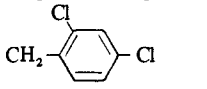
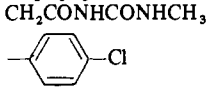
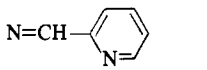
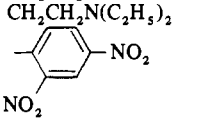
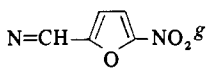
Table I. 1,4-Disubstituted Piperazines (II)

No.	R	X	Yield, %	Mp,[a] °C	Procedure[b]	Reaction[c] time, hr	Recrystn[d] solvent	Formula	Analyses
1	H	H(HCl)	75	290 dec	A	8	A	$C_{11}H_{13}N_3S \cdot HCl$	Cl, S
2	H	$CON(C_2H_5)$	54	86-87	B	0.5 (60°)	B	$C_{16}H_{22}N_4OS$	N, S
3	H	CH_3	58	89-90	B	48 (room temp)	B	$C_{12}H_{15}N_3S$	N, S
4	H	CHO	83	142-143	B	1 (50°)	S + C	$C_{12}H_{13}N_3OS$	N, S
5	H	$CH_2C_6H_5$	92	134-135	C	4	B + C	$C_{18}H_{19}N_3S$	N, S
6	H	$CH_2C(Br)=CH_2$	89	140-141	C	3	B	$C_{14}H_{16}BrN_3S$	Br, N, S
7			47	136-137	C	3	E (first), N (second)	$C_{18}H_{17}Cl_2N_3S$	Cl, N, S
8	H	$(CH_2)_4CH_3$	60	89-89.5	C	1.8	F	$C_{16}H_{23}N_3S$	N, S
9	H	NO	68	129-130	*e*		G	$C_{11}H_{12}N_4OS$	N, S
10	H	$CH(C_6H_5)_2$	57	166.5-167.5	C	1.5	H	$C_{24}H_{23}N_3S$	N, S
11	H	CH_2COOH	54	263 dec	C	1.8 (room temp)	I	$C_{13}H_{15}N_3O_2S$	N, S
12	O_2N	H(HCl)	26	250 dec	C	2 (room temp)	J	$C_{11}H_{12}N_4O_2S \cdot HCl$	Cl, S
13	O_2N	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	54	248-250 dec	E	5 (room temp)	K	$C_{17}H_{25}N_5O_2S \cdot HCl$	Cl, N
14	CH_3O	CH_3	60	102.5-103.5	D	9	L	$C_{13}H_{17}N_3OS$	N, S
15	CH_3O	H	71	152-153	A	2.5	N + C	$C_{12}H_{15}N_3OS$	N, S
16	H	$N=C(CH_3)_2$	20	122-124	F	1	F (first), N (second)	$C_{14}H_{18}N_4S$	N, S
17	CH_3O	$CH_2C_6H_5$	60	111-112	E	10	L	$C_{19}H_{21}N_3OS$	N, S
18	H	$CH_2CONHCONHCH_3$	83	205-207	C	1	O	$C_{15}H_{19}N_5O_2S$	N, S
19	H		70	208	E	1.5	E + T (1:3)	$C_{17}H_{16}ClN_3S$	N, S
20	H		65	165-166	F	1	N + H (1:1)	$C_{17}H_{17}N_5S$	N, S
21	H	$CH_2CH_2N(C_2H_5)_2$	58	54.5-55	E	1.8	P	$C_{17}H_{26}N_4S$	N, S
22[f]	H	CH_3	82	80-81	D	9	L (first), R (second)	$C_{12}H_{14}ClN_3S$	N, S
23[f]	H	CH_2CH_2OH	69	107.5-108.5	E	8.5	S + N (1:4)	$C_{13}H_{16}ClN_3OS$	N, S
24	OC_2H_5	$CH_2CH_2N(C_2H_5)_2$	49	52-52.5	E	9.2	P	$C_{19}H_{30}N_4OS$	N, S
25	H		83	210-213	C	2 (room temp)	T	$C_{17}H_{15}N_5O_4S$	N, S
26	H	 [g]	71	201-202	F	1.3	U	$C_{16}H_{15}N_5O_3S$	N, S
27	H	$COOCH_2CH_2CH_3$	84	88-89	C	*h*	N	$C_{15}H_{19}N_3O_2S$	N, S

[a] Melting points (uncorr) were taken on a Fisher-Johns block. [b] These procedures are described in the Experimental Section. [c] Unless otherwise specified, the reactions were carried out at reflux temps. [d] A, 92% O in water; B, petr ether (65-110°); C, CCl_4; E, acetone; F, O plus H_2O; G, O first, then triturated and washed with Et_2O; H, EtOAc; I, AcOH-MeOH; J, first O, second H_2O; 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. [e] Prepd according to a lit. method for making 1-(*p*-chlorophenyl)-4-nitrosopiperazine.[12] [f] Also bears Cl at the 4 position of the benzothiazole ring. [g] Prepd by acid treatment of 5-nitrofurfural diacetate followed by ether extn of the liberated aldehyde. [h] Heated to 60° for 5 min and set to stand overnight at room temp.

