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Anticoccidials. II.[1] Autoxidation and Structural Determination of 1-Benzylamino-3-substituted Guanidines

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In connection with our studies on anticoccidial agents, some 1-(4-chlorobenzylamino)-3-substituted guanidine tosylates (**3**) were prepared. The structure of the aminoguanidines was proven by autoxidation of **3** into the corresponding benzylideneaminoguanidine (**5**).

Keywords——Anticoccidial; base catalyzed autoxidation; structural determination; aminoguanidine; NMR

Discovery of the potent anticoccidial agent, robenidine [1,3-bis(4-chlorobenzylideneamino)guanidine hydrochloride],[3] prompted us to synthesize some substituted aminoguanidines. Treatment of substituted hydrazines with 2-methyl-2-isothiourea sulfate affords monosubstituted aminoguanidines of type **3** or **4**, depending upon the site of guanylation. The structure of these monosubstituted aminoguanidines has been determined by several methods.[4] Here we report on their preparation and facile structural determination using a new autoxidation of the disubstituted aminoguanidines obtained from 4-chlorobenzylhydrazine (**1**) and 1-substituted 2-methyl-2-isothiourea hydriodide (**2**) (Chart 1).

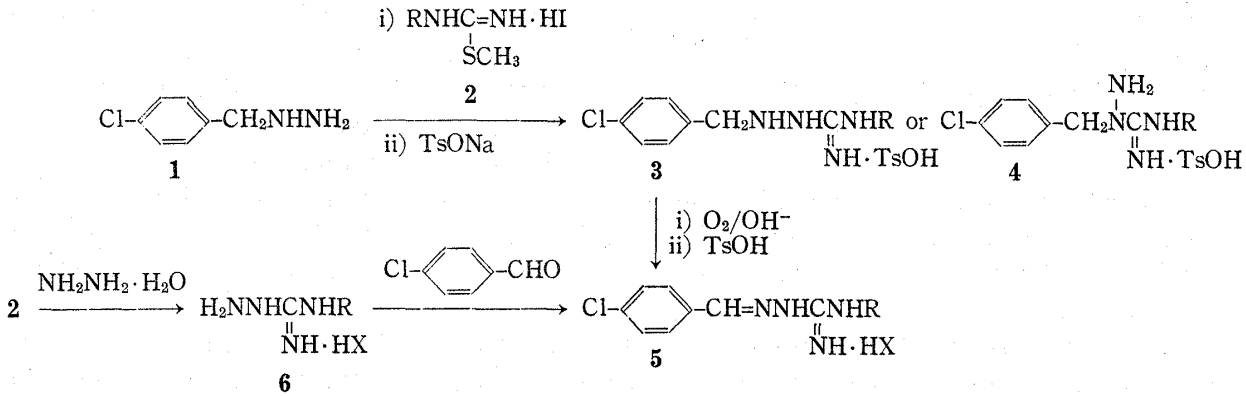

Chart 1

Reaction of 1-[2-(4-chlorophenoxy)ethyl]-2-methyl-2-isothiourea hydriodide (**2a**), prepared by known procedure,[4b] with **1**[5] in *n*-butanol and subsequent treatment of the product with

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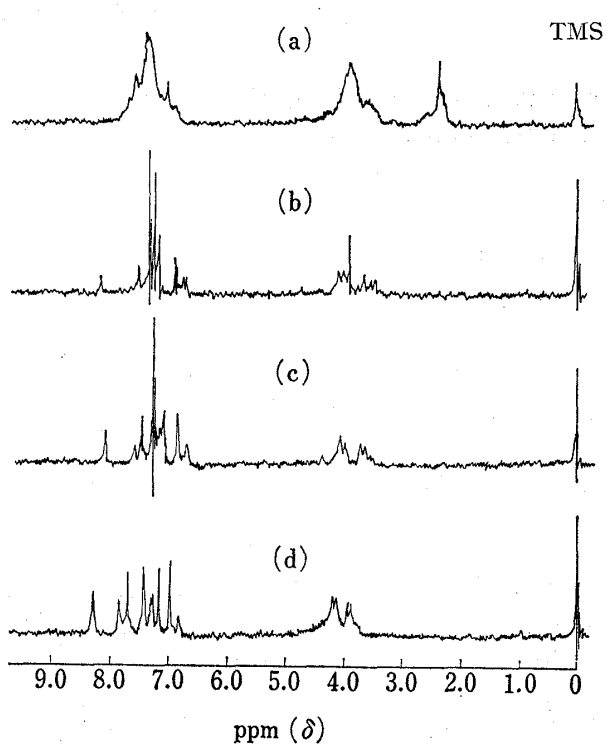


Fig. 1. NMR Spectra (60 MHz)

(a) 1-(4-Chlorobenzylamino)-3-[2-(4-chlorophenoxy) ethyl]-guanidine tosylate (**3a**) (DMSO-d_6).
(b) 3 hr after addition of $NaOD/D_2O$ and extraction with $CDCl_3$ ($CDCl_3$).
(c) 19 hr after addition of $NaOD/D_2O$ and extraction with $CDCl_3$ ($CDCl_3$).
(d) 1-(4-Chlorobenzylideneamino)-3-[2-(4-chlorophenoxy)-ethyl]guanidine (**5a**) hydriodide ($CDCl_3$).

