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Potential Antidiabetics VIII: 4-Arylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones, 4-Arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles, and 4-Arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles

H. G. GARG and CHANDRA PRAKASH

Abstract □ A series of 4-arylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones was synthesized for evaluation as antidiabetic agents from appropriate ethyl 2,3-dioxobutyrate 2-arylhydrazones and amino guanidine nitrate. Similarly, other series of compounds, *i.e.*, 4-arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles, and 4-arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles were synthesized by the cyclization of 3-arylhydrazono-2,3,4-pentanetriones and 1,3-diphenyl-2-arylhydrazono-1,2,3-propanetriones with amino guanidine nitrate, respectively.

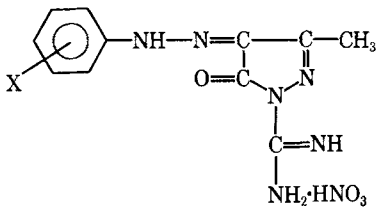
Keyphrases □ Pyrazole congeners—synthesis, screened for antidiabetic activity □ Antidiabetics, potential—pyrazole congeners synthesized, screened □ Hypoglycemic agents—pyrazole congeners synthesized, screened

Prompted by the observation (1) that 3,5-dimethylpyrazoles and isoxazoles lower the blood sugar, numerous congeners of pyrazoles were synthesized and their activity was assessed in these laboratories (2, 3). As a result of the role of *ν*-guanidobutyramide in lowering blood sugar and urea levels (4), the authors prepared several of the pyrazoles (I and II) containing two different biologically active moieties—*viz.*, guanyl and pyrazolyl.

4-Arylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones (Table I) were synthesized by the addition of a hot aqueous solution of amino guanidine nitrate to ethyl 2,3-dioxobutyrate 2-arylhydrazones under conditions similar to those used previously (5, 6).

4-Arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles (II*a*) and 4-arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles (II*b*) could not be obtained under these conditions, and a modified procedure was adopted. A hot aqueous solution of amino guanidine nitrate was added to an ethanolic solution of 3-phenylhydrazono-2,3,4-pentanetrione followed by 30% nitric acid until the pH of the reaction mixture became 1. The crystalline 4-phenylazo-*N'*-guanylnitrate-3,5-dimethylpyrazole started precipitating out after the reaction mixture was refluxed for 3 hr. and was allowed to stand for several hours at room temperature. By following similar conditions, other 4-arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles and 4-arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles were obtained. These derivatives are listed in Tables II and III.

All these compounds are highly colored and crystalline substances and are soluble in common organic solvents as well as in hot water.



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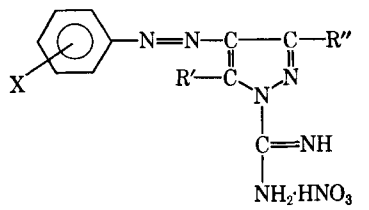

II*a*: R′ = R″ = CH_3

II*b*: R′ = R″ = C_6H_5

X = substituted phenyl

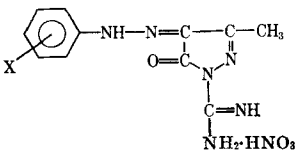

Table I—4-Arylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones (I)