References

(1) M. Verderame, *J. Med. Chem.*, **9**, 153 (1966); *ibid.*, **11**, 1090 (1968).
(2) H. W. Stewart, R. J. Turner, and J. J. Denton, *J. Org. Chem.*, **13**, 144 (1948).
(3) B. W. Horrom, M. Freifelder, and G. R. Stone, *J. Amer. Chem. Soc.*, 77, 753 (1955).
(4) T. Fujii, Japanese Patent 7230 (1954); *Chem. Abstr.*, **50**, 10138 (1956).
(5) M. Delalande, French Patent M 3287 (Cl. A61k, CO7d, June 8, 1966); *Chem. Abstr.*, **63**, 13292 (1965).
(6) J. C. Craig, W. P. Rogers, and M. E. Tate, *Aust. J. Chem.*, **9**, 397 (1956); *Chem. Abstr.*, **51**, 1963 (1957).
(7) C. B. Pollard and T. H. Wickers, *J. Amer. Chem. Soc.*, **76**, 1853 (1954).
(8) R. C. Elderfield and F. W. Short, *J. Org. Chem.*, **18**, 1099 (1953).
(9) J. Metzger and H. Plank, *Bull. Soc. Chim. Fr.*, 1692 (1956); *Chem. Abstr.*, **52**, 2839 (1958).
(10) Y. Mizuno, K. Adachi, and K. Nakamura, *J. Pharm. Soc. Jap.*, 72, 1266 (1952); *Chem. Abstr.*, **47**, 12357 (1953).
(11) H. Aspelund, *Suom. Kemistiseuran, Tiedonantoja*, **49**, 49 (1940); *Chem. Abstr.*, **35**, 2144 (1941).
(12) E. A. Conroy, U. S. Patent 2663706 (Dec 22, 1953); *Chem. Abstr.*, **49**, 4730 (1955).

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

Benjamin Blank,* Diana M. Nichols, and Praful D. Vaidya

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101.

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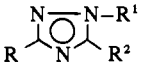
Impetus for a study of triazoles was provided by a report that certain 4-alkyl-5-aryl-4*H*-1,2,4-triazole-3-thiols produced hypoglycemia in normal and alloxan-diabetic rats. The potency of these compounds was comparable to that of N^1-(*p*-tolylsulfonamido)-N^3-(*n*-butyl)urea (tolbutamide) while their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

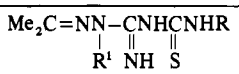
Table I. Substituted 1,2,4-Triazoles



No.	R	R^1	R^2	Mp, °C	Recrystn solvent	% yield	Formula[a]
1	NH_2	H	$C_6H_5CH_2NH$	148-149	C_6H_6-EtOH	28	$C_9H_{11}N_5$
2	NH_2	H	$C_6H_5(CH_2)_2NH$	117-119	EtOAc-C_6H_{14}	35	$C_{10}H_{13}N_5$
3	NH_2	H	*m*-$CH_3C_6H_4NH$	139-141	EtOAc-petr ether	24	$C_9H_{11}N_5$
4	NH_2	H	*o*-$CH_3C_6H_4NH$	164-166	H_2O	61	$C_9H_{11}N_5$
5	NH_2	H	*p*-$CF_3C_6H_4NH$	219-220	EtOAc-petr ether	57[b]	$C_9H_8F_3N_5$
6	NH_2	H	*p*-FC_6H_4NH	204-205	Me_2CO-petr ether	22[b]	$C_8H_8FN_5$
7	NH_2	H	*p*-$CH_3OC_6H_4NH$	201-202	H_2O	73	$C_9H_{11}N_5O$
8	NH_2	H	*m*-ClC_6H_4NH	163-164	MeOH	30	$C_8H_8ClN_5$
9	NH_2	H	*p*-ClC_6H_4NH	243	MeOH	42	$C_8H_8ClN_5$
10	NH_2	H	α-$C_{10}H_7NH$	180-181	H_2O	67	$C_{12}H_{11}N_5$
11	NH_2	H	β-$C_{10}H_7NH$	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]	$C_{12}H_9N_5$
13	NH_2	CH_3	C_6H_5NH	216-218	EtOH	20[b]	$C_9H_{11}N_5$
14	NH_2	CH_3	$C_6H_5CH_2S$	104-106	H_2O	68[c]	$C_{10}H_{12}N_4S$
15	NH_2	CH_3	SH	320-322[d]	Base-acid	21[e]	$C_3H_6N_4S$
16	NHAc	H	C_6H_5NH	178-179	MeC_6H_5	38[f]	$C_{10}H_{11}N_5O$
17	NHBz	H	C_6H_5NH	168-169	EtOH	53[f]	$C_{15}H_{13}N_5O$
18	NHAc	H	$C_6H_5CH_2S$	153-154	EtOH-H_2O	74[f]	$C_{11}H_{12}N_4O$
19	NHC_6H_5	H	$C_6H_5CH_2NH$	204-205	EtOAc-petr ether	33	$C_{15}H_{15}N_5$