an aqueous solution of sodium *p*-toluenesulfonate gave 1-(4-chlorobenzylamino)-3-[2-(4-chlorophenoxy)ethyl]guanidine tosylate (**3a**) as a single product in 28% yield. Its structure was confirmed as follows. The nuclear magnetic resonance (NMR) spectrum of **3a** was measured in dimethylsulfoxide (DMSO)-d_6. Then $NaOD/D_2O$ and $CDCl_3$ were added in excess to the solution and the mixture was shaken. After it had stood at room temperature for 3 and 19 hr, the NMR spectrum of the $CDCl_3$ layer was determined. The peak of benzyl protons of **3a** gradually disappeared and a new peak assigned to benzylidene proton appeared. The spectrum was similar to that of 1-(4-chlorobenzylideneamino)-3-[2-(4-chlorophenoxy)ethyl]guanidine (**5a**) hydriodide (Fig. 1). The oxidation product (68% yield) isolated from the $CDCl_3$ layer as tosylate was identical in all respects with **5a** tosylate which was prepared by condensation of 1-amino-3-[2-(4-chlorophenoxy)-ethyl]guanidine (**6a**) hydrochloride[4b] with *p*-chlorobenzaldehyde followed by treatment with sodium *p*-toluenesulfonate. These results proved that the structure of the aminoguanidine was **3a**, not **4a**.

Further investigation of the oxidation revealed that the reaction was accelerated in the presence of excess base, such as sodium hydroxide or potassium *tert*-butoxide but depressed by bubbling of nitrogen. This suggests that the reaction is the autoxidation[6] caused by dissolved oxygen and catalized by base.

Similarly, 1-(4-chlorobenzylamino)-3-(4-chlorophenethyl)guanidine tosylate (**3b**) was converted under the same conditions into the corresponding benzylideneaminoguanidine (**5b**)

Table I. Isothioureas

$$RNHC(=NH\cdot HI)SCH_3$$

Compd. No.	R	Recrystn. solvent	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	$4\text{-}ClC_6H_4OCH_2CH_2$	EtOH–ether	84	139—141	$C_{10}H_{13}ClN_2OS\cdot HI$	32.23 (31.95)	3.79 (3.66)	7.52 (7.26)
2b	$4\text{-}ClC_6H_4CH_2CH_2$	EtOH–ether	97	132—133	$C_{10}H_{13}ClN_2S\cdot HI$	33.68 (33.88)	3.96 (3.94)	7.85 (7.94)

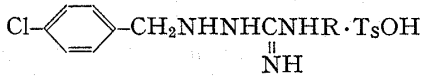
a) Determined with a Yanagimoto micro melting point apparatus.

6) H. Meister, *Ann. Chem.*, **679**, 83 (1964); O. Neunhoeffer and G. Lehmann, *Chem. Ber.*, **94**, 2960 (1961); L. Horner and J. Dehnert, *ibid.*, **96**, 786 (1963); G.M. Coppinger, *Tetrahedron*, **18**, 61 (1962).

tosylate in 55% yield. The reaction may be applicable to structural determination of the other aminoguanidines and related compounds.

All compounds studied are listed in Tables I to IV. None showed potent anticoccidial activity.[1)]

Table II. Benzylaminoguanidines



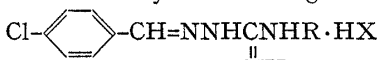
Compd. No.	R	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
3a	4-$ClC_6H_4OCH_2CH_2$	EtOH–petr. benzine	28	152—154.5	$C_{16}H_{18}Cl_2N_4O \cdot C_7H_8O_3S$	52.57 (52.41)	4.99 (4.74)	10.66 (10.68)
3b	4-$ClC_6H_4CH_2CH_2$	EtOH–ether	32	166—167	$C_{16}H_{18}Cl_2N_4 \cdot C_7H_8O_3S \cdot 1/4H_2O$	53.75 (53.74)	5.20 (5.06)	10.90 (10.93)

Table III. Aminoguanidines

Compd. No.	R	HX	Recrystn. solvent	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
6a	4-$ClC_6H_4OCH_2CH_2$	HCl	isoPrOH–ether	74	140—141	$C_9H_{13}ClN_4O \cdot HCl \cdot 1/4\ H_2O$	40.08 (40.11)	5.42 (4.89)	20.78 (20.91)
6b	4-$ClC_6H_4CH_2CH_2$	TsOH[a)]	EtOH–ether	56	157—159	$C_9H_{13}ClN_4 \cdot C_7H_8O_3S$	49.93 (49.93)	5.50 (5.40)	14.56 (14.50)

a) Hydriodide and hydrochloride: syrup.

