ides.[14-17] The information gained during the study of 33 substrates of 4 chemical types with a phosphamidase preparation reveals that the most active substrates are phosphorodi- or triamides and that the central grouping most suitable for modification in the design of substrate-like inhibitors is RR'NPON(N or O) in which R and/or R' are H or small alkyls.

Experimental Section

Chemistry.—Known phosphoramidic dichlorides used for the *in situ* preparation of the corresponding phosphoramidic acids (I–III, V–XI) were synthesized by the procedures indicated in Table I. Ir spectra of all dichlorides, recorded on a Beckman IR-8, were compatible with structures. Elemental analyses, where indicated only by symbols of the elements, are within ±0.4% of the theoretical values.

***N*-Isopropylphosphoramidic Dichloride.**—Reaction of *i*-$PrNH_2$ and $POCl_3$ (2:1) according to the method of Michaelis[18] yielded the white cryst product (Et_2O), mp 51–55° (Fisher–Johns apparatus, uncorr). *Anal.* ($C_3H_8Cl_2NOP$) N (Coleman N analyzer), Cl.[19]

***N,N*-Dibutylphosphoramidic Dichloride.**—Similarly prepd this compd was a colorless liquid, bp 122–124° (1.5 mm). *Anal.* ($C_6H_{18}Cl_2NOP$) C, H, Cl.[20]

Portions of 1 *N* NaOH were added to the phosphoramidic chlorides with magnetic stirring and maintenance of pH at 10–12 (Corning Model 12 pH meter) until solns were obtd. Dil HNO_3 (to pH 7.2–7.4) and then H_2O were added to make 0.03 *M* solns. A soln of the standard reference, phosphormidate, was similarly prepd from the monosodium salt.[21] Triplicate Cl^- analyses[19] were run on samples of these solns and the results are shown in Table I. NH_3 (2.0-ml sample) was determined using Conway microdiffusion dishes[22] with Obrink modification. Inorganic phosphate was detd according to a modified method of Lowry and Lopez[9] with color readings taken after exactly 4 min.[23]

Biology.—Substrates I–XI (0.006 *M*), 0.1 *M* acetate buffer (pH 6.0), and enzyme prepn 60–90 SAS (1.0 EU of phosphoramidate/ml)[3a] were incubated 10 min at 37°. These mixts are the same as those previously described[2] except 2-mercaptoethanol was deleted since it completely interfered with the method used for inorganic phosphorus analysis. Phosphoramidate (0.006 *M*) in lieu of a portion of the buffer soln was included in the mixts for the estimation of inhibitory activity. All detns were made in duplicate with standardization against the reference for each detn. The enzyme prepn was added to controls after incubation and cooling. Enzyme activity was stopped by the addition of equal vols of cold Cl_3CCOOH and, to separate incubation flasks, a NaOH soln of sufficient concn to adjust the pH to 4.0. Duplicate NH_3 detn were run on samples of the former solns and triplicate P analyses were conducted on the alkaline adjusted solns.

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New Compounds

Potential Antidiabetics. 9. Biological Activity of Some Pyrazoles[1]

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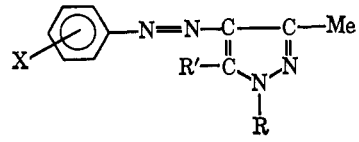
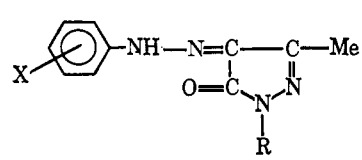
This paper describes the synthesis and evaluation of 4-arylazo-1-(guanyl nitrate)-3-methyl-5-phenylpyrazoles against diabetes mellitus and also includes the evaluation of earlier reported 4-arylazo-1-(2,4-dinitrophenyl)- 3,5- dimethylpyrazoles[2] and 4-arylhydrazono-1-carbamoyl-3-methyl-2-pyrazolin-5-ones[3] against viral infections, as well as 4-arylazo-1-(2,4-dinitrophenyl)-3-methyl-5-phenylpyrazoles[3] and 4-arylhydrazono-1-(2,4-dinitrophenyl)-3-methyl-2-pyrazolin-5-ones[4] against *Trichinella spiralis*.

Pharmacology. Antidiabetic Activity.—Compounds **2, 4, 5, 6, 11, 12, 17,** and **18** have been evaluated for their hypoglycemic activity in CF-1.5 mice (25–30 g) with the aid of a Technician Auto-Analyzer using the modified method of Hoffman.[5] No activity has been shown by these compounds.