[a] All compds were analyzed for C, H, N. [b] Cyclization effected with aqueous 50% HOAc. [c] Obtained by treating **15** with benzyl chloride.[3d] [d] With dec. [e] Cyclization effected with 3 *N* HCl. [f] **16** and **17** obtained by acylating **39**; **18** by acetylating 3-amino-5-benzylthio-1,2,4-triazole.[3d]

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



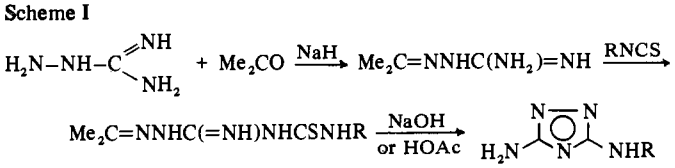
No.	R	R^1	Mp, °C	Recrystn solvent	% yield	Formula	Analyses
20	$C_6H_5CH_2$	H	92-94	$CHCl_3$-C_6H_{12}	25	$C_{12}H_{17}N_5S$	C, H, N, S
21	$C_6H_5(CH_2)_2$	H	113-115	C_6H_6-petr ether	51	$C_{13}H_{19}N_5S$	C, H, N, S
22	*m*-$CH_3C_6H_4$	H	160-161	EtOH	54	$C_{12}H_{17}N_5S$	C, H, N, S
23	*o*-$CH_3C_6H_4$	H	162-164	MeOH	65	$C_{12}H_{17}N_5S$	C, H, N, S
24	*p*-$CF_3C_6H_4$	H	172-173	$CHCl_3$	45	$C_{12}H_{14}F_3N_5S$	C, H, N
25	*p*-FC_6H_4	H	163-164	C_6H_6	67	$C_{11}H_{14}FN_5S$	C, H, N, S
26	*p*-$CH_3OC_6H_4$	H	163	MeOH	34	$C_{12}H_{17}N_5OS$	C, H, N, S
27	*m*-ClC_6H_4	H	168-170	EtOH	60	$C_{11}H_{14}ClN_5S$	C, H, N
28	*p*-ClC_6H_4	H	157-160	EtOH-H_2O	67	$C_{11}H_{14}ClN_5S$	C, H, N, S
29	α-$C_{10}H_7$	H	137	MeCN	59	$C_{15}H_{17}N_5S$	*a*
30	β-$C_{10}H_7$	H	163-164	EtOH	53	$C_{15}H_{17}N_5S$	C, H, N, S
31	1-Adamantyl	H	173-175	EtOH	35	$C_{15}H_{25}N_5S$	C, H, N, S
32	CH_3	H	103-105	H_2O	81	$C_6H_{13}N_5S$	C, H, N
33	C_2H_5	H	101-103	H_2O	70	$C_7H_{15}N_5S$	C, H, N
34	$CH_3(CH_2)_6$	H	58-60	EtOH-H_2O	24	$C_{12}H_{15}N_5S$	C, H, N
35	CH_2=CH CH_2	H	103-105	EtOH-H_2O	75	$C_8H_{15}N_5S$	C, H, N
36	C_6H_{11}	H	184-185	EtOAc	68	$C_{11}H_{21}N_5S$	C, H, N
37	C_6H_5	CH_3	168-169	EtOH	30	$C_{12}H_{17}N_5S$	C, H, N, S
38	C_6H_5	CH_3	165-167	EtOH	72	$C_{16}H_{17}N_5S$[b]	C, H, N, S

[a] Purity detd spectrally and by tlc. [b] Benzal 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 Me_2CO 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 discontd 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 H_2O and stirred. The pptd solid was filtered, suspended in 50% EtOH, stirred, refiltered, resuspended in Et_2O, 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 H_2O and the filtrate was adjusted to pH 5-6 with HOAc. The product pptd as H_2S was evolved. The solid was filtered and the filtrate was extd with EtOAc. The EtOAc phases were washed in turn with H_2O, 5% $NaHCO_3$, and H_2O. 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

†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 ±0.4% of the theoretical values.

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.

References

(1) M. Y. Mhasalkar, M. H. Shah, S. T. Nikam, K. G. Anantanarayanan, and C. V. Deliwala, *J. Med. Chem.*, **13**, 672 (1970).
(2) M. Y. Mhasalkar, M. H. Shah, S. T. Nikam, K. G. Anantanarayanan, and C. V. Deliwala, *ibid.*, **14**, 260 (1971).
(3) (a) L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, 3437 (1960); (b) *ibid.*, 3561 (1962); (c) F. Kurzer and K. Douraghi-Zadeh, *ibid.*, 932 (1965); (d) *ibid.*, 4448 (1965); (e) *ibid.*, 3912 (1965).
(4) M. Pesson and G. Polmanss, *C. R. Acad Sci.*, 247, 787 (1958).

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.

1922 South Ocean Lane
Fort Lauderdale, Florida
Alfred Burger