Table IV. Benzylideneaminoguanidines



Compd. No.	R	HX	Recrystn. solvent	Yield[a)] (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
5a	4-$ClC_6H_4OCH_2CH_2$	HI	isoPrOH–ether	79[b)]	158—159.5	$C_{16}H_{16}Cl_2N_4O \cdot HI$	40.10 (40.09)	3.58 (3.52)	11.69 (11.69)
		HCl	EtOH–ether	91	182—183	$C_{16}H_{16}Cl_2N_4O \cdot HCl \cdot 1/2H_2O$	48.44 (48.60)	4.57 (4.24)	14.12 (14.26)
		TsOH	EtOH		180—182	$C_{16}H_{16}Cl_2N_4O \cdot C_7H_8O_3S$	52.77 (52.71)	4.62 (4.52)	10.70 (10.70)
5b	4-$ClC_6H_4CH_2CH_2$	HI	isoPrOH–EtOH	33[b)]	85—95	$C_{16}H_{16}Cl_2N_4 \cdot HI \cdot 1/2C_3H_8O$	42.57 (42.16)	4.39 (4.37)	11.35 (11.46)
		TsOH	EtOH	21	200—202	$C_{16}H_{16}Cl_2N_4 \cdot C_7H_8O_3S$	54.44 (54.44)	4.77 (4.67)	11.04 (11.02)

a) Prepared by condensation of aminoguanidine salts with *p*-chlorobenzaldehyde.
b) Based on 2-methyl-2-isothiourea.

Experimental

NMR spectra were recorded with a Varian T-60 spectrometer (60 MHz) using tetramethylsilane (TMS) as an internal standard.

1-[2-(4-Chlorophenoxy)ethyl]-2-methyl-2-isothiourea Hydriodide (2a)——A mixture of 1-[2-(4-chlorophenoxy)ethyl]thiourea (1.15 g, 5 mmol) and methyl iodide (850 mg, 6 mmol) in EtOH (10 ml) was heated under reflux for 1 hr. The solution was evaporated and then ether was added to the residne. The crystalline product obtained was recrystallized giving colorless needles.

1-(4-Chlorobenzylamino)-3-[2-(4-chlorophenoxy)ethyl]guanidine Tosylate (3a)——A solution of 4-chlorobenzylhydrazine (**1**), obtained from **1** hydrochloride (240 mg, 1.2 mmol) and aqueous NaOH, and **2a** (373 mg, 1 mmol) in *n*-butanol (4 ml) was heated under reflux for 4 hr. The solvent was removed *in vacuo* and the residue was dissolved in a small amount of EtOH. To the solution, sodium *p*-toluenesulfonate (300 mg) in H_2O was added. The resulting solid was collected and recrystallized giving colorless prisms.

1-Amino-3-[2-(4-chlorophenoxy)ethyl]guanidine Hydrochloride (6a)——A mixture of **2a** (3.73 g, 10 mmol) and 90% hydrazine hydrate (556 mg, 10 mmol) in EtOH (30 ml) was heated under reflux for 3 hr. The solvent was removed *in vacuo* and the residual oil was dissolved in EtOH (30 ml). To the solution, silver chloride (2.86 g, 20 mmol) was added and the mixture was stirred for 2 hr in the dark. After removal of the solid by filtration, the filtrate was concentrated *in vacuo*. Treatment of the residue with ether afforded crystals which were collected and recrystallized giving colorless needles.

1-(4-Chlorobenzylideneamino)-3-[2-(4-chlorophenoxy)ethyl]guanidine (5a) Hydrochloride and 5a Tosylate——A solution of **6a** (265 mg, 1 mmol) and *p*-chlorobenzaldehyde (148 mg, 1.1 mmol) in EtOH (4 ml) was heated under reflux for 2 hr. The solution was taken to dryness and the residue was recrystallized to yield colorless needles (361 mg) of **5a** hydrochloride.

To a solution of **5a** hydrochloride (188 mg, 0.45 mmol) in EtOH (5 ml) was added sodium *p*-toluenesulfonate (131 mg, 0.68 mmol) in H_2O (1 ml). The resulting crystals were collected, washed with H_2O and recrystallized giving 149 mg (62% yield) of colorless needles of **5a** tosylate.

Conversion of 3a into 5a Tosylate——After determination of the NMR spectrum of **3a** (50 mg) in DMSO-d_6 (0.5 ml), 1 N NaOD (0.2 ml) and $CDCl_3$ (0.4 ml) were added to the solution and the mixture was shaken. The $CDCl_3$ layer was separated and spectra were taken 3 and 19 hr later. The solvent was removed *in vacuo* and the residue was extracted with ether. The etheral solution was washed with aqueous NaOH and saturated NaCl solution. After drying over anhydrous K_2CO_3, the ether was evaporated and the residue was dissolved in EtOH. To the solution, *p*-toluenesulfonic acid (50 mg) in H_2O was added. The resulting precipitate was collected and recrystallized from EtOH giving 34 mg (68% yield) of colorless prisms. mp 180—182°. UV λ_{max}^{EtOH} nm (ε): 288 (21000).

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