of H_2O solution of 0.9 g (0.075 mole) of $FeCl_3$ in 20 ml of EtOH was added. The reaction mixture was heated at 70° for 1 hr, concentrated, and the resulting precipitate collected by filtration was recrystallized from EtOH to light yellow prisms, mp 180—181°. Yield, 0.7 g (57.8 %). *Anal.* Calcd. for $C_{24}H_{28}O_2N_6S_2$: C, 58.03; H, 5.58; N, 16.92. Found: C, 57.83; H, 5.85; N, 16.58.

Acknowledgement The authors express their deep gratitude to Professor Haruo Saikachi, Kobe Gakuin University, for his encouragement throughout the course of this work. Thanks are also due to the Analytical Center of Kyoto University for elementary analyses.

[Chem. Pharm. Bull. 23(3) 673—676 (1975)]

UDC 615.011.4.014

Caking of δ-D-Gluconolactone Powder

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(Received July 8, 1974)

The sorption of water vapor and the caking behavior of δ-D-gluconolactone (DGL) have been studied. Severe caking of DGL was observed only when both the humidifying and the subsequent drying procedure were taken on it. The crushing strength of the cake increased with an increase in the amount of water evaporated in the drying process. These results may prove the conception that caking is mainly caused by solid bridges formed by the crystallization of dissolved DGL. The caking of DGL was influenced by the compaction state of powder beds. The crushing strength showed a trend to increase with decreasing porosity. It may be due to the increase in the number of total contact points between powder particles.

Powdered materials often exhibit to become caked during storage, reducing their commercial value. In the case of inorganic salts, sugar, feritilizers, *etc.*, it has been considered that caking is mainly caused by crystallization of dissolved substances from the saturated solutions formed on the surface of powder particles due to moisture sorption.[2] Factors known to affect caking of powders include moisture content, temperature, particle size, pressure under which the material is stored and time of storage. The effect of these factors on the extent of caking varies with materials. In addition, the actual caking phenomena are

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[1] Location: *a) Tempaku-cho, Tempaku-ku, Nagoya*; *b) Kashima-cho, Higashiyodogawa-ku, Osaka.*

[2] *e.g.* R.R. Irani, C.F. Callis, and T. Lin, *Ind. Eng. Chem.*, **51**, 1285 (1959); W.B. Pietsch, *Trans. Am. Soc. Mech. Eng., Ser. b.* (*J. Eng. Ind.*) **91**, 435; Y. Peleg and C.H. Mannheim, *J. Food Technol.*, **4**, 157 (1969).