No.	X	Yield, %	M.p.	Color[a]	Formula	Anal., % Calcd.	Found
1	2-NO_2	65	211°	DBN	$C_{11}H_{12}N_8O_6$	N, 31.81	N, 31.61
2	3-NO_2	65	233°	YN	$C_{11}H_{12}N_8O_6$	N, 31.81	N, 31.63
3	4-NO_2	70	251°	LtBN	$C_{11}H_{12}N_8O_6$	N, 31.81	N, 31.72
4	3-Cl	73	198°	VP	$C_{11}H_{12}ClN_7O_4$	Cl, 10.39	Cl, 10.29
5	4-Cl	75	245°	YN	$C_{11}H_{12}ClN_7O_4$	Cl, 10.39	Cl, 10.48
6	3-Me	60	221°	YP	$C_{12}H_{15}N_7O_4$	N, 30.52	N, 30.29
7	4-Me	68	223–225°	ON	$C_{12}H_{15}N_7O_4$	N, 30.52	N, 30.27
8	2-MeO	68	216°	ORP	$C_{12}H_{15}N_7O_5$	N, 29.08	N, 28.90
9	3-MeO	65	218°	DRN	$C_{12}H_{15}N_7O_5$	N, 29.08	N, 28.82
10	4-MeO	64	219°	ON	$C_{12}H_{15}N_7O_5$	N, 29.08	N, 28.64
11	4-EtO	70	218° (dec.)	ON	$C_{13}H_{17}N_7O_5$	N, 27.92	N, 27.68
12	4-SO_2NH_2	60	238°	YN	$C_{11}H_{14}N_8O_6S$	N, 29.01	N, 28.82
13	2,4-Me_2	64	235°	BN	$C_{13}H_{17}N_7O_4$	N, 29.25	N, 29.12
14	2,6-Me_2	65	204°	BN	$C_{13}H_{17}N_7O_4$	N, 29.25	N, 29.04
15	2,5-Cl_2	68	221°	GP	$C_{11}H_{11}Cl_2N_7O_4$	Cl, 18.88	Cl, 18.71
16	2,4-$(MeO)_2$	70	227°	BP	$C_{13}H_{17}N_7O_6$	N, 26.70	N, 26.57
17	2,5-$(MeO)_2$	70	189°	ChP	$C_{13}H_{17}N_7O_6$	N, 26.70	N, 26.52
18	2,5-$(EtO)_2$	72	136°	ChP	$C_{15}H_{21}N_7O_6$	N, 24.81	N, 24.61
19	4-Cl-2,5-$(MeO)_2$	60	252°	BP	$C_{13}H_{16}ClN_7O_6$	Cl, 8.84	Cl, 8.63
20	5-Cl-2,4-$(MeO)_2$	60	241°	BP	$C_{13}H_{16}ClN_7O_6$	Cl, 8.84	Cl, 8.59

[a] B, brown; Ch, chocolate; D, dark; G, golden; Lt, light; N, needles; O, orange; P, plates; R, red; V, violet; Y, yellow.

RESULTS

Few compounds of the series *N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones [namely, 4-phenylhydrazono-, 4-(3-nitrophenylhydrazono)-, 4-(3-methylphenylhydrazono)-, and 4-(4-methoxyphenylhydrazono)-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones] and of the series *N'*-guanylnitrate-3,5-dimethylpyrazoles [namely, 4-(2-nitrophenylazo)-, 4-(4-chlorophenylazo)-, 4-(3-methylphenylazo)-, 4-(2,4-dimethylphenylazo)-, and 4-(2,6-dimethylphenylazo)-*N'*-guanylnitrate-3,5-dimethylpyrazoles] have been evaluated for their hypoglycemic activity in CF-1-S mice (Carworth Farms, 25–30 g.). Doses of 1.5 mmoles/kg. compound were administered as carboxymethylcellulose suspensions. Controls received an equal volume of the vehicle. Blood samples (0.05 ml.) obtained from retrobulbar plexuses at 0, 3, and 5 hr. after dosing were analyzed for blood sugar with the aid of a Technician Auto-analyzing unit using the modified method of Hoffman (7). Results showed that these compounds were essentially inactive. The testing on other derivatives is in progress.

EXPERIMENTAL

Melting points were taken with a Kofler hot-stage-type apparatus and are uncorrected.

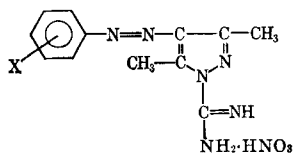

Table II—4-Arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles (II*a*)

