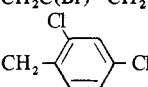
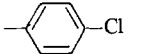

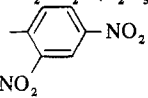



Table I. 1,4-Disubstituted Piperazines (II)

No.	R	X	Yield, %	Mp, ^a °C	Procedure ^b	Reaction ^c time, hr	Recrystn ^d solvent	Formula	Analy- ses
1	H	H(HCl)	75	290 dec	A	8	A	C ₁₁ H ₁₃ N ₃ S·HCl	Cl, S
2	H	CON(C ₂ H ₅)	54	86-87	B	0.5 (60°)	B	C ₁₆ H ₂₂ N ₄ OS	N, S
3	H	CH ₃	58	89-90	B	48 (room temp)	B	C ₁₂ H ₁₅ N ₃ S	N, S
4	H	CHO	83	142-143	B	1 (50°)	S + C	C ₁₂ H ₁₃ N ₃ OS	N, S
5	H	CH ₂ C ₆ H ₅	92	134-135	C	4	B + C	C ₁₈ H ₁₉ N ₃ S	N, S
6	H	CH ₂ C(Br)=CH ₂	89	140-141	C	3	B	C ₁₄ H ₁₆ BrN ₃ S	Br, N, S
7			47	136-137	C	3	E (first), N (second)	C ₁₈ H ₁₇ Cl ₂ N ₃ S	Cl, N, S
8	H	(CH ₂) ₄ CH ₃	60	89-89.5	C	1.8	F	C ₁₆ H ₂₃ N ₃ S	N, S
9	H	NO	68	129-130	e		G	C ₁₁ H ₁₂ N ₄ OS	N, S
10	H	CH(C ₆ H ₅) ₂	57	166.5-167.5	C	1.5	H	C ₂₄ H ₂₃ N ₃ S	N, S
11	H	CH ₂ COOH	54	263 dec	C	1.8 (room temp)	I	C ₁₃ H ₁₅ N ₃ O ₂ S	N, S
12	O ₂ N	H(HCl)	26	250 dec	C	2 (room temp)	J	C ₁₁ H ₁₂ N ₄ O ₂ S·HCl	Cl, S
13	O ₂ N	CH ₂ CH ₂ N(C ₂ H ₅) ₂ ·HCl	54	248-250 dec	E	5 (room temp)	K	C ₁₇ H ₂₅ N ₅ O ₂ S·HCl	Cl, N
14	CH ₃ O	CH ₃	60	102.5-103.5	D	9	L	C ₁₃ H ₁₇ N ₃ OS	N, S
15	CH ₃ O	H	71	152-153	A	2.5	N + C	C ₁₂ H ₁₅ N ₃ OS	N, S
16	H	N=C(CH ₃) ₂	20	122-124	F	1	F (first), N (second)	C ₁₄ H ₁₈ N ₄ S	N, S
17	CH ₃ O	CH ₂ C ₆ H ₅	60	111-112	E	10	L	C ₁₉ H ₂₁ N ₃ OS	N, S
18	H	CH ₂ CONHCONHCH ₃	83	205-207	C	1	O	C ₁₅ H ₁₉ N ₅ O ₂ S	N, S
19	H		70	208	E	1.5	E + T (1:3)	C ₁₇ H ₁₆ ClN ₃ S	N, S
20	H	N=CH- 	65	165-166	F	1	N + H (1:1)	C ₁₇ H ₁₇ N ₃ S	N, S
21	H	CH ₂ CH ₂ N(C ₂ H ₅) ₂	58	54.5-55	E	1.8	P	C ₁₇ H ₂₆ N ₄ S	N, S
22 ^f	H	CH ₃	82	80-81	D	9	L (first), R (second)	C ₁₂ H ₁₄ ClN ₃ S	N, S
23 ^f	H	CH ₂ CH ₂ OH	69	107.5-108.5	E	8.5	S + N (1:4)	C ₁₃ H ₁₆ ClN ₃ OS	N, S
24	OC ₂ H ₅	CH ₂ CH ₂ N(C ₂ H ₅) ₂	49	52-52.5	E	9.2	P	C ₁₉ H ₃₀ N ₄ OS	N, S
25	H		83	210-213	C	2 (room temp)	T	C ₁₇ H ₁₅ N ₅ O ₄ S	N, S
26	H	N=CH- 	71	201-202	F	1.3	U	C ₁₆ H ₁₅ N ₃ O ₃ S	N, S
27	H	COOCH ₂ CH ₂ CH ₃	84	88-89	C	h	N	C ₁₅ H ₁₉ N ₃ O ₂ S	N, S