Ia, R = —C(=NH)—NH_2·HNO_3
R' = Ph
b, R = DNP
R' = Me or Ph



IIa, R = DNP
b, R = $CONH_2$
X = Substituted phenyl

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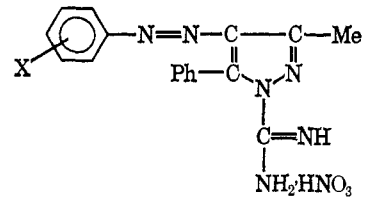
TABLE I

CHARACTERISTICS OF 4-ARYLAZO-1-(GUANYL NITRATE)-3-METHYL-5-PHENYLPYRAZOLES



No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	3-Cl	65	144	DON	$C_{17}H_{16}ClN_7O_3$	Cl, N
2	4-Cl	63	171	ON	$C_{17}H_{16}ClN_7O_3$	C, H, Cl, N
3	2-Me	67	178	BN	$C_{18}H_{19}N_7O_3$	C, H, N
4	3-Me	70	158	BN	$C_{18}H_{19}N_7O_3$	C, H, N
5	2-NO_2	70	139	ON	$C_{17}H_{16}N_8O_5$	C, H, N
6	3-NO_2	68	142	YN	$C_{17}H_{16}N_8O_5$	C, H, N
7	2-Br	72	148	OP	$C_{17}H_{16}BrN_7O_3$	Br, N
8	4-Br	70	176	ON	$C_{17}H_{16}BrN_7O_3$	C, H, N, Br
9	2-MeO	65	140	OYP	$C_{18}H_{19}N_7O_4$	C, H, N
10	2-EtO	70	163	YN	$C_{19}H_{21}N_7O_4$	C, H, N
11	4-EtO	72	160	ON	$C_{19}H_{21}N_7O_4$	C, H, N
12	4-SO_2NH_2	70	187	LtYN	$C_{17}H_{18}N_8O_5S$	C, H, S
13	2,3-Me_2	65	143	YP	$C_{19}H_{21}N_7O_3$	C, H, N
14	2,5-$(MeO)_2$	68	165	DYN	$C_{19}H_{21}N_7O_5$	C, H, N
15	2,4-$(MeO)_2$	70	174	OYN	$C_{19}H_{21}N_7O_5$	C, H, N
16	2,5-$(EtO)_2$	70	156	BP	$C_{21}H_{25}N_7O_5$	C, H, N
17	2,4-Cl_2	65	240	LtBP	$C_{17}H_{15}Cl_2N_7O_3$	C, H, Cl
18	2,4-Br_2	68	171	YON	$C_{17}H_{15}Br_2N_7O_3$	C, H, Br
19	2,5-Br_2	65	259	YON	$C_{17}H_{15}Br_2N_7O_3$	Br, N
20	2-Cl-6-Me	60	181	ON	$C_{18}H_{18}ClN_7O_3$	C, H, Cl

[a] B, brown; D, dark; Lt, light; N, needles; O, orange; P, plates; Y, yellow.

Antiviral Activity.—Ib [X = 3-Cl, 2,4-$(NO_2)_2$] and IIb [X = 2-Cl, 2-NO_2, 4-NO_2, and 4-SO_2NH_2] were screened for antiviral activity against Rhino virus 1059 and 33342 and Respiratory Syncytical Long. There was no plaque inhibition.

Anti-*Trichinella spiralis* Activity.—Tests on Ib [X = 4-Cl, 3-NO_2, 4-NO_2, 4-SO_2NH_2, and 2,5-Cl_2] and IIa [X= 4-Cl, 3-Cl, 4-NO_2, 3-NO_2, 2-NO_2, 4-SO_2NH_2, 2-Cl-4-NO_2, and 2,5-Cl_2] by oral administration to chicks at 0.05% of diet infected with *Eimeria tennela* showed essentially no activity.

Experimental Section

Melting points were taken with a Kofler hot-stage type apparatus and are uncorrected. 2-Arylhydrazono-1-phenylbutane-1,2,3-triones were prepd by the method of Garg, *et al.*[4]

4-(4-Chlorophenylazo)-1-(guanyl nitrate)-3-methyl-5-phenylpyrazole.—Equimolar quantities of aminoguanidine nitrate and 2-(4-chlorophenylhydrazono)-1-phenylbutane-1,2,3-trione (0.005 mole) were dissolved in hot EtOH (30 ml) and refluxed for 1 hr. To this was added 30% HNO_3 until the pH of the reaction mixt became 1. It was again refluxed for 4.5 hr. On cooling, shining crystals sepd out. The characteristics of the 4-arylazo-1-guanylnitrate-3-methyl-5-phenylpyrazoles prepd by similar methods are given in Table I.

Acknowledgment.—Thanks are due to Dr. M. Gordon, SKF Laboratories, and Dr. J. J. Denton, Lederle Laboratories, for making testing data available and to Professor W. U. Malik, for providing necessary facilities for this work. One of us (C. P.) is also thankful to the State C.S.I.R. (U. P.) for financial assistance.

2,5-Dimethoxy-4-methylphenylalanine

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Interest in the mode of action of centrally active phenethylamines, particularly the amphetamines,[1] prompts us to report the synthesis of the title compound (I), which was prepared during the course of other work. I is a possible amino acid precursor of the corresponding phenethylamine, which is 5 times as potent as mescaline.[2] The classical azlactone synthesis[3] of amino acids was unsuccessful because the benzaloxazolone could not be reduced either catalytically or with NaHg, but I was readily obtained from 2,5-dimethoxy-4-methylbenzyl chloride[4] by acetamidomalonate condensation and acidic hydrolysis.

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