No.	X	Yield, %	M.p.	Color[a]	Formula	Anal., % Calcd.	Found
1	2-NO_2	65	186°	OP	$C_{12}H_{14}N_8O_5$	N, 32.00	N, 31.78
2	4-NO_2	68	178°	DYP	$C_{12}H_{14}N_8O_5$	N, 32.00	N, 31.74
3	3-Me	60	189°	YN	$C_{13}H_{17}N_7O_3$	N, 30.72	N, 30.60
4	4-Me	64	193°	DYP	$C_{13}H_{17}N_7O_3$	N, 30.72	N, 30.54
5	3-Cl	60	195°	YP	$C_{12}H_{14}ClN_7O_3$	Cl, 10.45	Cl, 10.27
6	4-Cl	65	166°	OP	$C_{12}H_{14}ClN_7O_3$	Cl, 10.45	Cl, 10.34
7	2-Br	65	190°	YN	$C_{12}N_{14}BrN_7O_3$	Br, 20.83	Br, 20.61
8	4-Br	66	186°	OP	$C_{12}H_{14}BrN_7O_3$	Br, 20.83	Br, 20.64
9	2-MeO	70	195°	YN	$C_{13}H_{17}N_7O_4$	N, 29.25	N, 29.01
10	4-MeO	67	179°	YP	$C_{13}H_{17}N_7O_4$	N, 29.25	N, 29.07
11	4-EtO	68	181°	YP	$C_{14}H_{19}N_7O_4$	N, 28.08	N, 27.94
12	2,3-Me_2	64	196°	YP	$C_{14}H_{19}N_7O_3$	N, 29.42	N, 29.18
13	2,5-Me_2	60	194°	DYN	$C_{14}H_{19}N_7O_3$	N, 29.42	N, 29.29
14	3,4-Me_2	63	217°	YN	$C_{14}H_{19}N_7O_3$	N, 29.42	N, 29.27
15	2,4-$(MeO)_2$	65	185°	YP	$C_{14}H_{19}N_7O_5$	N, 26.84	N, 26.65
16	2,5-Br_2	65	213°	YP	$C_{12}H_{13}Br_2N_7O_3$	Br, 34.55	Br, 34.41
17	3,5-Cl_2	60	209°	LtYP	$C_{12}H_{13}Cl_2N_7O_3$	Cl, 18.98	Cl, 18.70
18	2-Cl-4-NO_2	63	178°	RP	$C_{12}H_{13}ClN_8O_5$	Cl, 9.23	Cl, 9.01
19	2-Cl-6-Me	68	176°	LtON	$C_{13}H_{16}ClN_7O_3$	Cl, 10.04	Cl, 9.78
20	5-Cl-2,4-$(MeO)_2$	65	195°	YP	$C_{14}H_{18}ClN_7O_5$	Cl, 8.88	Cl, 8.55

[a] See footnote *a* of Table I.

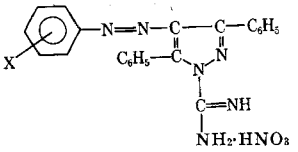

Table III—4-Arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles (II*b*)

No.	X	Yield, %	M.p.	Color[a]	Formula	Anal., % Calcd.	Found
1	2-NO_2	60	184°	YN	$C_{22}H_{18}N_8O_5$	N, 23.62	N, 23.23
2	3-NO_2	62	178°	OP	$C_{22}H_{18}N_8O_5$	N, 23.62	N, 23.32
3	4-NO_2	60	154°	BN	$C_{22}H_{18}N_8O_5$	N, 23.62	N, 23.29
4	2-Br	65	152°	LtOP	$C_{22}H_{18}BrN_7O_3$	Br, 15.74	Br, 15.42
5	4-Cl	60	160°	OP	$C_{22}H_{18}ClN_7O_3$	Cl, 7.65	Cl, 7.30
6	2-Me	55	134°	DYN	$C_{23}H_{21}N_7O_3$	N, 22.12	N, 21.89
7	4-Me	55	167°	LtOP	$C_{23}H_{21}N_7O_3$	N, 22.12	N, 21.81
8	3-MeO	68	186°	YP	$C_{23}H_{21}N_7O_4$	N, 21.35	N, 21.04
9	4-EtO	63	188°	YP	$C_{24}H_{23}N_7O_4$	N, 20.71	N, 20.43
10	4-SO_2NH_2	56	181°	LtRP	$C_{22}H_{20}N_8O_5S$	N, 22.04	N, 21.73
11	2,4-Me_2	55	191°	OP	$C_{24}H_{23}N_7O_3$	N, 21.44	N, 21.14
12	2,5-Me_2	50	112°	BP	$C_{24}H_{23}N_7O_3$	N, 21.44	N, 21.32
13	3,4-Me_2	50	183°	LtRP	$C_{24}H_{23}N_7O_3$	N, 21.44	N, 21.10
14	3,5-Me_2	53	171°	LtOP	$C_{24}H_{23}N_7O_3$	N, 21.44	N, 21.24
15	2,3-Cl_2	55	187°	LtRP	$C_{22}H_{17}Cl_2N_7O_3$	Cl, 14.25	Cl, 14.02
16	2,5-Cl_2	55	163°	YP	$C_{22}H_{17}Cl_2N_7O_3$	Cl, 14.25	Cl, 14.09
17	2-Cl-6-Me	62	185°	DYP	$C_{23}H_{20}ClN_7O_3$	Cl, 7.43	Cl, 7.21
18	4-Cl-2,5-$(MeO)_2$	65	245°	OP	$C_{24}H_{22}ClN_7O_5$	Cl 6.78	Cl, 6.56