^aMelting points (uncorr) were taken on a Fisher-Johns block. ^bThese procedures are described in the Experimental Section. ^cUnless otherwise specified, the reactions were carried out at reflux temps. ^dA, 92% O in water; B, petr ether (65-110°); C, CCl₄; E, acetone; F, O plus H₂O; G, O first, then triturated and washed with Et₂O; H, EtOAc; I, AcOH-MeOH; J, first O, second H₂O; K, abs O; L, petr ether (60-90°); N, petr ether (90-120°); O, EtOH; P, hexane; R, petr ether (30-60°); S, benzene; T, dioxane; U, not recrystd: washed with O then ether. ^ePrepd according to a lit. method for making 1-(p-chlorophenyl)-4-nitrosopiperazine.¹² ^fAlso bears Cl at the 4 position of the benzothiazole ring. ^gPrepd by acid treatment of 5-nitrofurfural diacetate followed by ether extn of the liberated aldehyde. ^hHeated to 60° for 5 min and set to stand overnight at room temp.

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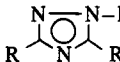
Synthesis of 1,2,4-Triazoles as Potential Hypoglycemic Agents

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Impetus for a study of triazoles was provided by a report that certain 4-alkyl-5-aryl-4H-1,2,4-triazole-3-thiols produced hypoglycemia in normal and alloxan-diabetic rats. The potency of these compounds was comparable to that of *N*¹-(p-tolylsulfonamido)-*N*³-(n-butyl)urea (tolbutamide) while their duration of action was greater.^{1,2} Consequently,

Table I. Substituted 1,2,4-Triazoles

							Formula ^a
No.	R	R ¹	R ²	Mp, °C	Recrystn solvent	% yield	
1	NH ₂	H	C ₆ H ₅ CH ₂ NH	148-149	C ₆ H ₅ -EtOH	28	C ₉ H ₁₁ N ₅
2	NH ₂	H	C ₆ H ₅ (CH ₂) ₂ NH	117-119	EtOAc-C ₆ H ₁₄	35	C ₁₀ H ₁₃ N ₅
3	NH ₂	H	<i>m</i> -CH ₃ C ₆ H ₄ NH	139-141	EtOAc-petr ether	24	C ₉ H ₁₁ N ₅
4	NH ₂	H	<i>o</i> -CH ₃ C ₆ H ₄ NH	164-166	H ₂ O	61	C ₉ H ₁₁ N ₅
5	NH ₂	H	<i>p</i> -CF ₃ C ₆ H ₄ NH	219-220	EtOAc-petr ether	57 ^b	C ₉ H ₈ F ₃ N ₅
6	NH ₂	H	<i>p</i> -FC ₆ H ₄ NH	204-205	Me ₂ CO-petr ether	22 ^b	C ₈ H ₈ FN ₅
7	NH ₂	H	<i>p</i> -CH ₃ OC ₆ H ₄ NH	201-202	H ₂ O	73	C ₉ H ₁₁ N ₅ O
8	NH ₂	H	<i>m</i> -ClC ₆ H ₄ NH	163-164	MeOH	30	C ₈ H ₈ ClN ₅
9	NH ₂	H	<i>p</i> -ClC ₆ H ₄ NH	243	MeOH	42	C ₈ H ₈ ClN ₅
10	NH ₂	H	α-C ₁₀ H ₇ NH	180-181	H ₂ O	67	C ₁₂ H ₁₁ N ₅
11	NH ₂	H	β-C ₁₀ H ₇ NH	202	EtOH-petr ether	35	C ₁₂ H ₁₁ N ₅
12	NH ₂	H	1-Adamantyl-NH	185-188	EtOAc-petr ether	30 ^b	C ₁₂ H ₉ N ₅
13	NH ₂	CH ₃	C ₆ H ₅ NH	216-218	EtOH	20 ^b	C ₉ H ₁₁ N ₅
14	NH ₂	CH ₃	C ₆ H ₅ CH ₂ S	104-106	H ₂ O	68 ^c	C ₁₀ H ₁₂ N ₄ S
15	NH ₂	CH ₃	SH	320-322 ^d	Base-acid	21 ^e	C ₃ H ₅ N ₄ S
16	NHAc	H	C ₆ H ₅ NH	178-179	MeC ₆ H ₅	38 ^f	C ₁₀ H ₁₁ N ₅ O
17	NHBz	H	C ₆ H ₅ NH	168-169	EtOH	53 ^f	C ₁₅ H ₁₃ N ₅ O
18	NHAc	H	C ₆ H ₅ CH ₂ S	153-154	EtOH-H ₂ O	74 ^f	C ₁₁ H ₁₂ N ₄ O
19	NHC ₆ H ₅	H	C ₆ H ₅ CH ₂ NH	204-205	EtOAc-petr ether	33	C ₁₅ H ₁₅ N ₅

