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-isothiurea 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-isothiurea hydriodide (2) (Chart 1).

Chart 1

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

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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 ₆ H ₄ OCH ₂ CH ₂	EtOH-petr. benzine	28	152—154.5	C ₁₆ H ₁₈ Cl ₂ N ₄ O · C ₇ H ₈ O ₃ S	52.57 (52.41)	4.99 (4.74)	10.66 (10.68)
3b	4-ClC ₆ H ₄ CH ₂ CH ₂	EtOH-ether	32	166—167	C ₁₆ H ₁₈ Cl ₂ N ₄ · C ₇ H ₈ O ₃ S · 1/4H ₂ O	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 ₆ H ₄ OCH ₂ CH ₂	HCl	isoPrOH-ether	74	140—141	C ₉ H ₁₃ ClN ₄ O · HCl · 1/4 H ₂ O	40.08 (40.11)	5.42 (4.89)	20.78 (20.91)
6b	4-ClC ₆ H ₄ CH ₂ CH ₂	TsOH ^{a)}	EtOH-ether	56	157—159	C ₉ H ₁₃ ClN ₄ · C ₇ H ₈ O ₃ S	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 ₆ H ₄ OCH ₂ CH ₂	HI	isoPrOH-ether	79 ^{b)}	158—159.5	C ₁₆ H ₁₆ Cl ₂ N ₄ O · HI	40.10 (40.09)	3.58 (3.52)	11.69 (11.69)
		HCl	EtOH-ether	91	182—183	C ₁₆ H ₁₆ Cl ₂ N ₄ O · HCl · 1/2H ₂ O	48.44 (48.60)	4.57 (4.24)	14.12 (14.26)
		TsOH	EtOH		180—182	C ₁₆ H ₁₆ Cl ₂ N ₄ O · C ₇ H ₈ O ₃ S	52.77 (52.71)	4.62 (4.52)	10.70 (10.70)
5b	4-ClC ₆ H ₄ CH ₂ CH ₂	HI	isoPrOH-EtOH	33 ^{b)}	85—95	C ₁₆ H ₁₆ Cl ₂ N ₄ · HI · 1/2C ₃ H ₈ O	42.57 (42.16)	4.39 (4.37)	11.35 (11.46)
		TsOH	EtOH	21	200—202	C ₁₆ H ₁₆ Cl ₂ N ₄ · C ₇ H ₈ O ₃ S	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-isothiurea.

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 residue. 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 H₂O 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 H₂O (1 ml). The resulting crystals were collected, washed with H₂O 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 CDCl₃ (0.4 ml) were added to the solution and the mixture was shaken. The CDCl₃ 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 ethereal solution was washed with aqueous NaOH and saturated NaCl solution. After drying over anhydrous K₂CO₃, the ether was evaporated and the residue was dissolved in EtOH. To the solution, *p*-toluenesulfonic acid (50 mg) in H₂O was added. The resulting precipitate was collected and recrystallized from EtOH giving 34 mg (68% yield) of colorless prisms. mp 180–182°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 288 (21000).

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