[a] See footnote *a* of Table I.

Ethyl 2,3-dioxobutyrate-2-arylhydrazones (5), 2,3,4-pentanetrione 3-arylhydrazones (6), and 1,3-diphenyl-2-arylhydrazono-1,2,3-propanetriones (8) were prepared by coupling diazotized anilines with ethyl acetoacetate, 2,4-pentanedione, and 1,3-diphenyl-1,3-propanedione, respectively.

4-Phenylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-one (I)—Amino guanidine nitrate (0.86 g., 0.005 mole) in water (10 ml.) was added to ethyl 2,3-dioxobutyrate-2-phenylhydrazone (1.17 g., 0.005 mole) in ethyl alcohol (15 ml.). It was refluxed for 2 hr. and then glacial acetic acid (4 ml.) was added. The reaction mixture was again refluxed for 3 hr. On cooling, shining brown crystals of 4-phenylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-one separated out. These were recrystallized from alcohol (70% yield), m.p. 223°.

Anal.—Calcd. for $C_{11}H_{13}N_7O_4$: C, 42.99; H, 4.23; N, 31.92. Found: C, 43.26; H, 4.61; N, 31.80.

The characteristics of other 4-arylhydrazono-*N'*-guanylnitrate-3-methyl-2-pyrazolin-5-ones are given in Table I.

4-Phenylazo-*N'*-guanylnitrate-3,5-dimethylpyrazole (II*a*)—A hot aqueous solution of amino guanidine nitrate (0.005 mole) was added to 2,3,4-pentanetrione-3-phenylhydrazone (1.02 g., 0.005 mole) in ethyl alcohol (15 ml.). To this was added 30% nitric acid until the pH of the reaction mixture became 1. It was then refluxed for 4 hr. On cooling, shining yellow crystals of 4-phenylazo-*N'* guanylnitrate-3,5-dimethylpyrazole separated out. They were recrystallized from ethyl alcohol (75% yield), m.p. 163°.

Anal.—Calcd. for $C_{12}H_{15}N_7O_3$: C, 47.21; H, 4.91; N, 32.13. Found: C, 46.94; H, 5.32; N, 31.89.

The characteristics of other 4-arylazo-*N'*-guanylnitrate-3,5-dimethylpyrazoles prepared similarly are given in Table II.

4-Phenylazo-*N'*-guanylnitrate-3,5-diphenylpyrazole (II*b*)—This was prepared from 1,3-diphenyl-2-phenylhydrazono-1,2,3-propanetrione (1.64 g., 0.005 mole) and amino guanidine nitrate (0.005 mole) by the same procedure used for the preparation of 4-phenylazo-*N'*-guanylnitrate-3,5-dimethylpyrazole (II*a*). The product obtained was recrystallized from alcohol in 65% yield as dark-brown needles, m.p. 101°.

Anal.—Calcd. for $C_{22}H_{19}N_7O_3$: C, 61.53; H, 4.42; N, 22.84. Found: C, 61.18; H, 4.73; N, 22.62.

The characteristics of other 4-arylazo-*N'*-guanylnitrate-3,5-diphenylpyrazoles are given in Table III.

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