^aAll compds were analyzed for C, H, N. ^bCyclization effected with aqueous 50% HOAc. ^cObtained by treating **15** with benzyl chloride. ^dWith dec. ^eCyclization effected with 3 N HCl. ^f**16** and **17** obtained by acylating **39**; **18** by acetylating 3-amino-5-benzylthio-1,2,4-triazole. ^g

Table II. 3-(Isopropylidenaminoamidino)-1-(substituted)thioureas

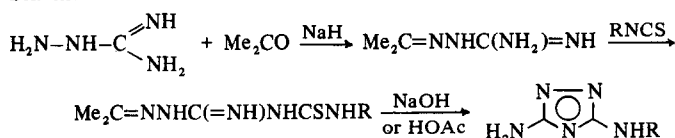
$\text{Me}_2\text{C}=\text{NN}-\text{CNHCNHR}$ $\begin{array}{c} \quad \parallel \quad \parallel \\ \text{R}^1 \text{ NH } \text{ S} \end{array}$							
No.	R	R ¹	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
20	C ₆ H ₅ CH ₂	H	92-94	CHCl ₃ -C ₆ H ₁₂	25	C ₁₂ H ₁₇ N ₅ S	C, H, N, S
21	C ₆ H ₅ (CH ₂) ₂	H	113-115	C ₆ H ₆ -petr ether	51	C ₁₃ H ₁₉ N ₅ S	C, H, N, S
22	<i>m</i> -CH ₃ C ₆ H ₄	H	160-161	EtOH	54	C ₁₂ H ₁₇ N ₅ S	C, H, N, S
23	<i>o</i> -CH ₃ C ₆ H ₄	H	162-164	MeOH	65	C ₁₂ H ₁₇ N ₅ S	C, H, N, S
24	<i>p</i> -CF ₃ C ₆ H ₄	H	172-173	CHCl ₃	45	C ₁₂ H ₁₄ F ₃ N ₅ S	C, H, N
25	<i>p</i> -FC ₆ H ₄	H	163-164	C ₆ H ₆	67	C ₁₁ H ₁₄ FN ₅ S	C, H, N, S
26	<i>p</i> -CH ₃ OC ₆ H ₄	H	163	MeOH	34	C ₁₂ H ₁₇ N ₅ OS	C, H, N, S
27	<i>m</i> -ClC ₆ H ₄	H	168-170	EtOH	60	C ₁₁ H ₁₄ ClN ₅ S	C, H, N
28	<i>p</i> -ClC ₆ H ₄	H	157-160	EtOH-H ₂ O	67	C ₁₁ H ₁₄ ClN ₅ S	C, H, N, S
29	α-C ₁₀ H ₇	H	137	MeCN	59	C ₁₅ H ₁₇ N ₅ S	<i>a</i>
30	β-C ₁₀ H ₇	H	163-164	EtOH	53	C ₁₅ H ₁₇ N ₅ S	C, H, N, S
31	1-Adamantyl	H	173-175	EtOH	35	C ₁₅ H ₂₅ N ₅ S	C, H, N, S
32	CH ₃	H	103-105	H ₂ O	81	C ₆ H ₁₃ N ₅ S	C, H, N
33	C ₂ H ₅	H	101-103	H ₂ O	70	C ₇ H ₁₅ N ₅ S	C, H, N
34	CH ₃ (CH ₂) ₆	H	58-60	EtOH-H ₂ O	24	C ₁₂ H ₁₅ N ₅ S	C, H, N
35	CH ₂ =CH CH ₂	H	103-105	EtOH-H ₂ O	75	C ₈ H ₁₅ N ₅ S	C, H, N
36	C ₆ H ₁₁	H	184-185	EtOAc	68	C ₁₁ H ₂₁ N ₅ S	C, H, N
37	C ₆ H ₅	CH ₃	168-169	EtOH	30	C ₁₂ H ₁₇ N ₅ S	C, H, N, S
38	C ₆ H ₅	CH ₃	165-167	EtOH	72	C ₁₆ H ₁₇ N ₅ S ^b	C, H, N, S

^aPurity detd spectrally and by tlc. ^bBenzal rather than isopropylidene derivative.

a series of novel 1,2,4-triazoles was prepared as shown in Scheme I.

Selected compounds were tested for hypoglycemia and/or antiobesity activity and were inactive.

Scheme I



Experimental Section†

3-(Isopropylideneaminoamidino)-1-aryl(alkyl)thioureas. To a stirred, cooled suspension of 0.2 mole of NaH in 280 ml of dry

†Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

Me₂CO was added carefully 0.1 mole of aminoguanidine sulfate. Care was taken to keep the temp below 25°. When the addn was complete, the mixt was stirred under reflux for 30 min. Heating was discont and 0.2 mole of the appropriate isothiocyanate was added rapidly. Heating was resumed for 2 hr (4 hr for alkyl isothiocyanates; method of Kurzer and coworkers).³ The mixt was poured into a large vol of ice H₂O and stirred. The pptd solid was filtered, suspended in 50% EtOH, stirred, refiltered, resuspended in Et₂O, stirred, filtered, and dried. It was best to follow the course of the reaction by tlc. In some instances a prolonged reaction time was required, e.g., **31** required a 90-hr reflux.

3-Amino-5-substituted-amino-1,2,4-triazoles, A. The thiourea (0.1 mole) was suspended in 300 ml of 1.5 N NaOH and stirred under reflux until soln was effected, and then for an addl 15 min. The soln was filtered into a large vol of ice H₂O and the filtrate was adjusted to pH 5-6 with HOAc. The product pptd as H₂S was evolved. The solid was filtered and the filtrate was extd with EtOAc. The EtOAc phases were washed in turn with H₂O, 5% NaHCO₃, and H₂O. After drying, the solvent was removed and the residue was combined with the initially formed solid and the whole purified.

B (5, 6, 12, 13). The thiourea (0.02 mole) and 125 ml of 50% aqueous HOAc were stirred under reflux until the solid dissolved

and then for an addl 30 min (H_2S evolved). The soln was filtered and cooled and the pH adjusted to 8 with aqueous NH_3 . The solid was filtered, washed, and purified.

Repeated attempts to cyclize the alkyl thioureas (20-36) to the corresponding diaminotriazoles were unsuccessful.

3-Acylamino-5-anilino-1,2,4-triazoles (16-18). The acyl chloride (0.03 mole) was added dropwise to a cooled, stirred soln of 0.03 mole of the aminotriazole in 250 ml of dry Me_2CO contg 3 ml of pyridine. Stirring was contd overnight at room temp and the soln was dild with cold H_2O . The pptd solid was filtered and purified.

3-Anilino-5-benzylamino-1,2,4-triazole (19). A mixt of 5.3 g (0.03 mole) of 39, 3.2 g (0.03 mole) of $PhCHO$, and Raney Ni in EtOH was hydrogenated at 80-120° under a pressure of 40-120

kg/cm² of H_2 .⁴ The catalyst was filtered and the filtrate was evapd to give the crude product.

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Book Reviews

Cyclic AMP. By G. Alan Robison, Reginald W. Butcher, and Earl W. Sutherland. Academic Press, New York, N. Y. 1971. xii + 531 pp. 16 × 23.5 cm. \$17.50.

This is the definitive book on cyclic nucleotides, their properties and functions, and on the enzymes that surround their biosynthesis and bioconversions. Beyond that, the authors take a broad experimental and philosophical view of the classification of biocatalysts, based on their relation to cyclic AMP. If their suggestions are adopted, our present semantics of hormones and vitamins will have to be revised, and we will have a more rational nomenclature in these fields. For the organic chemist, Th. Posternak has contributed a concise chapter on all chemical and synthetic aspects of cyclic nucleotides, and the biochemistry and pharmacology of cyclic nucleotides other than cyclic AMP are considered in a special chapter by Joel G. Hardman. The main body of the book is devoted to cyclic AMP,

and its relation to the actions of all kinds of hormones, especially the catecholamines, glucagon and insulin, and steroids. Professor Sutherland has introduced the book with an authoritative recollection of the events that led to the discovery of cyclic AMP, and the important role of lipolysis in these early experiments is reemphasized in a separate chapter on this subject. The text is written lucidly, and should be understandable to medical students and experimental biologists alike. At every juncture there are suggestions for further researches, and loopholes in the explanations of experimental observations are discussed with unbiased frankness. The authors deserve admiration and gratitude from their readers for pulling together thousands of facts and ideas in one of the most exciting fields of biochemistry and medicine.

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